EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 10
144-149
Year: 2018

# "CORONARY TORTUOSITY" A CAUSE OF MYOCARDIAL ISCHEMIA

**Ankush Gupta*[1] and Nalin K. Mahesh[2]**

[1]Assistant Professor, Department of Medicine and Cardiology, Base Hospital Delhi Cantt, 110010, India.
[2]Professor and HOD, Department of Medicine and Cardiology, Base Hospital Delhi Cantt, 110010.

***Corresponding Author: Dr. Ankush Gupta**
Assistant Professor, Department of Medicine and Cardiology, Base Hospital Delhi Cantt, 110010, India.

**Article Received on 28/07/2018** **Article Revised on 18/08/2018** **Article Accepted on 08/09/2018**

**ABSTRACT**
Coronary artery tortuosity is a common angiographic finding. Its relation with coronary artery disease is not clear. Patient with coronary tortuosity and without significant obstructive coronary artery disease may present with chronic stable angina. These patients are often labeled as normal coronaries and remained symptomatic with angina on exertion. Coronary artery should be recognized as non-obstructive cause of myocardial ischemia.

**KEYWORDS:** Coronary artery tortuosity.

## INTRODUCTION

During the past two decades, our understanding for the patho-physiology of CAD has undergone a remarkable evolution. Previously considered as a lipid storage disease, it is currently viewed as an inflammatory disorder. The appreciation of arterial remodeling has expanded attention beyond stenosis, evident by angiography to encompass the biology of non-stenotic plaques. Revascularization can effectively relieve ischemia, but need to explore the non-obstructive causes of coronary ischemia is being felt. Coronary artery disease (CAD) is the leading cause for mortality and morbidity worldwide.[1, 2] It severely affects the quality of life. Gold standard for the diagnosis of coronary artery disease is coronary angiography. Coronary tortuosity (CT) is a common coronary angiographic finding encountered by cardiologist. Its association with hypertension, impaired left ventricular relaxation and possibly myocardial ischemia has been suggested.[3–7] CT has been linked to advanced age, atherosclerosis, hypertension and DM.[8, 9] Study by Yang Li et al.[9] linked CT positively with hypertension and females but negatively with the CAD. Tortuous coronaries could hamper the left ventricular function and have been associated with the ventricular dysfunction.[4] CT may cause reversible myocardial perfusion defects and chronic stable angina.[7, 10] Patients with CT often experience the effort-induced chest pain that typically disappears at rest.[3] These clinical features indicate that tortuous coronaries may reduce the coronary perfusion pressure. However, only limited clinical data directly supports this assumption.

### Pathophysiology of Coronary Tortuosity

Arteries are normally straight for efficient transportation of blood to the distal organs. However, arterial remodeling may be the adaptive change in response to various stimuli leading to tortuosity[8], frequently involving the coronary arteries.[8, 9] However, the clinical importance and etiology of CT is still not clear. Intraluminal traction and pressure in the coronary artery are the two forces that tend to lengthen the vessel. These two forces are opposed by retractive force, which is equal and opposite to the sum of intraluminal traction and pressure. Normally this balance between two opposite forces results in stable length of coronary artery. The retractive force in the artery is generated almost entirely by elastic materiel in arterial wall known as elastin. Degeneration of this elastin results in imbalance between these opposing forces and thus can lead to elongation and arterial tortuosity. In general, coronary tortuosity is a result of age-dependent or pathological degeneration of the elastin. Arterial tortuosity syndrome, a rare autosomal recessive connective tissue disorder, is an example of pathological degeneration of elastin, which is associated with generalized tortuosity and elongation of all major arteries. Aorta, cerebral and coronary arteries are commonly involved in this tortuosity syndrome. The etiology of tortuous variants in other cases is considered mainly acquired and linked with advanced age, atherosclerosis, small cardiac size and hypertension.[3]

### Coronary Tortuosity (CT) as a cause of Myocardial Ischemia

Typical angina with an objective evidence of ischemia without obstructive coronary artery disease in patients with tortuous coronaries may be due to compression of

the coronaries during cardiac systole.[11] It is also suggested that CT may causes reduction in coronary pressure distal to the tortuous segment leading to myocardial ischemia.[5] In a study by Li et al.[12] they found that increasing CT severity can result in more decrease of coronary perfusion pressure and myocardial ischemia. In another study by Li et al.[10], it was observed that CT is associated with reversible myocardial perfusion defects in patients with chronic stable angina (CSA) and normal coronaries. They proposed that CT may lead CSA by decreasing coronary pressure distal to tortuous segment. Changes in endothelial function due to traction and pressure factors that tend to lengthen the artery may induce symptoms of ischemia at low rates of effort despite absence of significant CAD.[13] In a study comparing the coronary artery calcium (CAC) scoring in subjects having CSA with or without CT, it was found that there was significant high level of CAC score in CT group as compare to NCT groups.[14] These results indicate that CT is associated with subclinical atherosclerosis regardless of the presence of actual obstructive coronary artery disease. Cunningham et al.[15] observed that atherosclerosis in coronaries is facilitated by severe tortuosity. Thus, coronary atherosclerosis is more common in subjects with CT, likely due to non-laminar blood flow. Blood flow associated shear stress is an essential component for the development of coronary atherosclerosis[16] and of vulnerable plaque rupture.[17] Davutoglu et al.[18] observed that CT was associated increased carotid intima thickness and increased incidence of retinal artery tortuosity. They concluded that CT is strongly associated with subclinical coronary atherosclerosis. However, some studies found negative correlation between CT and significant CAD.[9, 19] Therefore, CT may be associated with subclinical coronary atherosclerosis in the absence of significant CAD. Patients with CSA and CT should be treated as ischemic patients and drugs that causes plaque stabilization and offer benefits in atherosclerosis may better be given.

Fluid mechanical theories give reasonable explanation for hemodynamic effect of CT and for the pressure reduction distal to tortuous segment. Tortuous arteries cause higher energy loss than straight arteries, causing reduction in perfusion pressure. There are two reasons for energy loss in the tortuous coronaries leading to reduction in perfusion pressure. One is energy loss caused by friction via shear stress other is loss due to non-laminar perpendicular flow due to centrifugal effect. This may be explained as follows: Energy loss due to friction (ΔEfr) in a straight tube can be calculated using Poiseuille's law: Δ Efr =32 n l v/d2 (n = blood viscosity; l = length of the artery; v= blood flow velocity; d = diameter of the artery). Arterial curves associated with CT causes extra energy loss (Figure 1), almost entirely caused by non-laminar flow, which is caused because blood has to separate from the wall due to a sharp bend. Sharp bends generate increased centrifugal pressure (Pco) on section AB in the outside bend and the decrease in pressure (Pci) on section CD in the inside bend. This difference in pressures at sharp bends causes blood flow to separate from the vessel wall; this is associated with non-laminar perpendicular flow and additional energy loss due to separation (ΔEsep) [20]. Studies have reported that non-Newtonian influence measured and calculated patterns of main and transverse flow in a 90° bend of an artery during systole and diastole.[21]

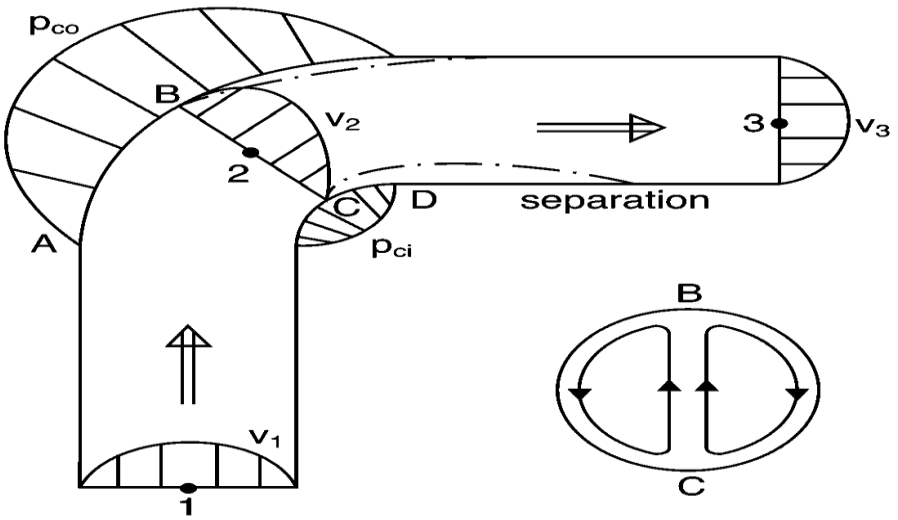


**Figure1: Arterial curves associated with CT causes extra energy loss (Figure 1), almost entirely caused by non-laminar flow, which is caused because blood has to separate from the wall due to a sharp bend. Sharp bends generate increased centrifugal pressure (Pco) on section AB in the outside bend and the decrease in pressure (Pci) on section CD in the inside bend. This difference in pressures at sharp bends causes blood flow to separate from the vessel wall; this is associated with non-laminar perpendicular flow and additional energy loss due to separation (ΔEsep).**

It is observed from model measurements that at non-laminar water flow sites in a tube only small amount of energy loss is due to transverse flow. Acute angled curvature/bends, however, will cause high-energy losses because of separation.[22] Nippert et al.[22] showed a relation between radius (R)/tube width (D) and ΔEsep/ΔEfr for non-laminar flow in a 90° bend of a rectangular wooden tube (Figure 2). The energy due to friction ΔEfr is nearly constant for different R/D values and is almost equal to ΔEfr in straight arteries.

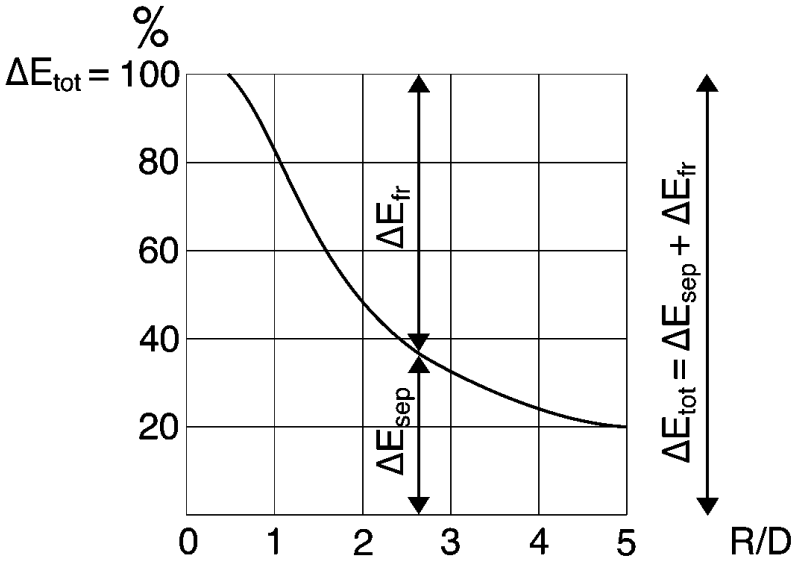


**Figure 2: Nippert showed a relation between radius (R)/tube width (D) and ΔEsep/ΔEfr for non-laminar flow in a 90° bend of a rectangular wooden tube The energy loss by flow separation ΔEsep at R/D = 2 is equal to the energy loss due to friction ΔEfr; so the total energy loss in the bend is twice as high as in a straight tube. At Radius/Diameter = 1 the total energy loss is five times more (ΔEsep = appr. 4 ΔEfr).**

The loss of energy by separation of flow ΔEsep at R/D = 2 is equal to the loss of energy by friction ΔEfr; so the total energy loss in the bend is twice as high as in a straight tube. At R/D = 1 the total energy loss is even 5 times more (ΔEsep = approx. 4 ΔEfr). In Figure 3, two 90° bends with R1/D=3 and R2/D=1 are drawn. It may be observed that the total energy loss at R2 is much higher than at R1.

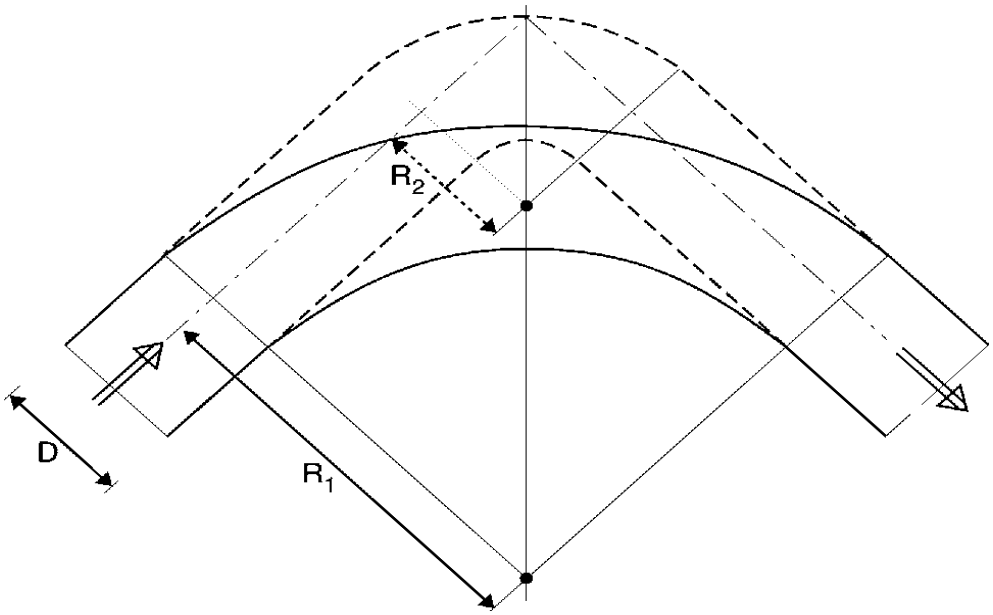


**Figure 3: Figure shows two 90° bends with R1/D=3 and R2/D=1.. The total energy loss at R2 is much higher than at R1.**

Thus, it is logical to say that coronary pressure decreases after multiple bends due to loss of energy as explained above. This decrease in coronary pressure may be the cause of myocardial ischemia leading to angina without obstructive CAD. Intracoronary pressure measurement using Doppler tipped guide wire showed significant reduction in coronary pressure distal to tortuous segment.[23] The relationship between CT and CAD is still debatable. Studies have shown both positive and negative correlation between CT and CAD.

**CT as a cause of thrombosis**

Thrombosis has been observed in tortuous blood vessels; for example, in internal carotid arteries[24] and in umbilical cords.[25] Thrombosis can be triggered by chemical and physical stimulants in the blood vessel. Chemical mechanisms include injury to the vascular endothelium[26], rupture of atherosclerotic plaque[27], and hypercoagulable states.[26] A physical mechanism is high fluid shear stress.[27] Tortuosity in the artery can cause high fluid shear stress, likely promoting thrombosis in the absence of chemical mechanisms. One recent in vivo study on rats observed thrombus formation in uninjured tortuous venules but not in straight venules.[28] Based on CFD simulations, the authors suggested that thrombosis was caused by increased fluid shear stress due to altered blood flow from bending of the initially straight venules. However, the underlying physical mechanisms are still poorly understood. Microvessels are embedded within all tissue, distribute blood throughout the entire body, and play a role in inflammation.[29] Thus, the study of pathological processes in microvessels, such as thrombosis, is essential to understand associated diseases and to develop novel therapies. For instance, micro vessel thrombosis has been observed in patients with DIC in clinical, experimental, and autopsy settings.[30] In the microvessel thrombosis in both arterioles and venules, animal models have shown that thrombi formed in vivo are mainly composed of platelets.[31] Hence, platelets are crucial in microvessel thrombosis including both arterioles and venules. Under thrombogenic stimulus, platelets become activated and adhere to each other and to the endothelial surface through glycoproteins in the platelet surface, various plasma proteins, and a fibrin network.[27] High shear stresses, along with various chemical agonists, induce platelet activation and thrombus formation.[27] Activated platelets activate other platelets by releasing platelet agonists.[27] Curvature of tortuous vessels alters fluid shear stress and fluid velocity and thus likely initiates shear-induced platelet activation and increases platelet collisions. These two physical mechanisms (i.e., shear-induced activation and collisions) can promote platelet adhesion, aggregation and thrombus formation. Therefore, understanding the interactions between individual platelets is critical to understand the physical mechanisms of tortuosity-induced thrombus formation

**CT causing Recurrent SCAD**

It has been reported that patients with SCAD often exhibit CT. CT is highly prevalent in the SCAD population and is associated with recurrent SCAD. Recurrent SCAD most often occurs within segments of CT. SCAD is an increasingly recognized cause of acute coronary syndrome affecting a young, apparently healthy population.[32, 33] SCAD can involve dissection within the media, with intramural hematoma formation, coronary intima, or both.[33, 34] An intimal dissection is often seen on angiography as a diffuse stenosis, making the diagnosis of SCAD a challenge.[35] Intramural hematoma involving the outer two thirds of the media is the most common pathological finding in patients with SCAD.

There are multiple potential mechanisms by which CT may be involved in the occurrence of SCAD. In a canine model, Dobrin et al[36] showed that elastin is responsible for arterial load bearing properties (as opposed to collagen) and that elastin deficiency allows vessel elongation and results in arterial tortuosity. Other investigators have shown that elastin has an essential role in arterial development and its deficiency results in subendothelial smooth muscle cell proliferation leading to arterial tortuosity.[37] Other potential mechanisms may be related to disturbances of arterial blood flow. Sharp bends because of arterial tortuosity result in fluid separation and disruption of laminar flow, resulting in high energy loss and increased shear stress on the vessel wall.[3] This increased shear stress may weaken the vessel wall, predisposing to SCAD. Shear stress causes endothelial cell disruption and increases its permeability and triggers the release of prostaglandins and stimulation of underlying smooth muscle cells.[38] Interestingly, CT was more common (80%) than extracoronary vasculopathy (70%) in patients with SCAD who underwent vascular screening, showing that CT may be a more useful clinical association to make the diagnosis of SCAD. Women aged <60 years presenting with evidence of ACS should be carefully screened for SCAD. The presence of CT on angiography should be a potential clue to the diagnosis and should trigger a thorough review for evidence of luminal narrowing, disruption, or reduced blood flow.

**CONCLUSION**

Coronary tortuosity is a common angiographic finding. Coronary tortuosity is commonly found in females and hypertensive patients. Patients with coronary tortuosity have low incidence of CAD but, can present with chronic stable angina and objective evidence of myocardial ischemia, in the absence of significant obstructive coronary artery disease. Isolated coronary tortuosity in patients with chronic stable angina is often ignored and is labeled as normal coronaries. These patients remain symptomatic with angina with multiple health care visits, affecting their quality of life. These patients may be offered treatment with antiplatelets, statins and antianginal drugs to improve their quality of life.

**REFERENCES**


1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A. Heart disease and stroke statistics—2010 update A report from the American Heart Association. Circulation, 2010 Feb 23; 121(7): e46-215.
2. Zhang XH, Lu ZL, Liu L. Coronary heart disease in China. Heart, 2008 Sep 1; 94(9): 1126-31.
3. Zegers ES, Meursing BT, Zegers EB, Ophuis AO. Coronary tortuosity: a long and winding road. Netherlands Heart Journal, 2007 May 1; 15(5): 191-5.
4. Turgut O, Yilmaz A, Yalta K, Yilmaz BM, Ozyol A, Kendirlioglu O, Karadas F, Tandogan I. Tortuosity of coronary arteries: an indicator for impaired left ventricular relaxation?. The international journal of cardiovascular imaging, 2007 Dec 1; 23(6): 671-7.
5. Jakob M, Spasojevic D, Krogmann ON, Wiher H, Hug R, Hess OM. Tortuosity of coronary arteries in chronic pressure and volume overload. Catheterization and cardiovascular diagnosis, 1996 May 1; 38(1): 25-31.
6. Gaibazzi N. Less than "straight" anginal symptoms. International journal of cardiology, 2011 May 5; 148(3): 385-6.
7. Gupta A, Panda P, Sharma YP, Mahesh A, Sharma P, Mahesh NK. Clinical Profile of Patients with Coronary Tortuosity and its Relation with Coronary Artery Disease. International Journal of Cardiology and Cardiovascular Research, 2018; 4(2): 066-071.
8. Han HC. Twisted blood vessels: symptoms, etiology and biomechanical mechanisms. Journal of vascular research, 2012 Mar 14; 49(3): 185-97.
9. Li Y, Shen C, Ji Y, Feng Y, Ma G, Liu N. Clinical implication of coronary tortuosity in patients with coronary artery disease. PloS one, 2011 Aug 31; 6(8): e24232.
10. Yang LI, Nai-feng LI, Zhong-ze GU, Yong CH, Jun LU, Yi FE, Gen-shan MA, Cheng-xing SH. Coronary tortuosity is associated with reversible myocardial perfusion defects in patients without coronary artery disease. Chin Med J, 2012 Oct 19; 125(19): 3581-3.
11. Satish G, Nampoothiri S, Kappanayil M. Arterial Tortuosity Syndrome Phenotypic Features and Cardiovascular Manifestations. Circulation, 2008 Jun 10; 117(23): e477-8.
12. Li Y, Shi Z, Cai Y, Feng Y, Ma G, Shen C, Li Z, Liu N. Impact of coronary tortuosity on coronary pressure: numerical simulation study. PloS one, 2012 Aug 14; 7(8): e42558.
13. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. Journal of the American College of Cardiology, 2007 Jun 26; 49(25): 2379-93.
14. El Tahlawi M, Sakrana A, Elmurr A, Gouda M, Tharwat M. The relation between coronary tortuosity and calcium score in patients with chronic stable angina and normal coronaries by CT angiography. Atherosclerosis, 2016 Mar 31; 246: 334-7.
15. Cunningham KS, Gotlieb AI. The role of shear stress in the pathogenesis of atherosclerosis. Laboratory investigation, 2005 Jan 1; 85(1): 9-23.
16. Wentzel JJ, Corti R, Fayad ZA, Wisdom P, Macaluso F, Winkelman MO, Fuster V, Badimon JJ. Does shear stress modulate both plaque progression and regression in the thoracic aorta?: Human study using serial magnetic resonance imaging. Journal of the American College of Cardiology, 2005 Mar 15; 45(6): 846-54.
17. C.G. Santos-Gallego, B. Picatoste, J.J. Badim_on, Pathophysiology of acute coronary syndrome, Curr. Atheroscler. Rep, 2014 Apr; 16(4): 401.
18. Davutoglu V, Dogan A, Okumus S, Demir T, Tatar G, Gurler B, Ercan S, Sari I, Alici H, Altunbas G. Coronary artery tortuosity: comparison with retinal arteries and carotid intima-media thickness. Kardiologia polska, 2012 Dec; 71(11): 1121-8.
19. Groves SS, Jain AC, Warden BE, Gharib W, Beto RJ. Severe coronary tortuosity and the relationship to significant coronary artery disease. West Virginia Medical Journal, 2009 Jul 1; 105(4): 14-8.
20. Rouse H. Fluid mechanics for hydraulic engineers.
21. Gijsen FJ, Allanic E, Van de Vosse FN, Janssen JD. The influence of the non-Newtonian properties of blood on the flow in large arteries: unsteady flow in a 90 curved tube. Journal of biomechanics, 1999 Jul 31; 32(7): 705-13.
22. Nippert H. *Über den Strömungsverlust in gekrümmten Kanälen* (Doctoral dissertation). Ingenieurswesens, 1929; 320.
23. DÖRTLEMEZ Ö, METİN M, ÇENGEL A, ALKAN M, CAYMAZ O, DÖRTLEMEZ H. Tortuosity of Coronary Arteries: A New Cause of Myocardial Ischemia. Gazi Medical Journal, 1993; 4(3).
24. Owens AP, Mackman N. Tissue factor and thrombosis: The clot starts here. Thrombosis & Haemostasis, 2010 Sep 1; 104(3): 432-9.
25. Sato Y, Benirschke K. Umbilical arterial thrombosis with vascular wall necrosis: clinicopathologic findings of 11 cases. Placenta, 2006 Jul 31; 27(6): 715-8.
26. Cacciapuoti F. Some considerations about the hypercoagulable states and their treatments. Blood Coagulation & Fibrinolysis, 2011 Apr 1; 22(3): 155-9.
27. Wootton DM, Ku DN. Fluid mechanics of vascular systems, diseases, and thrombosis. Annual review of biomedical engineering, 1999 Aug; 1(1): 299-329.
28. Liu Q, Mirc D, Fu BM. Mechanical mechanisms of thrombosis in intact bent microvessels of rat mesentery. Journal of biomechanics, 2008 Aug 28; 41(12): 2726-34.

29. Lipowsky HH. Microvascular rheology and hemodynamics. Microcirculation, 2005 Jan 2; 12(1): 5-15.
30. Gando S. Microvascular thrombosis and multiple organ dysfunction syndrome. Critical care medicine, 2010 Feb 1; 38: S35-42.
31. RUMBAUT RE, SLAFF DW, BURNS AR. Microvascular thrombosis models in venules and arterioles in vivo. Microcirculation, 2005 Jan 1; 12(3): 259-74.
32. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, Blin D, Machecourt J. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. European Journal of Cardio-Thoracic Surgery, 2009 Feb 1; 35(2): 250-4.
33. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, Gersh BJ, Khambatta S, Best PJ, Rihal CS, Gulati R. Clinical features, management and prognosis of spontaneous coronary artery dissection. Circulation. 2012 Jul 16: CIRCULATIONAHA-112.
34. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, Escaned J, Bañuelos C, Hernandez R, Macaya C. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. Journal of the American College of Cardiology, 2012 Mar 20; 59(12): 1073-9.
35. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. Catheterization and Cardiovascular Interventions, 2014 Dec 1; 84(7): 1115-22.
36. Dobrin PB, Schwarcz TH, Baker WH. Mechanisms of arterial and aneurysmal tortuosity. Surgery, 1988 Sep; 104(3): 568-71.
37. Li DY, Brooke B, Davis EC, Mecham RP, Sorensen LK, Boak BB, Eichwald E, Keating MT. Elastin is an essential determinant of arterial morphogenesis. Nature, 1998 May 21; 393(6682): 276-80.
38. Fry DL. Arterial intimal-medial permeability and coevolving structural responses to defined shear-stress exposures. American Journal of Physiology-Heart and Circulatory Physiology, 2002 Dec 1; 283(6): H2341-55.