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Predictive Medicine: Computational Techniques in Therapeutic Decision-Making

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ABSTRACT The current paradigm for surgery planning for the treatment of cardiovascular disease relies exclusively on diagnostic imaging data to define the present state of the patient, empirical data to evaluate the efficacy of prior treatments for similar patients, and the judgement of the surgeon to decide on a preferred treatment. The individual variability and inherent complexity of human biological systems is such that diagnostic imaging and empirical data alone are insufficient to predict the outcome of a given treatment for an individual patient. We propose a new paradigm of *predictive medicine* in which the physician utilizes computational tools to construct and evaluate a combined anatomic/physiologic model to predict the outcome of alternative treatment plans for an individual patient. The predictive medicine paradigm is implemented in a software system developed for Simulation-Based Medical Planning. This system provides an integrated set of tools to test hypotheses regarding the effect of alternate treatment plans on blood flow in the cardiovascular system of an individual patient. It combines an internet-based user interface developed using Java and VRML, image segmentation, geometric solid modeling, automatic finite element mesh generation, computational fluid dynamics, and scientific visualization techniques. This system is applied to the evaluation of alternate, patient-specific treatments for a case of lower extremity occlusive cardiovascular disease. Comp Aid Surg 4:231–247 (1999). ©1999 Wiley-Liss, Inc.

INTRODUCTION

Significant advances have been made in the diagnosis and treatment of cardiovascular disease since the introduction of modern medical imaging technology and surgical and pharmacologic therapeutic options. In recent years, three-dimensional (3D) cardiovascular imaging techniques and medical visualization software have enabled physicians to interactively view the cardiovascular anatomy externally and even to "fly through" blood vessels in order to examine sites of disease.[27,30,37–40] In addition to obtaining anatomic data, physicians can obtain physiologic data from a variety of sources, including Doppler ultrasound and magnetic resonance imaging. It is now possible to obtain time-resolved 3D flow fields in the cardiovascular system using magnetic resonance imaging (MRI) techniques in a matter of minutes.[14] In parallel with these developments in diagnostic methods, therapeutic options including conventional surgical repair, minimally invasive endoluminal approaches, and drug and gene therapy have emerged. Within these different classes of therapeutic options lie many more subclasses. The physician must choose

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between a variety of devices and pharmacologic agents, in addition to choices amongst different classes of therapeutic options.

The multitude of therapeutic choices which are available to a physician has led to a complex decision-making process. At present, this decision-making process is based largely on experience and empirical data, and involves predicting the outcome of a selected therapy for an individual patient using information from "similar" therapies applied previously to other "similar" patients. This process can be enhanced with statistical decision support tools, but these tools still rely primarily on empirical data which might not reflect the condition of that individual subject.[16] In essence, this decision-making process is rich with information about the present and the past for other subjects, but lacks information or predictions about the future for the individual patient.

In a wide range of disciplines, predictions of future states are made on the basis of simulation techniques and theoretical models initialized with data from the past and present. Increasingly, these simulation methods are implemented on computers. In the engineering disciplines the use of computers is often divided into three distinct areas: Computer-Aided Design, Computer-Aided Engineering, and Computer-Aided Manufacturing. The role of simulation is most prominent in Computer-Aided Engineering, where mathematical models are implemented using numerical methods to evaluate designs developed using Computer-Aided Design software. After an appropriate design is identified using conventional and Computer-Aided Engineering methods, Computer-Aided Manufacturing methods are used to control the machinery used to fabricate a product.

In medicine, two significant recent developments in the application of computer technology are computer-aided surgical planning and image-guided surgery. Contemporary computer-aided surgical planning software is analogous to Computer-Aided Design tools and image-guided surgery developments are analogous to Computer-Aided Manufacturing tools. These tools are largely anatomy-based, e.g., creating anatomic models from imaging data to address issues of surgical approach and to aid the surgeon in implementing a treatment plan. In the field of neurosurgery these techniques are aiding surgeons in repairing cerebral aneurysms and arterio-venous malformations, and in resecting tumors.[17,21,29,42] Similar methods are being employed for a wide range of applications including craniofacial, orthopedic, lung, prostate, and liver surgery planning.[13,52] However, surgery planning must not only address questions of surgical approach but also expected outcome. The prediction of future-states, e.g., the efficacy of a treatment option for restoring blood flow or the performance of a device implanted in the cardiovascular system, requires a procedure for simulating physiologic function in addition to the diagnostic imaging data defining the anatomy of the individual patient. The fundamental shortcoming of contemporary computer-aided surgical planning methodology is that it lacks the *simulation* tools analogous to the Computer-Aided Engineering tools used in engineering applications.

For the cardiovascular system, the simulation of physiologic function includes the modeling of the complex fluid mechanical behavior of blood. Fortunately, significant progress has been made in understanding and modeling cardiovascular blood flow. Hemodynamic, or blood fluid mechanical, conditions, including velocity, shear stress, and pressure, play an important role in the modulation of vascular adaptation and the localization of vascular disease.[15,23,53–55] In recent years, computer simulation software has enabled scientists to construct and evaluate models of human anatomy and physiology and test hypotheses regarding the role of hemodynamic factors in vascular adaptation and disease.[25,34–36,45–48] As these investigations are designed to be compared with patterns of adaptation and disease for the population as a whole, these investigations are typically conducted based on idealized computer models representing "average" anatomy and physiologic conditions.

In addition to the investigation of the role of biomechanical factors in adaptation and disease, computer simulation technology can also be applied to the design of surgical procedures, e.g., the construction of anastomoses with improved hemodynamic conditions[24] or the evaluation and design of orthopedic procedures.[4–11] These investigations are typically performed based on idealized, not patient-specific, models, but can provide substantial quantitative information and improve surgical practice.

In the predictive medicine paradigm proposed herein, a physician would use diagnostic data to reconstruct a model of an individual's anatomy and physiology, and then use simulation techniques, implemented in a simulation-based medical planning software system, to predict the response of that patient to alternate treatments under different physiologic states. Clearly, the success of predictive medicine techniques is dependent upon how faithfully the mathematical model reflects the actual anatomy and physiology of the individual, and on how efficiently the simulations can be performed. For blood flow in the human vascular system, the patient-specific anatomic model is derived from 3D imaging techniques including CT and MRI. The patient-specific physiologic model is, in comparison to the anatomic model, an abstract model based on the equations governing blood flow in arteries and on patient-specific diagnostic data, e.g., measurements of blood flow and pressure. Once the patient-specific model is created, the predictions of the consequences of treatments can be made based on the simulation of blood flow in models that reflect the proposed treatments. This simulation of blood flow can be performed using techniques from computational fluid dynamics on high-performance computers.[46]

A software system developed for simulation-based medical planning is introduced. This system provides an integrated set of tools to test hypotheses regarding the effect of alternate treatment plans on vascular hemodynamics, and was applied to a clinical case of lower extremity vascular disease to predict the effect of multiple alternate treatment plans on blood flow and pressure.

MATERIALS AND METHODS

We have created a comprehensive software framework for simulation-based medical planning. This software system, ASPIRE (Advanced Surgical Planning Interactive Research Environment), has an internet-based user interface developed using the Java programming language and the Virtual Reality Modeling Language (VRML). In addition, this system includes image segmentation, geometric solid modeling, automatic finite element mesh generation, computational fluid dynamics, and scientific visualization techniques.

Custom visualization software was developed for the visualization and segmentation of medical imaging data.[31,32] A geometric modeler was embedded in this visualization environment to allow the user to interactively fit curves to sets of points representing the cross-section of a blood vessel, group and skin these curves to create a NURB surface, then cap and bound this surface to create a solid object of a single blood vessel.[51] The individual blood vessels are then unioned together to form a single solid model of a portion of the vascular system. This solid model, generated from patient-specific imaging data, represents the patient's vascular anatomy prior to treatment. This preoperative model can then be modified by enlarging vessels to simulate angioplasty and adding vascular bypass grafts using solid modeling Boolean procedures. The pre- and post-operative model is then discretized using an automatic finite element mesh generator.[43]

In general, the model of the patient's physiology includes the governing equations for blood flow, boundary and initial conditions, and constitutive properties of the blood and vessel wall. As a first approximation, the blood is treated as a Newtonian fluid and the blood vessels are treated as being rigid. The boundary conditions for the simulations can be obtained using patient-specific diagnostic data, e.g., MRI measurements of blood flow.

Once the patient-specific model is created, a prediction of the consequences of treatments requires the simulation of blood flow in models that reflect the proposed treatments. The finite element method is employed in the present investigation, as it is well suited to the complex geometric models encountered in vascular modeling. The finite element method employed is based on the theory of stabilized finite element methods developed by Hughes and colleagues.[2,18,19] The method is described in detail by Taylor et al.[46] as it is implemented in the commercial finite element program Spectrum.[3] The computational method employed has been shown via analytical and experimental validation studies to yield accurate solutions for pulsatile flow problems.[46]

Another critical issue in the application of computational techniques to surgical planning is the visualization and interpretation of the computed results. For blood flow, alternative techniques to visualize flow fields include velocity vectors, streamlines, particles, and isosurfacing techniques, as well as contouring techniques for scalar fields such as pressure. In addition to scientific visualization techniques, simple x-y plots are essential for interpreting computed results. Figure 1 describes the overall procedure for simulation-based medical planning, starting with the acquisition of patient data and ending in a comparison of alternate treatments.

A typical surgery planning session starts by examining a case presentation. Patient history, medical imaging data, and vascular lab data are examined through a web browser, as shown in Figure 2 for a case of lower extremity occlusive disease. A pre-operative 3D geometric model of the blood vessels can also be seen in Figure 2.

The next step in the surgery planning process is the specification of a treatment plan. This is done

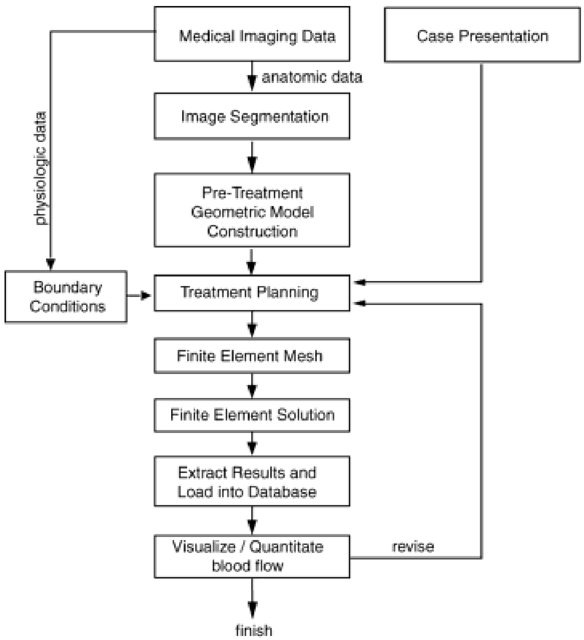

Fig. 1. Flowchart of overall procedure for Simulation-Based Medical Planning.

by drawing a treatment on a surgical sketchpad, as shown in Figure 3. This interactive functionality is implemented using the Java programming language and allows the user to specify the starting and ending locations of vascular bypass grafts. Once the graft is drawn on the sketchpad, a menu appears to allow the user to specify graft characteristics, including dimensions, material, and manufacturer. At present, this data is used in an external program to create a new "postoperative" geometric solid model, e.g., by unioning the preoperative anatomic model with a vascular bypass graft.[46]

Once the treatment plan is constructed, the next step is to perform calculations to simulate the blood flow in the postoperative model. The geometric model is discretized using automatic finite element mesh generation techniques.[43] Physiologic boundary conditions are established based on a model of flow resistance derived from pre-operative data and calculations. Blood flow in the post-operative models is computed under a variety of physiologic states, including resting and exercise conditions.[47,48] Once the blood flow analyses have been performed, the results are viewed by using the system in the treatment evaluation mode. As shown in Figure 4, quantitative results for blood pressure, flow velocity, and volume flow rate can be examined in a set of graphical display windows. These graphical tools can be used to compare the blood flow before and after a treatment plan or to compare the results of two alternate plans. In addition to the graphical display windows, the surgeon can visualize 3D models of the preoperative or postoperative geometry, pressure, or blood flow using the two VRML windows.

CLINICAL CASE

In order to test the concept of predictive medicine, we created a "mock" clinical case and applied our simulation-based medical planning methodology. The base anatomy for this case was generated by extracting the luminal boundaries from a normal subject. This subject was injected with a contrast agent (Gd-DPTA) and then imaged using a phase-contrast MR angiographic sequence from the chest down to the feet with a 1.5 T GE Signa system.[1] A total of 384 slices were acquired in three scans of 128 slices, with in-plane resolution of 0.9375 mm and slice thickness of 1.8 mm.

The mock clinical case created from this base anatomy is that of a 57-year-old man who presents with claudication pain in his right hip and buttocks. Upon physical examination, a blue big toe and non-healing ulcerations are noted on the right foot. The prior medical history includes unsuccessful angioplasties of the right iliac artery and right superficial femoral artery. A schematic summarizing the result of diagnostic imaging is shown in Figure 5, where the right iliac artery is noted to be completely occluded, the left iliac artery has a 50% reduction in diameter, the right superficial femoral artery has a diffuse 50% reduction in diameter, and the left superficial femoral artery is completely occluded. There are many different surgical and non-surgical treatments which could be attempted to correct this patient's clinical problems, but any successful procedure would have to increase the blood flow to the right leg, in order to eliminate the pain experienced upon walking, and to the right foot if the wound is to heal. The pre-operative geometric model and three of the most common procedures, given this particular patient's clinical presentation and observed disease, are shown in Figure 6. These procedures were modeled and compared to see which treatment would produce the best hemodynamic outcome for this specific case. A finite element mesh was generated for each of the geometric models. Figure 7 shows the surface of the finite element mesh generated for the case of the aorto-femoral bypass with a proximal end-to-side anastomosis of the graft to the aorta (Figure 6b).

Resting flow conditions were used to assess

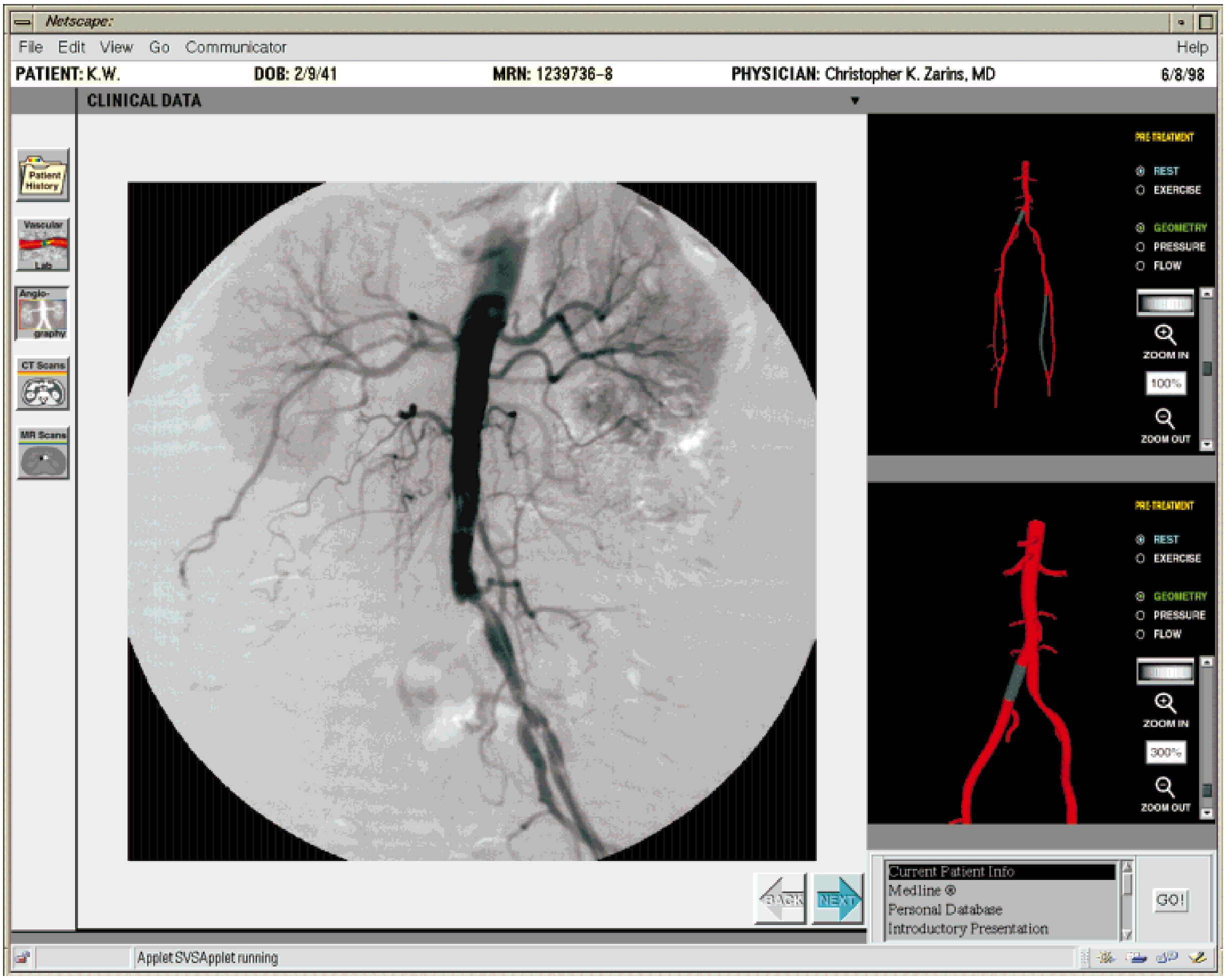

Fig. 2. ASPIRE user interface in clinical data mode running in the web browser Netscape. Angiographic data is shown in the main window for a patient with lower extremity occlusive disease. Shown in the two panels on the right are 3D models constructed from pre-operative MRI data. Pre-operative anatomy and physiology data can be examined and visualized using the Virtual Reality Modeling Language (VRML).

the blood flow in the foot needed for wound healing. Exercise flow conditions were used to assess the blood flow in the right leg under walking conditions. The boundary conditions for pre-operative and post-operative computations were prescribed as follows. First, pre-operative analyses under resting and exercise steady flow conditions were performed with a specified volume flow rate through each boundary based on literature data for flow distribution.[20] This pre-operative analysis was used to compute the average pressure distribution at each outflow boundary. Second, a unique resistance value was computed for each outflow boundary based on a relationship between pressure and volume flow rate of the form $P = QR$, where P is the mean pressure, Q is the volume flow rate, and R is the resistance to flow. For each outflow boundary, the same resistance value was used for all of the post-operative analyses for each surgical plan. Using this strategy, the volume flow rate Q and pressure P were calculated (not specified) for each of the boundaries for each of the surgical plans. The nonlinear evolution equations governing blood flow for each treatment plan were then solved for the velocity and pressure fields over 3 cardiac cycles with 200–300 time steps per cardiac cycle using 8 processors of a Silicon Graphics Origin 2000® parallel computer.

This system for Simulation-Based Medical Planning was demonstrated at the 1998 Society for Vascular Surgery (SVS) meeting. For this demonstration, this system was applied to predict the effect of multiple alternate treatment plans on blood flow and pressure under resting and exercise

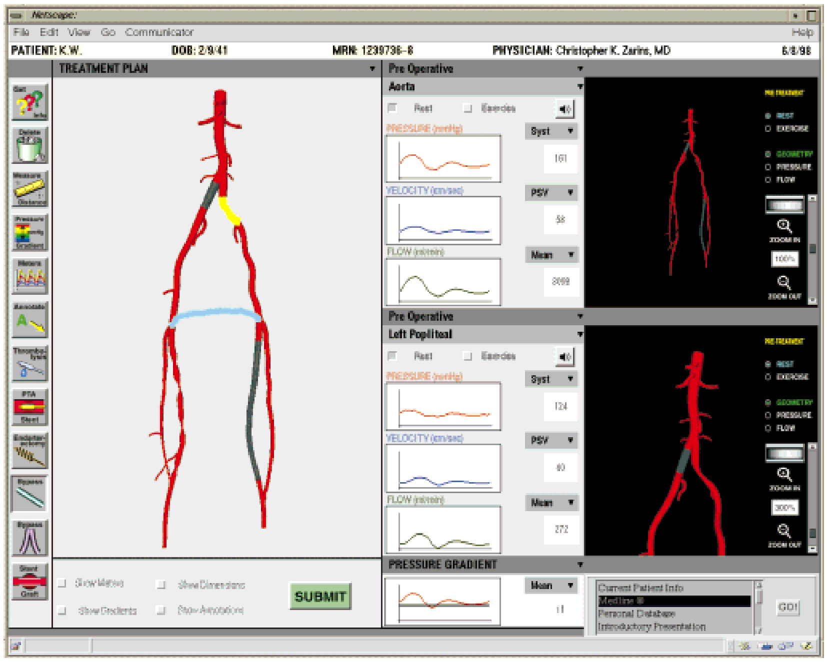

Fig. 3. ASPIRE user interface in treatment planning mode. Shown on the far left are a variety of buttons to query the model and implement treatment options. These treatment options are sketched on a 2D projection of a pre-operative model. The red portion of the model represents the luminal surface of the blood vessels. The yellow portion represents the location where an angioplasty is to be performed to dilate a diseased blood vessel. The light blue line represents the locations where a femoral-to-femoral bypass is to be introduced. A graphical panel is shown to the right of the surgical plan. This panel allows for the extraction of quantitative comparisons of pressure, velocity, and volume flow at standard or user-defined measurement locations.

conditions for the clinical case of lower extremity vascular disease described above. Four prominent vascular surgeons (all former presidents of the SVS) were selected based on their clinical experience; three of the four surgeons had little prior computer experience. All of the surgeons were given 15–20 minutes of training the day prior to the demonstration. At the start of the demonstration, the surgeons were presented with the clinical case and asked to use the system to implement and evaluate one of four possible surgical plans. The display from each of the SGI Octane® computers used by the vascular surgeons was projected to a large display screen for viewing by the audience of vascular surgeons and affiliated health care professionals.

RESULTS

Figure 8 shows the pressure contours at peak systole for the preoperative model and the three treatment plans under resting conditions. An ideal procedure would have minimal pressure losses to transport blood from the aorta to the peripheral vessels. The aorto-femoral bypass procedure with a proximal end-to-side anastomosis (Fig. 8b) resulted in the lowest pressure losses of any procedure. The aorto-femoral bypass procedure with a proximal end-to-end anastomosis (Fig. 8c) had similarly favorable results at the level of the popliteal arteries, but had a significant pressure loss for blood flowing retrograde through the left iliac artery stenosis to the distal aorta. The angioplasty with femoral-to-femoral bypass graft (Fig. 8d) had the greatest pressure losses of any procedure. Also evident for this procedure is the significant pressure loss from the aorta to the left femoral artery and then across the femoral-femoral bypass graft.

Figure 9 depicts the pressure waveforms under resting conditions at right and left femoral arteries for the pre-operative and post-operative cases. Note the relatively low pressures in the right femoral artery pre-operatively, and the fact that the angioplasty with femoral-to-femoral bypass graft has lower pressures in the right femoral artery than either aorto-femoral bypass procedure. In the left femoral artery, the pressures are elevated for the aorto-femoral bypass procedures and compared to the pre-operative pressure

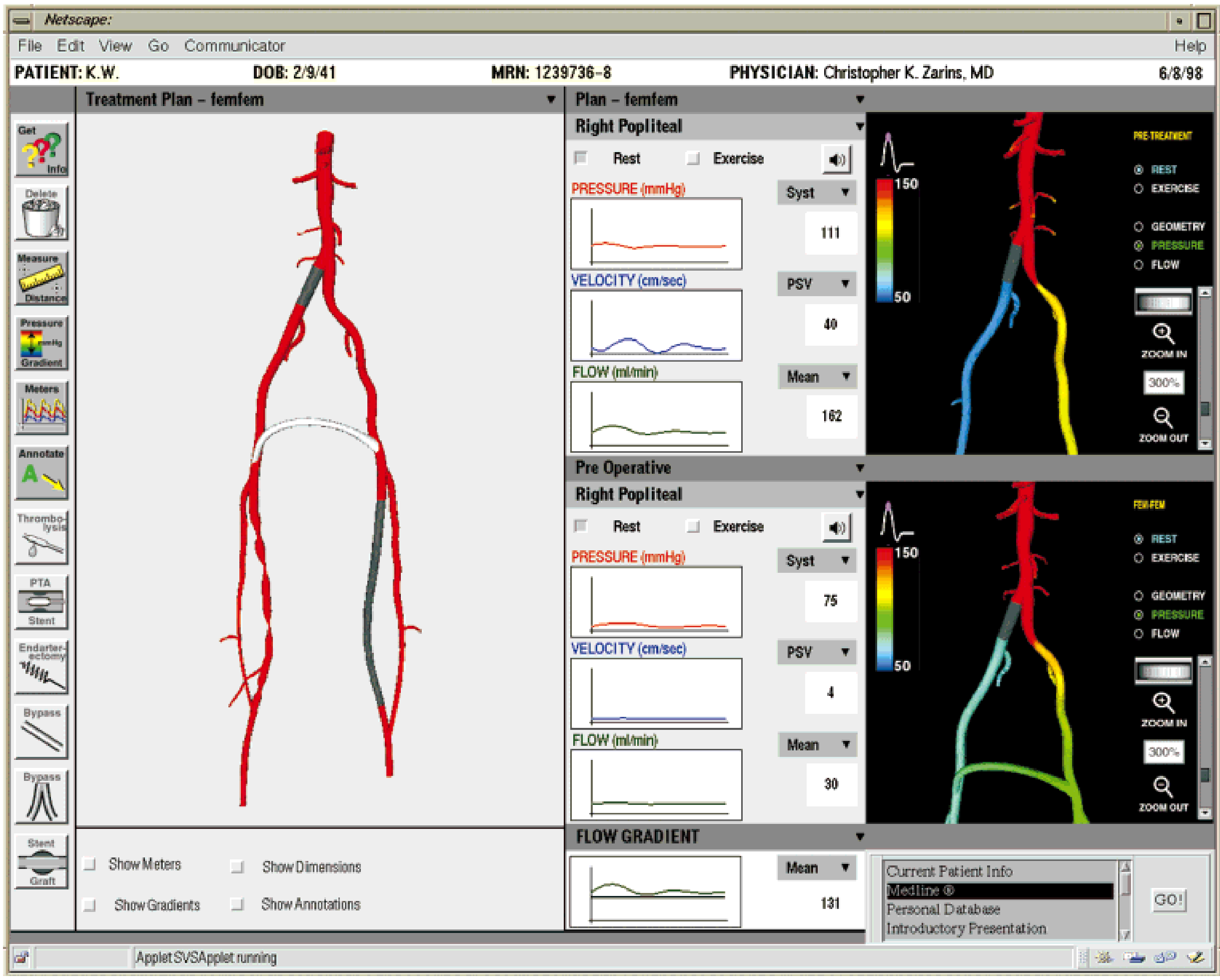

Fig. 4. ASPIRE user interface in treatment evaluation mode. The increase in flow at the level of the right popliteal artery is examined quantitatively by comparing the pre-operative volume flow to the post-operative volume flow. The panel at the right allows the qualitative comparison of the pressure contours under resting conditions for the pre-operative case and the implemented surgical procedure.

waveform. For the angioplasty with femoral-to-femoral bypass graft, the peak systolic pressure is predicted to actually decrease compared to the pre-operative peak systolic pressure due to the substantially increased left femoral artery flow resulting from this procedure.

Table 1 details a comparison between the computed mean flow rates under resting conditions for the pre-operative simulation and the three treatment plans. Note, in particular, the mean flow rates for the alternate treatment plans at the levels of the aortic bifurcation and the right popliteal artery. For the case of the aorto-femoral bypass procedure with the end-to-end anastomosis, the flow at the level of the aortic bifurcation is exactly the flow that will perfuse the inferior mesenteric and lumbar arteries. It is noted that the flow rate at the level of the aortic bifurcation is only 15 ml/min for this case. In addition, in all cases, the flow increases in the right popliteal artery compared to the pre-treatment case, with the greatest improvements in flow seen for the aorto-femoral bypass procedures.

The demonstration at the 1998 Society for Vascular Surgery (SVS) meeting was completed with no technical difficulties encountered. Each of the four vascular surgeons on the panel successfully used the software system to solve the clinical case presented in this live demonstration. Figure 10 shows the panelists using the software system as well as the display from one of the computers projected on a large screen for viewing by the audience.

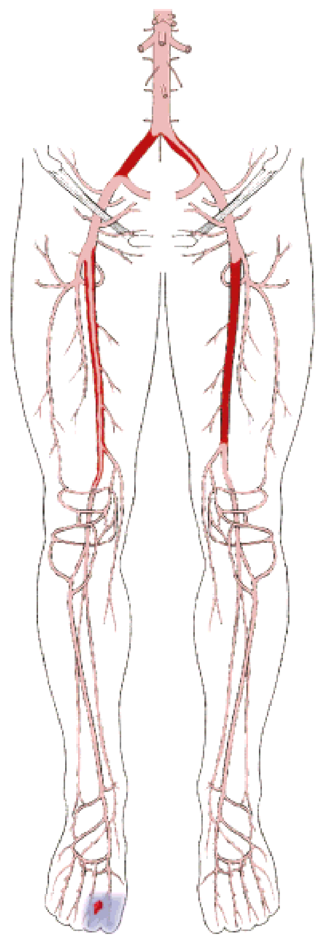

Fig. 5. Schematic illustrating result of diagnostic imaging for patient with nonhealing wound in right foot.

DISCUSSION

A software system developed for Simulation-Based Medical Planning was introduced and applied to examine the effect of different treatment plans on blood flow and pressure for a case of lower extremity vascular disease. The significance of the clinical findings is discussed, followed by an analysis of the modeling assumptions and techniques employed. Finally, the role of simulation techniques in medicine of the future is considered.

The computational analyses of blood flow for the case of lower extremity occlusive disease generated a wealth of information regarding blood flow and pressure for the treatments examined. It must be emphasized that these findings are patient-specific, and could be different for a different subject with different anatomy or physiologic conditions. Clearly, clinical studies will be necessary to test the validity of these findings, and, as in the case of new theoretical tools introduced in other fields, new experimental studies will be initiated to test predictions.

Of particular interest to the vascular surgeons on the SVS panel was the prediction that the aorta-femoral bypass plan with a proximal end-to-end anastomosis (AFB w/ E-E) had a very low flow rate (15 ml/min) at the level of the aortic bifurcation under resting conditions (see Table 1 and also note the lower pressures at the level of the aortic bifurcation in Figure 7c). This is of concern since for this particular case it would be expected to lead to a significantly reduced blood flow to the lower intestine and colon. This finding might lead the vascular surgeon to reimplant the inferior mesenteric artery into the side of the bypass graft. Alternatively, some vascular surgeons have suggested that this finding might lead them to perform an angioplasty on the left common iliac artery when performing this procedure to ensure adequate retrograde flow to the inferior mesenteric artery.

An additional finding which generated considerable discussion at the SVS meeting was the result that the treatment plan with the angioplasty and femoral-to-femoral bypass graft had only 50% of the flow at the level of the right popliteal artery compared to the two procedures with aorto-femoral bypass grafting (see Table 1). Ultimately, the angioplasty with femoral-to-femoral bypass graft still requires blood flow for two legs to flow down one iliac artery. With quantitative, patient-specific information at their disposal, the vascular surgeon could weigh the increased trauma, yet improved blood flow, of the aorto-femoral bypass procedures with the less invasive nature, yet inferior blood flow, of the angioplasty and femoral-to-femoral bypass procedure. Once again, the conclusion drawn is patient-specific, and the key point is that the surgeons will have quantitative predictions of outcomes to augment their professional experience in the decision-making process.

Simulation-based medical planning requires the creation of patient-specific anatomic and physiologic models. The complexity of the cardiovascular system requires that assumptions be made for these models. In regards to the individual patient's vascular anatomy, it is assumed that only the major arteries which can be detected with diagnostic imaging methods need to be included in the computational model. This is justified based on the fact that the physician intervenes to restore blood flow only in the major arteries and does not treat the small vessels. The effect of the small vessels in the downstream vasculature is modeled through the boundary conditions. The patient-specific physio-

(a) (b) (c) (d)

Fig. 6. Geometric models for alternate treatment plans for the case of lower extremity occlusive disease examined: (a) anatomic description with stenoses and occlusions shown, (b) aorto-femoral bypass graft with proximal end-to-side anastomosis, (c) aorto-femoral bypass graft with proximal end to end anastomosis, (d) balloon angioplasty in left common iliac artery with femoral-to-femoral bypass graft.

logic model and pre-operative flow distribution was defined based on literature data for flow distributions.[20] In general, the pre-operative flow distribution will be defined based on pre-operative imaging data, e.g., volume flow rates obtained using phase-contrast MRI techniques.

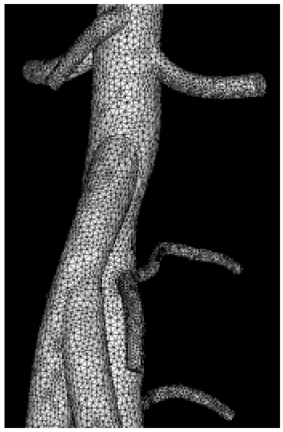

Fig. 7. Close-up of finite element mesh for aorto-femoral bypass with end-to-side anastomosis.

The key software elements of the ASPIRE simulation-based medical planning system are the internet-based user interface, the image segmentation methods, geometric solid modeling, automatic finite element mesh generation, boundary condition specification, computational fluid dynamics, and scientific visualization techniques. The authors have developed and implemented methods for each of these component technologies, but further improvements are needed before the system can be used clinically. These component technologies, and the assumptions which they employ, are discussed in turn.

The user interface to the ASPIRE system uses Java and the Virtual Reality Modeling Language (VRML) to ensure that the system works in a distributed computing environment. This enables interaction with models and simulation results across a network from a variety of platforms. Some of the limitations of the current user interface include the fact that the sketch-pad operates in a two-dimensional (2D) mode and must be supplemented by auxiliary 3D data supplied by the user, since all treatment plans are inherently three-dimensional. As noted previously, in the present system, the segmentation, geometric modeling, and computations are performed external to the user interface. At present, it is not feasible to distribute all of the image segmentation and geometric model construction steps of the treatment planning process. In particular, the creation of the pre-operative geometric model, which involves interacting with very large 3D image data sets, is currently not feasible in a fully distributed mode. However, we have been successful in implementing distributed geometric modeling and finite element mesh generation techniques using the Java Native Interface (JNI) and the Remote Method Invocation (RMI) facility. It is probable that, after a pre-treatment model is constructed and loaded into a database, interventions can be implemented using a distributed, client-server paradigm. In addition, the visualization of post-operative results can be performed using the present internet-based methods. Future enhancements in the distributed capabilities of this system will be enabled by the developments underway in the Internet2 program.

The 3D visualization of medical imaging data sets is performed using either volume rendering or surface rendering techniques. Volume rendering methods have significant application in allowing for the visualization of anatomic features without the segmentation of image data. However, in order to extract quantitative data and construct mathematically accurate data models, surface modeling and rendering techniques are most appropriate. For surface rendering techniques, surfaces within the volume are commonly approximated by a polygonal mesh (a set of contiguous 2D primitives), extracted using threshold-based Marching Cubes techniques with connectivity criteria.[26] Although suitable for visualization, polygonal meshes do not provide representations most appropriate for geometric quantification and analysis, and are often too dense for distributed visualization applications of vascular geometry. An alternative approach to constructing surface models is using B-spline surfaces skinned from cross-sectional data or B-spline patches fitted directly to surface triangulations.[22] These inherently smooth surfaces can be connected together using geometric modeling Boolean operators to obtain anatomic models of the vasculature.[32] In addition, these surfaces can be defined with highly compact data structures appropriate for distributed visualization applications. In the present case, we have created vascular geometric models by lofting B-spline surfaces through circular and elliptical cross-sections fitted to contour data on 2D slices.[32,46] Recently, we have extended this 2D segmentation technique to include piecewise linear surfaces lofted through piecewise linear contours extracted using a level-set method.[49] This new approach has the advantage of more accurately representing the vessel boundaries, but has not yet been fully implemented within our software framework.

The finite element mesh generation techniques employed resulted in largely isotropic discretizations, although curvature-based refinement techniques were used to achieve element sizes

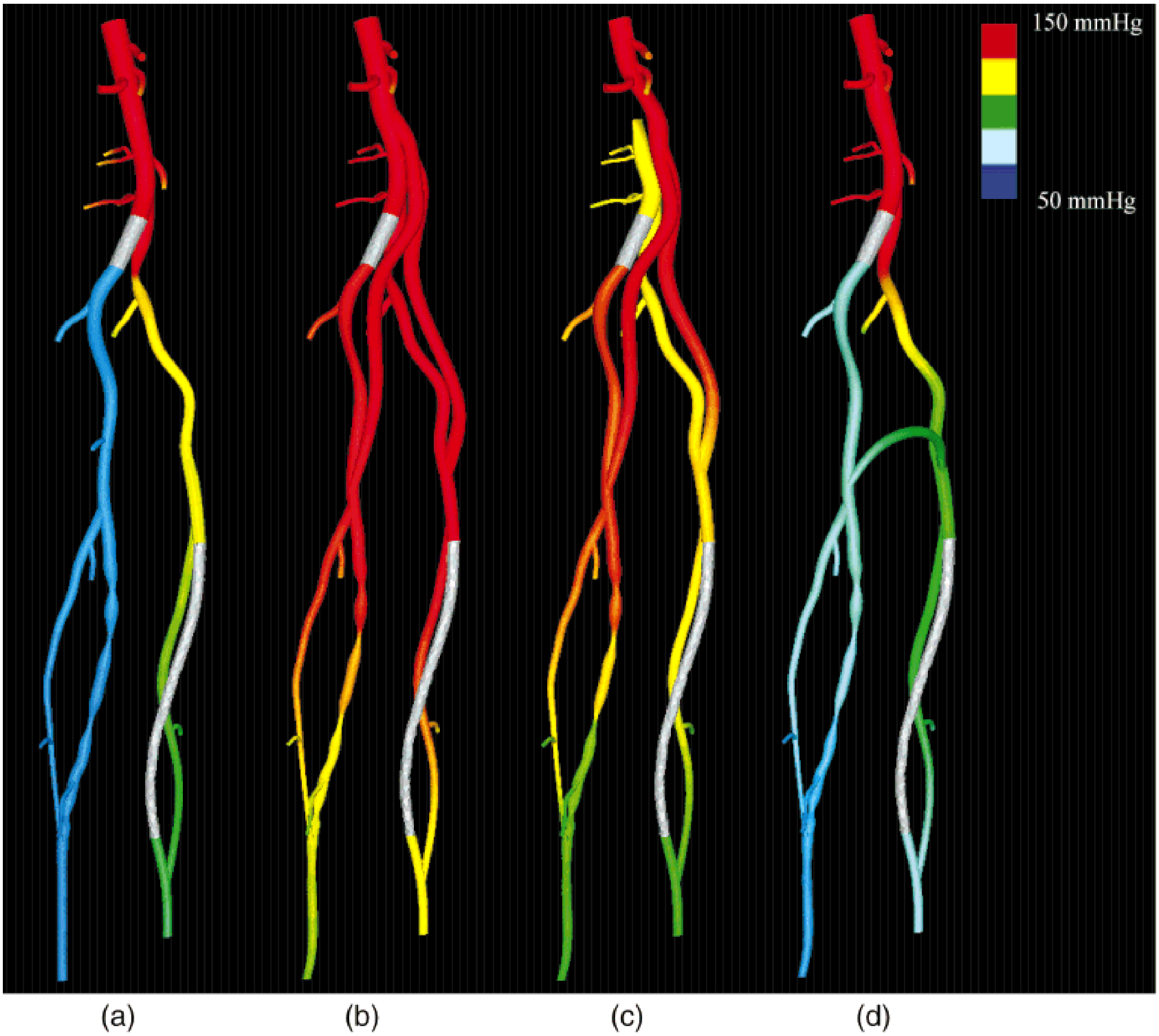

Fig. 8. Pressure distribution under resting conditions at peak systole for (a) pre-operative model, (b) aorto-femoral bypass graft with proximal end-to-side anastomosis, (c) aorto-femoral bypass graft with proximal end-to-end anastomosis, (d) balloon angioplasty in left common iliac artery with femoral-to-femoral bypass graft.

which were appropriate for smaller branch vessels. New finite element mesh generation techniques are needed which are more suitable for the discretization of arterial geometric models. These new mesh generators, incorporating curvature-based refinement and boundary layer mesh generation techniques, could result in finite element meshes which require 5–10 times fewer finite elements for a given blood flow solution accuracy, as compared to conventional methods based on isotropic mesh refinement. This will enable up to a 100-fold decrease in solution time for blood flow computations. Clearly, these new mesh generation methods are essential for the clinical application of simulation-based medical planning systems.

One of the greatest difficulties in applying predictive methods for vascular surgery planning is the specification of appropriate "post-operative" boundary conditions for the computational analyses. This problem arises from the fact that most computational methods for modeling blood flow require the specification of flow rate or pressure as boundary conditions, while the purpose of using computational methods for treatment planning is often to predict changes in these quantities. Quite simply, the effect of a cardiovascular intervention

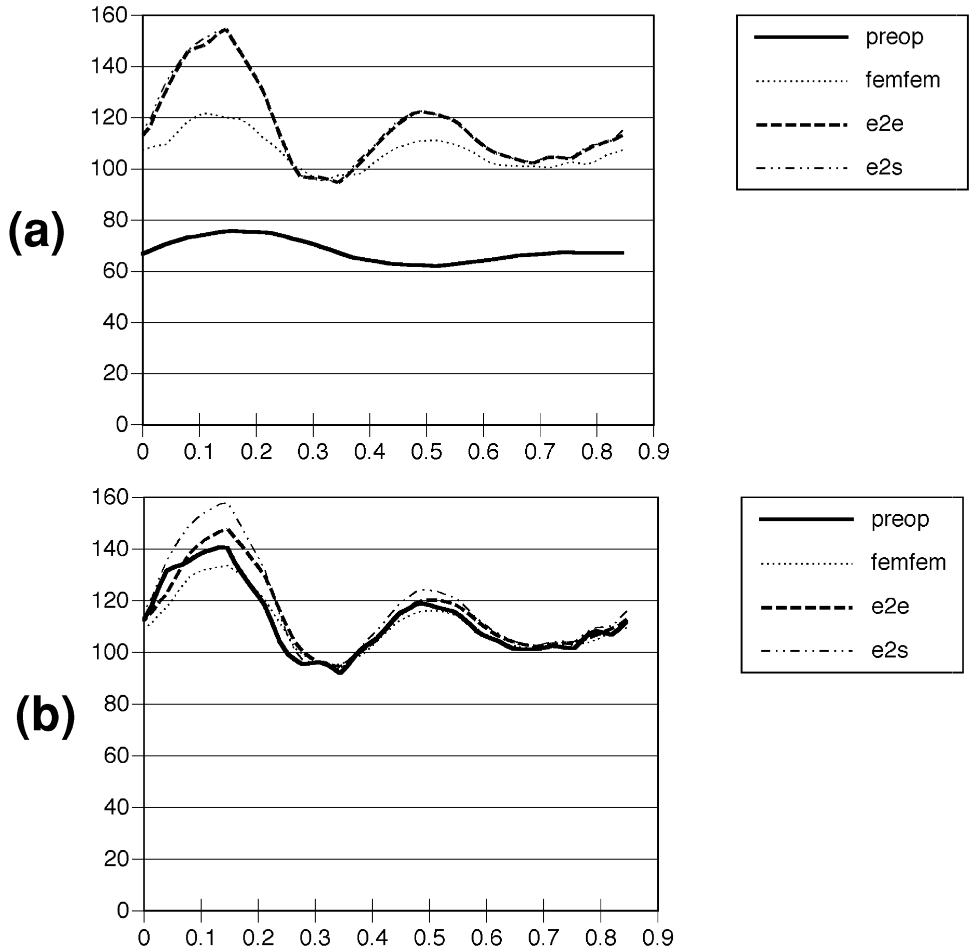

Fig. 9. Pressure (mm Hg) vs. time (sec) over 1 cardiac cycle under resting conditions at (a) right and (b) left femoral arteries for pre-operative model (preop), balloon angioplasty in left common iliac artery with femoral-to-femoral bypass graft (femfem), aorto-iliac bypass graft with proximal end-to-end anastomosis (e2e), aorto-iliac bypass graft with proximal end-to-side anastomosis (e2s).

on flow rate or pressure is unknown prior to the procedure being performed, and flow rate and pressure are thus inappropriate boundary conditions for predictive modeling.

The approach we have adopted is to divide the cardiovascular system into two parts, one representing the major arteries where more detailed flow information is desired or which will be altered due to the cardiovascular treatment, and the other representing the vasculature upstream or downstream of the first part. The second part is assumed to be outside of the region of interest and although it might be affected by changes in blood flow or pressure, it will not be directly altered by the cardiovascular treatment. The first part of the cardiovascular system is then modeled using a 3D patient-specific anatomic model and governing equations formulated to represent 3D flow fields, vessel wall mechanics, and interactions with devices or pharmaceuticals. The second part of the cardiovascular system, that which is outside the primary region of interest (the first part), is modeled using a simplified description of cardiovascular function. In the present case, this simplified description involves specifying a constant peripheral resistance, R, for each outflow boundary. Finally, the 3D model (the first part) is coupled to the simplified model (the second part) by enforcing the continuity of pressure and volume flow rate at the interface between these two domains. For the present case, this reduces to a linear relation of the form $P = QR$, where P is the mean pressure, Q is the volume flow rate, and R is the resistance to flow. The simple constant resistance approach im-

Table 1. Mean Flow Rate (ml/min)

Artery	Pretreatment	AFB w/E-S	AFB w/E-E	Angioplasty w/Fem-Fem
Abdominal Aorta	3009	3460	3460	3460
Aortic Bifurcation	670	307	15	1062
Right Internal Iliac	134	156	212	144
Left Internal Iliac	464	148	150	335
Right Femoral	216	615	663	444
Left Femoral	464	550	781	747
Right Popliteal	30	283	309	162
Left Popliteal	272	351	362	290

plemented thus far is entirely adequate for the steady flow conditions, but has limited applicability for pulsatile flow where the resistance will be a function of time. Current efforts are focused on the implementation of vascular network models based on one-dimensional wave propagation theory. Additionally, the changes in the distal resistance due to autoregulatory factors will need to be included in future versions of this vascular surgery planning system.

The effect of vessel compliance was not considered in the present investigation. Prior investigations of flow in deformable models have shown that, in general, incorporating the effect of compliance does not significantly change the flow fields.[12,34,44] It should be noted that, although neglecting wall distensibility may not have a major effect on the primary flow field, the incorporation of wall mechanics in these studies is important for other reasons, including the description of the stress environment within the vessel walls and the interaction between deformable vessels and vascular devices. In summary, the use of rigid models for simulation-based medical planning should be viewed only as a first approximation.

A Newtonian constitutive model for viscosity was employed in the present investigation. It is generally accepted that this is a reasonable first approximation to the behavior of blood flow in large arteries. Perktold et al.[33] examined non-Newtonian viscosity models for simulating pulsatile flow in carotid artery bifurcation models. They concluded that the shear stress magnitudes predicted using non-Newtonian viscosity models resulted in differences on the order of 10% as compared with Newtonian models. Once again, the use of Newtonian models for blood rheology should be viewed only as a first approximation. Future studies should incorporate non-Newtonian rheologic models.

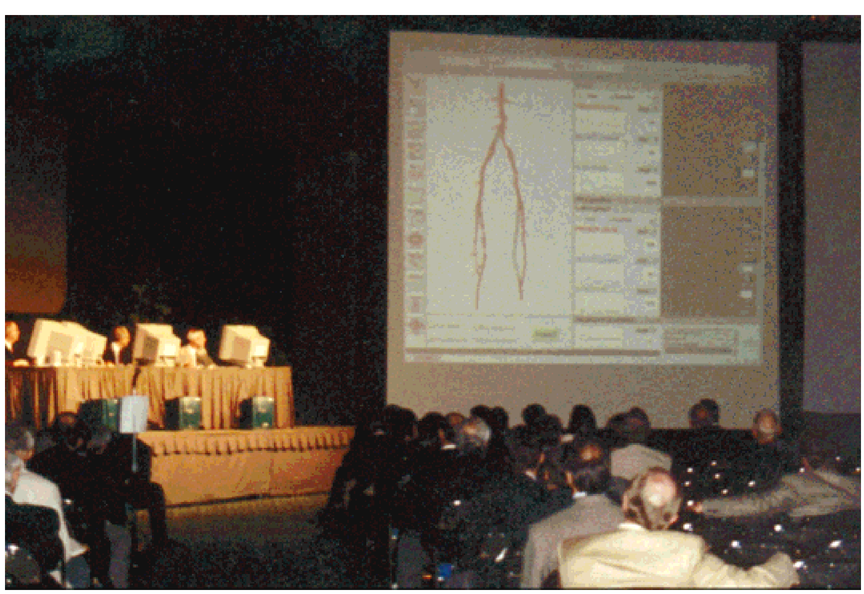

Fig. 10. Photograph of demonstration illustrating panel of surgeons on-stage and projection to audience.

Computational performance is a significant issue in deploying simulation-based medical planning systems. With current software algorithms and hardware capabilities, the present calculations required approximately 20 hours of CPU time per analysis using 6 subdomains and 8 processors on a Silicon Graphics Origin 2000 parallel computer. The present computations require the simultaneous solution of approximately 500,000 nonlinear equations which must be solved at hundreds of time points per cardiac cycle. It is anticipated that, with increased software and hardware performance, more complex problems will be solved. The competing demands of solution accuracy and computational efficiency will have to be reconciled with the time and economic constraints of the surgery planning process. For many interventions, days or weeks can elapse between the times when imaging data is acquired and when a treatment is implemented, but clearly it would not be economically viable to expend weeks of computational time in treatment planning for a given case. However, it is likely that 1–2 hours of total time expended for a given patient and the evaluation of multiple treatment plans would be economically feasible for many cases. This will be achievable in the near future with improvements in computer software, hardware, and networking.

Computational investigations of blood flow require validation using analytical solutions and *in vitro* and *in vivo* experimental methods. We have validated our finite element methods to model blood flow in arteries using analytical solutions for pulsatile flow,[50] and with laser Doppler anemometry velocity data obtained by Loth[28] for steady and pulsatile flow in an *in vitro* model of an end-to-side anastomosis.[46] It was observed in these studies that the computational results compared favorably qualitatively and quantitatively with the analytical solution and experimental data (less than 10% error at most points). The present computations were performed with the same degree of finite element mesh refinement as these prior validation studies. Validation studies in progress include *in vitro* studies in deformable vessel models and *in vivo* studies comparing subject-specific computational solutions to time-resolved 3D phase-contrast MRI velocity data.

Clinical validation studies are essential for the development and ultimate utilization of Simulation-Based Medical Planning systems. This is particularly true considering the number of assumptions that are required to model blood flow in the human cardiovascular system. Some of the critical points to consider in regard to the patient-specific anatomic models include an assessment of the accuracy in reconstructing anatomic models from imaging data, the accuracy with which static models represent the actual, dynamic, human anatomy, and the extent of the vascular anatomy that needs to be included in these models. The creation of the abstract patient-specific physiology models is more difficult than the creation of patient-specific anatomic models in that it is easier to conceptualize how a treatment will alter the anatomy, but not obvious how a treatment will alter the physiologic response. As noted previously, this relates to the boundary conditions imposed on the computational flow solutions. Extensive experimentation will be required to identify and validate patient-specific physiologic models. Methods for estimating the error in the predictive simulations will be required as the uncertainty in the input conditions will be reflected in the uncertainty in the results. Stochastic methods will ultimately be essential ingredients in any Simulation-Based Medical Planning system.

It is acknowledged that contemporary methods for simulating blood flow in the cardiovascular system are crude compared to the true complexity and elegance of human function. However, these tools provide a means for evaluating treatment plans for individual patients which are simply not possible without predictive methods. We believe that these predictive methods will add value to the contemporary treatment planning process, but ultimately this question will have to be answered by clinical trials.

It is important to note that the information provided by computer simulations of blood flow provides only a portion of the data which are needed to design a treatment plan. Numerous other factors, including the morbidity and mortality of the procedure, must be considered. For example, a physician might choose a less invasive procedure even though it leads to less favorable blood flow than an open procedure. The utilization of predictive methods will enable a physician to make this choice with knowledge of the tradeoffs which would likely occur.

The predictive medicine paradigm, whereby a physician would use diagnostic data to reconstruct a model of an individual's anatomy and physiology, and then use simulation techniques, implemented in a simulation-based medical planning software system, will have important applications in medicine of the future. This approach could allow physicians to "design" improved, patient-specific treatment plans. It is instructive to reconsider the "doorway to the future" described by Satava and Jones in light of these recent developments in predictive medicine.[41] They describe a future scenario whereby diagnostic anatomic and physiologic data are obtained as a patient passes through a physician's doorway and a "medical avatar" is created to help with patient education, preoperative planning, surgical simulation, and post-operative follow-up. With the predictive medicine paradigm proposed herein, a physician would not only "simulate" a procedure, but actually implement and quantitatively evaluate alternate treatment plans using simulation-based medical planning software systems like those described in this paper. This ability to predict outcomes of alternate interventions could emerge as a critical component of medicine of the future.

CONCLUSIONS

The clinical application of predictive, simulation-based medical planning techniques is a fundamentally new approach to treatment planning. In the case of cardiovascular disease, these methods could enable physicians to "design" patient-specific treatment plans that improve blood flow. Presumably, with knowledge of the effect of hemodynamic conditions on vascular adaptation and disease, and the determination of the optimal hemodynamic conditions for an individual patient, better treatments can be devised to improve patient care.

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