POLİTEKNİK DERGİSİ

JOURNAL of POLYTECHNIC

ISSN: 1302-0900 (PRINT), ISSN: 2147-9429 (ONLINE)
URL: http://dergipark.org.tr/politeknik

Patient specific cardiovascular disease modelling based on the computational fluid dynamics simulations: segmentation and hemodynamic model of a thoracic artery

Hesaplamalı akışkanlar dinamiği simülasyonlarına dayalı hastaya özel kardiyovasküler hastalık modellemesi: torasik arterin segmentasyonu ve hemodinamik modeli

***Yazar(lar) (Author(s))**: Levent AYDIN[1], Serdar KUCUK[2], Ozgur CAKIR[3]*

ORCID[1]: 0000-0003-2926-2824

ORCID[2]: xxxx-xxxx-xxxx-xxxx

ORCID[3]: xxxx-xxxx-xxxx-xxxx

Bu makaleye şu şekilde atıfta bulunabilirsiniz(To cite to this article): Aydin L., Kucuk S. ve Cakir O., "Patient specific cardiovascular disease modelling based on the computational fluid dynamics simulations: segmentation and hemodynamic model of a thoracic artery", ***Journal of Polytechnic***, 23(4): 1213-1218, (2020).

Erişim linki (To link to this article): http://dergipark.org.tr/politeknik/archive

DOI: **10.2339/politeknik.616293**

Patient Specific Cardiovascular Disease Modelling Based on The Computational Fluid Dynamics Simulations: Segmentation and Hemodynamic Model of a Thoracic Artery

Highlights

- *A patient specific thoracic artery model is segmented based on the MRI images,*
- *A thoracic aneurysm disease model is simulated to assess blood flow changes and stress during the circulation.*

Graphical Abstract

In this study, a patient specific thoracic artery model is first segmented based on the MRI images and then a thoracic aneurysm disease model is simulated to assess blood flow changes, for maximum flow condition, and generated stress during the circulation.

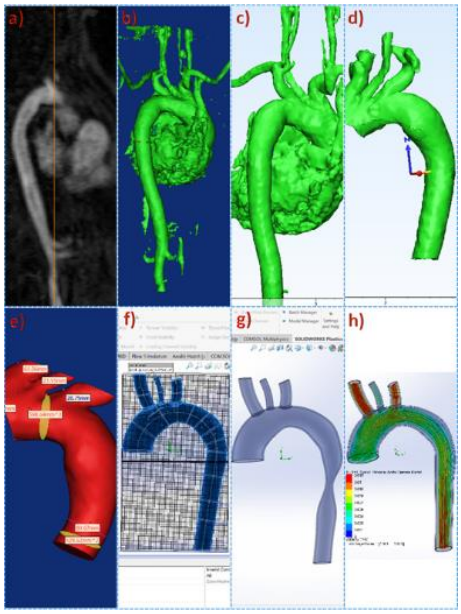


Figure. A

Aim

The aim of this study is to obtain a patient specific thoracic artery model and perform fluid dynamic simulations based on the predefined disease conditions.

Design & Methodology

MIMICS software was utilized to segment the artery model. Subsequently, target artery model was imported into SolidWorks to perform simulation scenarios based on the aneurysm progression.

Originality

Patient specific thoracic artery segmentation is presented step by step. Finally, the STL artery model file was utilized in simulations with predefined conditions to observe effects of aneurysms in advance.

Findings

Blood flow velocity values were increased during the systole up to 0.2m/s and decreased during the diastole down to 0.02m/s on each region of the vessel. Maximum 0.0002MPa vonMises stress generated in more progressed aneurysm disease model

Conclusion

Patient specific thoracic artery segmentation and disease model simulation are presented. Progression of a vascular disease may be simulated in advance by utilizing this segmented 3D model.

Declaration of Ethical Standards

Ethical permission was received by the Ethics and Research Committee of Kocaeli University (Reference Number: KU GOKAEK 2019/204).

Hesaplamalı Akışkanlar Dinamiği Simülasyonlarına Dayalı Hastaya Özel Kardiyovasküler Hastalık Modellemesi: Torasik Arterin Segmentasyonu ve Hemodinamik Modeli

Araştırma Makalesi / Research Article

Levent AYDIN[1*], Serdar KUCUK[2], Ozgur CAKIR[3]

[1]Gedik Meslek Yüksek Okulu, Biyomedikal Cihaz Teknolojileri Bölümü, İstanbul Gedik Üniversitesi, Türkiye
[2]Mühendislik Fakültesi, Biyomedkal Müh. Bölümü, Kocaeli Üniversitesi, Türkiye
[3]Tıp Fakültesi, Radyoloji Bölümü, Kocaeli Üniversitesi, Türkiye

(Geliş/Received : 06.09.2019 ; Kabul/Accepted : 07.12.2019)

ÖZ

Günümüzde kardiyovasküler hastalıklar, çoğunlukla koroner arter hastalıkları önde gelen ölüm nedenleri arasında bulunmaktadır. Bir arterdeki mevut akış dinamiği, kardiyovasküler bir rahatsızlığın önceden teşhis edilebilmesinde büyük önem taşımaktadır. Bununla birlikte, hemodinamik parametreler, doğrudan ölçülemediği için, gerçekçi fizyolojik simülasyonlar elde edilmesinde beyin ve kalp damar cerrahisi alanlarında hesaplamalı yöntemler oldukça yaygın bir şekilde kullanılmaktadır. Bu çalışmada, hastaya özgü bir torasik arter modelinin, MRI görüntüleri temelli segmentasyonu gerçekleştirilerek, bu model üzerinde önceden tanımlanmış koşullar altında kan akışı değişikliklerini değerlendirmek üzere bir torasik anevrizma hastalığı simüle edilmiştir.

Anahtar Kelimeler: Hastalık modeli, hesaplamalı akışkanlar mekaniği, kardiyovasküler hastalık, torasik arter, anervrizma.

Patient Specific Cardiovascular Disease Modelling Based on the Computational Fluid Dynamics Simulations: Segmentation and Hemodynamic Model of a Thoracic Artery

ABSTRACT

Nowadays cardiovascular diseases (CVDs), mostly coronary artery diseases become a leading cause of death. Flow dynamics of a vessel is important to diagnose a CVD in advance. However, hemodynamic parameters may not be measured directly. Hence, computational methods are increasingly being used in the fields of neurosurgery and cardiovascular surgery to obtain realistic physiological simulations. In this study, a patient specific thoracic artery model is first segmented based on the MRI images and then a thoracic aneurysm disease model is simulated to assess blood flow changes under the predefined conditions.

Keywords: Disease model, computational fluid dynamics, cardiovascular disease, thoracic artery, aneurysm.

1. INTRODUCTION

Nowadays cardiovascular diseases (CVDs), mostly coronary artery diseases, hearth attack and stroke, become a leading cause of death. More than 17 million people died in 2016 according to a study of the World Health Organization (WHO) although most of the diseases can be prevented [1]. Moreover, CVDs cause almost 6 million deaths in the European Union (EU) countries [2]. American Heart Association Council (AHA) has also reported that an average of 1 death occurs every 38 seconds in America [3]. CVDs such as Coronary heart disease, Cerebrovascular disease, Peripheral arterial disease, Rheumatic heart disease, Congenital heart disease and Deep vein thrombosis and pulmonary embolism, are a group of disorders of the hearth and blood vessels that mainly caused by a blood flow blockage or a hemodynamic condition like high blood pressure in a weak spot of a vessel. Therefore, knowledge of the vessel physiology and pathology, blood flow mechanics and hemodynamic behaviors, are of great importance to diagnose or treat the CVDs in advance [4].

An artery is composed of several tissue layers namely: i) Tunica intima, the innermost layer of an artery, ii) Tunica media, enclosing surface of the intima and iii) Tunica externa or Tunica adventitia, the outermost layer of an artery, that naturally aligned, biomechanically elastic and strong enough to stand the required blood pressure during

**Sorumlu Yazar (Corresponding author)*
e-posta : levent.aydin@gedik.edu.tr

circulation in body [5]. The intima layer is formed with endothelial cells that directly affect the vessel physiology owing to the interaction between the blood flow and endothelium. Changes in the flow may cause a vascular pathogenesis. The intima layer is surrounded with the media layer formed with smooth muscle cells (SMCs). Thickness of the media layer may vary according to the vessel type. The media layer is the thickest layer of an artery while it is thinner than the externa layer in veins. The elasticity of a vessel is also related to thickness ratio of both media and externa layers or vessel diameter. Therefore, more elastic behavior is expected in larger arteries with regards to pulsatile blood flow (Womersley flow) control. The externa layer is mostly comprised of collagen that guides to SMCs by means of micro fibers to achieve the required cellular alignment in a vessel structure. Furthermore, collagen layer protects the inner layers from the environmental risks in a body. Each tunica layer is supported with internal and external elastic membranes and elastic fibers.

Flow dynamics of a vessel is important for diagnosis or prognosis of a CVD [6]. Since blood directly interacts with endothelial layer during the circulation, a morphological change may be emerged by means of triggered chemical pathways owing to the deformation response of the endothelium against the generated shear forces (Wall Shear Stress - WSS) in a vessel. In this case, it may be vital to guide and determine the symptoms of an onset or a progression of CVDs [7,8]. Therefore, physiological responses of healthy and diseased vessels are compared with each other to achieve a meaningful difference in terms of flow conditions and shear stress distribution [9]. However, hemodynamic parameters may not be measured directly and even blood flow hemodynamics require detailed assumptions to create a realistic physiological model [9,10].

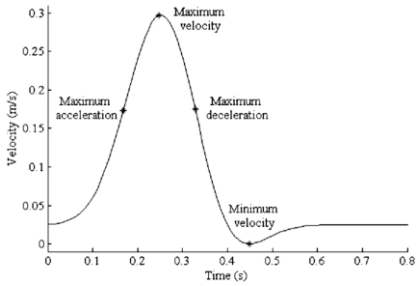
Recently, computational methods are increasingly being used in the fields of neurosurgery and cardiovascular surgery, atherosclerosis and aneurysm cases, to obtain realistic hemodynamic simulations [11,12]. Besides, these simulations may be utilized in surgical planning [13,14]. Thus, efficiency of the computational simulations is improved as well as patient's quality of life by means of the developed patient-specific disease models [15]. In this study, a patient specific thoracic artery model is first segmented based on the MRI images and then a thoracic aneurysm disease model is simulated to assess blood flow changes, for maximum flow condition, and generated stress during the circulation.

2. MATERIAL AND METHOD

34-year-old patient (female) who has a Coarctation of the Aorta (CoA or CoAo), aortic narrowing, history was participated to this study during the raw image acquisition process. Medical scanning was performed at the Radiology Department, Faculty of Medicine Kocaeli University, using a 64-row multi-slice computed tomography system (Aquillion 64, Toshiba Medical Systems, Tokyo, Japan). Ethical permission was received by the Ethics and Research Committee of Kocaeli University (Reference Number: KU GOKAEK 2019/204). Thoracic aorta model was obtained from the Picture Archiving and Communication System (PACS) server of the Radiology Department. System parameters were set to: 120kVp (photon energy spectrum), 80mA (tube current), 125mAs (time x milliamperes) with a collimation of 64 x 0.5mm and a rotation time of 0.5s in the raw data acquisition step. In addition, a contrast media (100mL) and a saline solution (40 mL) were injected with respectively at the same injection rate. Image reconstruction process was performed at: 7mm for section thickness, 0.3mm for overlapping steps and 700mm2 for FoV (Field of View) with an automated exposure control (2.5mm overlap). Thus, the raw data acquisition process was completed.

MIMICS software (v19) was utilized in image segmentation step and a reference model of the aorta was automatically reconstructed by means of the default tools and functions of the software. Noise reducing filters such as binomial blur and mean tools were also used to reduce undesired noise from the region of interest on each two-dimensional (2D) slice. Segmentation process was performed using the Thresholding tool at optimized value for target soft tissue (144 - Hounsfield Unit, HU as lower threshold, and 446 HU as higher threshold for this study). These parameters were ideal to obtain exact contour of the target model in a maximum allowable noisy form for this case [22]. Segmentation step was completed after each image section was masked and highlighted by a different color. Subsequently, three-dimensional (3D) calculation function was used at high quality to reconstruct the 3D processable raw model. The surface geometry of the model was manually cleared via 3-Matic software (v11, Materialise) according to the raw image geometries in MIMICS. Polygon Area Mark tool under the Mark - Area Mark menu was used to select each noisy surface and marked surfaces were deleted. The gaps on deleted surfaces were determined as Bad Contours and then fixed respectively using the Fill Hole Freeform tool under the Fix menu. The Fill Hole Freeform process was performed at High triangulation quality and formed in Tangent shape to achieve desired detail on processed surfaces. Finally, 3D reconstructed model was saved as Standard Tessellation Language (STL) file (although STL is a common file extension, it is not possible to perform simulation analysis to target model in all cases). Therefore, thoracic aorta model was created by means of SolidWorks (Dassault Systemes, v2016) according to the obtained manual measurements in MIMICS. After manual modelling, flow simulation tool was utilized to obtain blood flow simulation during the systole and diastole phases (0-0.8s). Finally, an aneurysm condition was simulated on the same aorta model to obtain blood flow properties using the predefined parameters as listed in Table 1.

Table 1. Flow simulation parameters

Properties	Group	Parameter	Value	Ref.
Initial Conditions, SolidWorks	Thermodynamic parameters	Pressure	15998.6Pa[a] 10665.7Pa[a]	[16]
		Temperature	309.8K[b]	-
	Velocity parameters (for each direction, Systole, S and Diastole, D)	T=0s (S)	0.025m/s[c]	
		T=0.1s (S)	0.05m/s[c]	
		T=0.2s (S)	0.2m/s[c]	
		T=0.3s (S)	0.275m/s[c]	
		T=0.4s (D)	0.024m/s[c]	
		T=0.5s (D)	0.012m/s[c]	
		T=0.6s (D)	0.026m/s[c]	
		T=0.7s (D)	0.025m/s[c]	
		T=0.8s (D)	0.025m/s[c]	
				[17]
	Turbulance Parameters	Turbulence Intensity	2%[d]	-
		Turbulence Length	0.000433943299m[d]	-
User Defined Material Properties, Solidworks	Item Properties	Density	1060kg/m^3[e]	[18]
		Dynamic Viscosity	0.0035Pas[e]	[18]
		Specific Heat (Cp)	3617 J/(kgK)[f]	[19]
		Thermal conductivity	0.52 W/(mK)[f]	[20]
Vessel Parameters, Solidworks	Thickness	Each vessel	1.5mm ±0.3mm[g]	-
	Length	Descending A.	137.25mm[g]	-
	Diameter (these values were the endpoints of each region)	Ascending A.	39.21mm[g]	-
		Descending A.	20.25mm[g]	-
		Brachio Cephalic T.	14mm[g]	-
		L. Carotid	7mm[g]	-
		L. Subclavian	11.5mm[g]	-
	Mass Flow Rate, T=0s (S) (this value was recalculated for each condition of the pulsatile waveform)	Ascending A.	0.00323989 kg/s[h]	[21]
		Descending A.	0.000862575 kg/s[h]	[21]
		Brachio Cephalic T.	0.000409955 kg/s[h]	[21]
		L. Carotid	0.000104145 kg/s[h]	[21]
		L. Subclavian	0.000278515 kg/s[h]	[21]
Aneurysm Disease Model, Solidworks	Descending A.	Diameter	down to 20mm	-
			down to 10mm	-

[a] Pressure was determined according to Systole and Diastole conditions (120-80 mmHg in terms of Pa).

[b] Body temperature (in terms of K).

[c] Velocity was determined according to Systole and Diastole conditions during a pulsatile waveform (in terms of m/s).

[d, e, f] Default values.

[g] Manually measured in MIMICS.

[h] Calculated using the Mass Flow's equation (m = ρ x V x A where ρ: Density of the flowing liquid or gas, in kg/m^3, V: Flow speed, in m/s, A: Flow area, in m^2 and m: Mass flow rate, in kg/s).

3D modelling and flow simulation of the reference thoracic aorta model, including the aneurysm condition, are illustrated step by step in Figure 1.

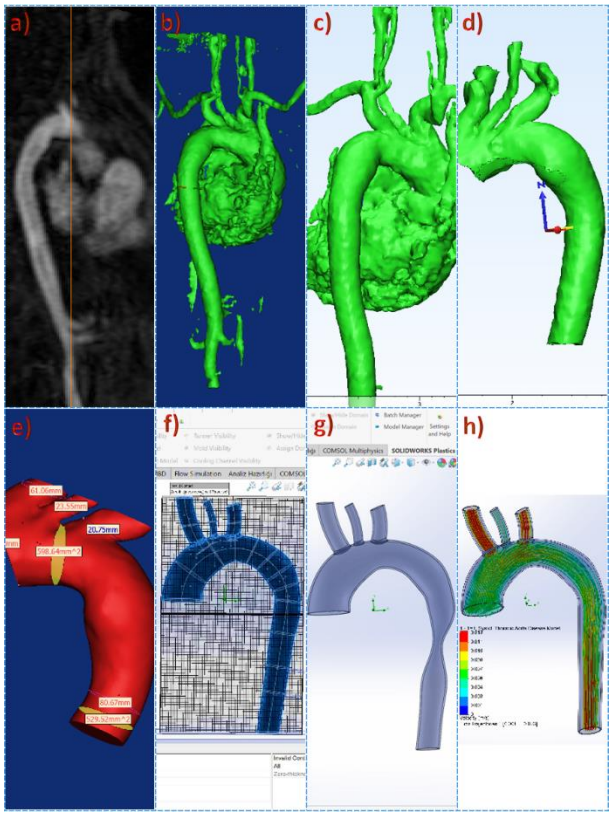


Figure 1. Step by step 3D modelling and flow simulation of the patient specific thoracic aorta and aneurysm disease model. a) An image of the 3D raw model, based on non-filtered DICOM images in Sectra workspace, a 3D DICOM viewer of the default system software that does not allow 3D model exporting or processing, b) 3D reconstruction of the raw images in a noisy form via MIMICS, c) Manual noise cleaning in 3-Matic, d) Manual surface reconstruction and fixing the geometrical errors of 3D raw model in 3-Matic, e) Manual vessel diameter measurements in MIMICS, f) 3D modelling of the thoracic artery in SolidWorks based on the manual measurements in MIMICS, g) Modelling the aneursym disease scenario (ADS) in SolidWorks and h) Flow simulation analysis of the thoracic aorta model, including aneurysm condition, during the each phases of the pulsatile blood flow.

3. RESULT AND DISCUSSION

According to the results, blood flow velocity values were obtained as desired on each thoracic aorta model, increased during the systole and decreased during the diastole on each region of the vessel. Besides, the velocity values in aneurysm disease model were also increased with regards to the geometrical narrowing. Blood flow velocities of each vessel model are illustrated in Figure 2.

Finite element analysis (FEA) results of a more progressed aneurysm disease model, based on the flow simulation (blood pressure) analysis and vessel

parameters that stated in Table 1, are illustrated in Figure 3 (T=0.2s systole condition only and vessel diameter was decreased down to 10mm, 25mm default).

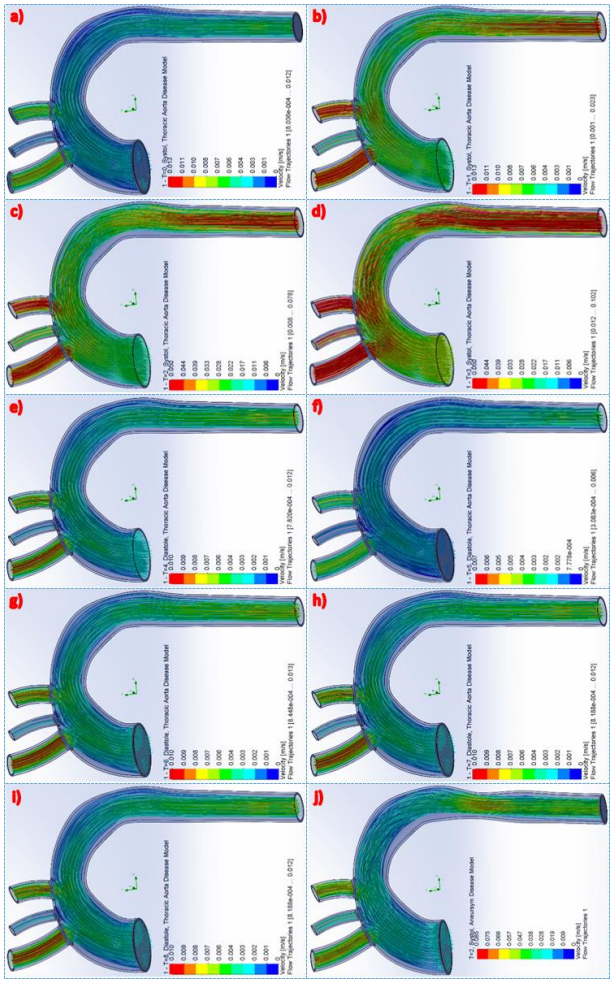


Figure 2. Blood flow velocities of each thoracic aorta model (pressure values were set to optimal values according to each systole and diastole conditions). a) T=0s systole (velocity: Red - 0.013 m/s and Blue - 0 m/s), b) T=0.1s systole (velocity: Red - 0.013 m/s and Blue - 0 m/s), c) T=0.2s systole (velocity: Red - 0.05 m/s and Blue - 0 m/s), d) T=0.3s systole (velocity: Red - 0.05 m/s and Blue - 0 m/s), e) T=0.4s diastole (velocity: Red - 0.01 m/s and Blue - 0 m/s), f) T=0.5s diastole (velocity: Red - 0.007 m/s and Blue - 0 m/s), g) T=0.6s diastole (velocity: Red - 0.01 m/s and Blue - 0 m/s), h) T=0.7s diastole (velocity: Red - 0.01 m/s and Blue - 0 m/s), i) T=0.8s diastole (velocity: Red - 0.01 m/s and Blue - 0 m/s) and j) T=0.2s systole, aneurysm disease model, vessel diameter was decreased down to 20 mm (25mm default, T = time, velocity: Red - 0.085 m/s and Blue - 0 m/s). [Note that velocity parameters of Table 1 belong to Ascending Aorta regions (obtained from literature) and distribution of blood flow velocities (newly calculated) are illustrated in Figure 2]

Blood flow velocities were obtained as a) 0.05m/s (T=0s), b) 0.01m/s (T=0.1s), c) 0.039m/s (T=0.2s), d) 0.044m/s (T=0.3s), e) 0.005m/s (T=0.4s), f) 0.002m/s (T=0.5s), g) 0.006m/s (T=0.6s), h) 0.006m/s (T=0.7s), i) 0.0065m/s (T=0.8s) and j) 0.07m/s (T=0.2s) at ADS regions. On the other hand, a vonMises stress at 2.89MPa was generated with a material displacement of 0.007mm on the arch of aorta model (vessel diameter was decreased down to 10 mm at ADS region) at Systole phase (T=0.2s).

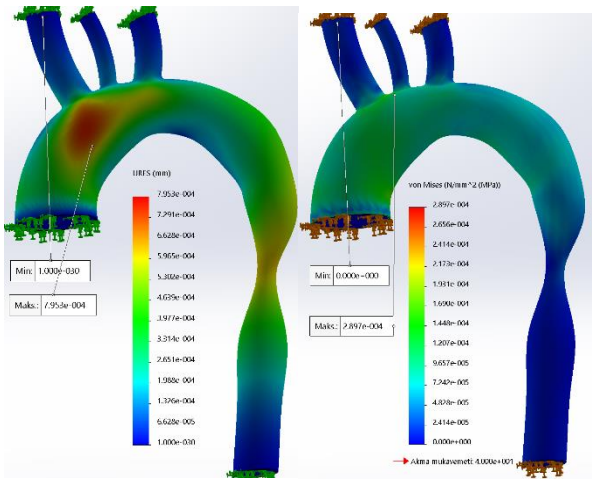


Figure 3. Blood flow velocity based FEA results (T=0.2s systole condition only and vessel diameter was decreased down to 10mm). a) Material displacement values under the applied fluid dynamics and b) Generated vonMises stress against the blood flow.

6. CONCLUSION

Although computational fluid dynamics with the liquid-material interaction may help to obtain physiological information and biological response under the specified conditions that may not be measured directly, simulations require more precise definitions to achieve more realistic results. Since medical imaging technologies may allow to export target anatomical model in a STL file extension and although STL is a common file extension, it is not possible to perform a dynamic simulation analysis to target model in all cases. Therefore, the target model may require to be modeled manually or a 3rd party software such as Comsol, Abaqus or Fluent may be utilized to overcome the lack of STL file support especially in dynamic analysis [23,24]. On the other hand, researchers may perform static analysis on an STL file by means of a tool such as Power Surfacing or may apply directly to the generated mesh surfaces of the model in SolidWorks [25]. In addition, FEA of a blood vessel may require to define biomechanical properties of each vessel tissue layer separately. Thus, more accurate shear rates, regarding to the blood flow, may be obtained [26]. Furthermore, some parameters such as gravity or temperature may also be involved.

According to results of simulation, blood flow velocity is affected by ADS regarding to the decrease on the vessel diameter (Normal:25 mm, ADS: 20 mm). The velocities are almost doubled for Systole phase (T=0.2s) at ADS regions (Normal: 0.039m/s, ADS: 0.07m/s). Material

displacements are mostly observed at the arch of aorta and ADS regions due to the curvature changes on laminar blood flow path. Although blood flow velocities may vary regarding to the vessel geometry or predefined parameters such as blood and flow conditions, similarities of the flow velocity are confirmed from the previous studies [27]. In addition, Reynolds number (Re), a ratio of the inertial forces to viscous forces, can be calculated to determine the blood flow type (Laminar or Turbulent) for each pulsatile blood flow phase by using determined blood flow velocities at ADS regions. High Re up to 4000 indicates that inertial forces are dominant while low Re up to 2300 indicates viscous forces are significant. As Re may vary during the pulsatile blood flow, it is important to calculate the WSS affected by turbulent flow, according to natural geometry of the vessel or an implanted stent, to predict biomechanical stress on the vessel walls [28]. It should be noticed that vessel walls are assumed as rigid and blood is assumed as fully Newtonian to simplify calculations as well as removing branched vessel geometries [29-31]. However, it may not give the real accurate results since these conditions are accepted as ideal.

Disease modeling may be guide to obtain physiological responses against a patient specific progression scenario or predict symptoms of a CVD. Thus, development of a disease, such as a development stage or a rupture of an aneurysm or even a hypertension, may be simulated to calculate the damage [32]. Furthermore, simulation analysis may be useful for surgical planning and even preventive management as well as it may be utilized in drug research responses or even aging effects (European Commission supported projects, Research and Innovation in the field of ICT for Health, Wellbeing & Ageing Well: Cardioproof, EurValve, SmartTool) [33].

DECLARATION OF ETHICAL STANDARDS

Ethical permission was received by the Ethics and Research Committee of Kocaeli University (Reference Number: KU GOKAEK 2019/204).

REFERENCES

[1] *who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)*, "WHO, Fact Sheets", (08.12.2019).

[2] *ehnheart.org/cvd-statistics.html*, "European Cardiovascular Disease Statistics, CVD Statistics", (08.12.2019).

[3] *heart.org/-/media/data-import/downloadables/heart-disease-and-stroke-statistics-2018---at-a-glance-ucm_498848.pdf*, "American Heart Association, Heart Disease And Stroke Statistics", (08.12.2019).

[4] Mohammed Y., "Three dimensional finite-element modeling of blood flow in elastic vessels: effects of arterial geometry and elasticity on aneurysm growth and rupture", ***Master thesis***, Ryerson University, Toronto, Canada, (2010).

[5] Canstein C. et al., "3D MR flow analysis in realistic rapid-prototyping model systems of the thoracic aorta: comparison with in vivo data and computational fluid dynamics in identical vessel geometries", ***Magnetic Resonance in Medicine***: An Official Journal of the International Society for Magnetic Resonance in Medicine, 59(3): 535-546, (2008).

[6] Van Pelt R., Nguyen H., Ter Haar Romeny B., Vilanova A., "Automated segmentation of blood-flow regions in large thoracic arteries using 3D-cine PC-MRI measurements", ***International Journal of Computer Assisted Radiology and Surgery***, 7(2): 217-224, (2012).

[7] Howe G., "Multiphysics simulation of a coronary artery", ***Master thesis***, Faculty of California Polytechnic State University, San Luis Obispo, (2013).

[8] Secomb T.W., "Hemodynamics," ***Comprehensive Physiology***, 6(2): 975-1003, (2011).

[9] Zarandi M.M., Mongrain R., Bertrand O.F., "Non-newtonian hemodynamics and shear stress distribution in three dimensional model of healthy and stented coronary artery bifurcation", ***Comsol Conference***, Boston, 1-5, (2010).

[10] Tado R., Deoghare A. B., Pandey K. M., "Computational Study of Blood Flow Analysis for Coronary Artery Disease", ***International Journal of Biomedical and Biological Engineering***, 12(2): 35-39, (2018).

[11] Ohhara Y. et al., "Investigation of blood flow in the external carotid artery and its branches with a new 0D peripheral model", ***Biomedical Engineering Online***, 15(1): 16, (2016).

[12] Takizawa K. et al., "Patient-specific computer modeling of blood flow in cerebral arteries with aneurysm and stent", ***Computational Mechanics***, 50(6): 675-686, (2012).

[13] Fishman E.K., Kuszyk B.S., Heath D.G., Cabral B.., "Surgical planning for liver resection", ***Computer***, 29(1): 64-72, (1996).

[14] Taylor C.A., Hughes T.J.R., Zarins C.K., "Finite element modeling of blood flow in arteries", ***Computer Methods in Applied Mechanics and Engineering***, 158(1-2): 155-196, (1998).

[15] Bai-Nan X. et al., "Hemodynamics model of fluid–solid interaction in internal carotid artery aneurysms", ***Neurosurgical Review***, 34(1): 39-47, 2011.

[16] *heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings*, "Heart, Understanding Blood Pressure Readings, Healthy and unhealthy blood pressure ranges", (08.12.2019).

[17] Laín S., Caballero A. D., "Simulation of unsteady blood flow dynamics in the thoracic aorta", ***Ingeniería e Investigación***, 37(3): 92-101, (2017).

[18] Wain A.J.R. et al., "Blood flow through sutured and coupled microvascular anastomoses: a comparative computational study", ***Journal Of Plastic, Reconstructive & Aesthetic Surgery***, 67(7): 951-959, (2014).

[19] *itis.swiss/virtual-population/tissue-properties/database/heat-capacity*, "It Is Foundation, Tissue Properties", (08.12.2019).

[20] *itis.swiss/virtual-population/tissue-properties/database/thermal-conductivity*, "It Is Foundation, Tissue Properties", (08.12.2019).

[21] Prieto E.S., "Computational fluid dynamics indicators to improve cardiovascular pathologies", ***Doctoral thesis***, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain, (2016).

[22] Aydin L. et al., "Surgical Planning And Additive Manufacturing Of An Anatomical Model: A Case Study Of A Spine Surgery", ***Medical Robotics - New Achievements***, IntechOpen, DOI: 10.5772/intechopen.89950, (2019).

[23] Liu X., et al., "Three-dimensional hemodynamics analysis of the circle of Willis in the patient-specific nonintegral arterial structures", ***Biomechanics And Modeling In Mechanobiology***, 15(6): 1439-1456, (2016).

[24] Randles A., Frakes D., Leopold J., Jane A., "Computational fluid dynamics and additive manufacturing to diagnose and treat cardiovascular disease", ***Trends In Biotechnology***, 35(11): 1049-1061, (2017).

[25] Aydin L. et al., "Development And Biomechanical Validation Of Medical Insoles To Prevent Foot Ulcers On Diabetic Patients By Means Of Thermoplastic Elastomers And Additive Manufacturing Technologies", ***Medical Technologies Congress (TIPTEKNO)***, IEEE, 1-4, (2019).

[26] Zaucha M. et al., "Biaxial biomechanical properties of self-assembly tissue-engineered blood vessels", ***Journal Of The Royal Society İnterface***, 8(55): 244-256, (2010).

[27] Deep D., "A study of blood flow in normal and dilated aorta", ***PhD. Thesis***, Purdue University, Indiana, (2014).

[28] Caballero A.D., Laín S. A., "Review On Computational Fluid Dynamics Modelling In Human Thoracic Aorta", ***Cardiovascular Engineering And Technology***, 4(2): 103-130, (2013).

[29] Hyman J., Knapp R., Scovel J., "High order finite volume approximations of differential operators on nonuniform grids", ***Physica D: Nonlinear Phenomena***, 60(1-4): 112-138, (1992).

[30] Nerem R., "Vascular fluid mechanics, the arterial wall, and atherosclerosis", ***Journal Of Biomechanical Engineering***, 114(3): 274-282, (1992).

[31] Nataf P., Lansac E., "Dilation of the thoracic aorta: medical and surgical management", ***Heart***, 92(9): 1345-1352, (2006).

[32] Fung G. et al., "On stent-graft models in thoracic aortic endovascular repair: a computational investigation of the hemodynamic factors", ***Computers In Biology And Medicine***, 38(4): 484-489, (2008).

[33] European Commission, "Research And Innovation In Digital Solutions For Health, Wellbeing And Ageing - An Overview", ***Digital Single Market - Technical Report***, 1-94, (2019).