CARDIOLOGY Rounds®

As presented in the Rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Endothelial Shear Stress: Impact on Atherosclerosis

By ANTONIO ROCCA MD, PHD, FRCPC and JUAN CARLOS MONGE MD, FRCPC

Atherosclerosis, a disease that can have devastating consequences, afflicts a large proportion of people in the industrialized world and, increasingly, in developing countries as well. Atherosclerosis is a chronic inflammatory condition of large- and medium-sized vessels that has serious consequences on the cardiovascular (CV) system, leading to the development of myocardial infarction (MI) and stroke. One million MIs and 500,000 coronary deaths occur in the United States (US) each year.[1] Peripheral vascular disease is also a major consequence of the atherosclerotic process. The ensuing morbidity and mortality rates are high and are rising as the population ages. Through an enhanced understanding of the mechanisms leading to the development of the atherosclerotic process, it is hoped that novel methods for screening the disorder can be developed that will significantly impact its most negative consequences. This issue of *Cardiology Rounds* discusses the pathophysiology of atherosclerosis and the impact of the different types of shear stress on the progression of atherosclerotic plaque.

An examination of the nature, location, and characteristics of atherosclerotic lesions reveals that other, perhaps more important, determinants are responsible for the development of atherosclerotic plaque. By themselves, traditional risk factors for the development of atherosclerosis do not adequately determine or explain the location and nature of atherosclerotic lesion progression. A novel paradigm for the development of atherosclerosis involves the local hemodynamic effects of shear stress. Varying levels of shear stress can significantly impact the nature of the atherosclerotic process. By manipulating the determinants of endothelial shear stress (ESS), the development or progression of atherosclerosis may be modulated to potentially provide future clinical benefits.

Pathophysiology

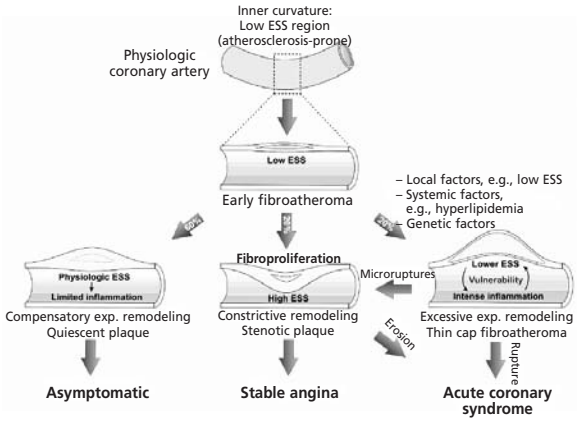
The incidence of atherosclerosis is rising in epidemic proportions throughout the western world. Fatty streaks are increasingly found in autopsy studies in young populations.[2] This process is typified by the accumulation of oxidized low-density lipoprotein (LDL) within the intimal layer of the endothelium. Cytokine elaboration promotes the accumulation of macrophages, derived from monocytes, which are mobilized from the circulation into the intimal layer. With the upregulation of scavenger receptors on macrophages, the uptake of oxidized LDL results in the formation of foam cells. Simultaneously, smooth muscle cells are incorporated into the intimal layer where they begin to elaborate extracellular matrix, leading to the formation of a fibrous cap. The foam cells and dying smooth muscle cells contribute to the lipid core.[1] This process is propagated by the traditional risk factors for atherosclerosis, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, and genetic predisposition.

Differentiation of vulnerable plaques versus fibrous plaques

Pathological studies have defined 2 distinct forms of plaques: the thin cap or vulnerable plaque and the thick-walled fibrous cap, which is relatively resistant to rupture. These 2 distinct pathological phenomena may determine very different clinical conditions. The fibrous cap usually correlates with a presentation of ongoing stable angina, whereas, the patient with vulnerable plaque most often presents with an acute coronary syndrome that, at times, culminates in sudden death.[3,4] The vulnerable or rupture-prone plaque is also characterized by a large lipid core and the

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Figure 1: Proposed natural history of early fibroatheroma and implications for vascular remodeling[11]



presence of increased macrophage activity.[5] The development of an early fibroatheroma into either a fibrous cap or vulnerable plaque is, in part, determined by the effects of varying shear stress on the local vascular remodeling process (Figure 1).

Ruptured plaques and the clinical dilemma of screening

Most ruptured plaques begin as clinically silent fibroatheromas that do not significantly impact the luminal diameter and, thus, do not produce a significant disruption in coronary flow. Therefore, it is not surprising that these early lesions are clinically silent, not only in terms of anginal symptoms, but also during the various methods of stress testing.[5] What is unsettling, however, is that an early fibroatheroma under the appropriate local hemodynamic conditions can become a vulnerable plaque, which is at risk of rupture. This process can rapidly progress to occlude the coronary artery, leading to an MI.[3,4]

Despite the difficulties in detecting early vulnerable plaques associated with current stress-testing techniques (eg, exercise or pharmacological stress myocardial perfusion imaging), these tests are quite sensitive in diagnosing flow-limiting plaques. These are usually plaques that have developed thick, fibrous caps with a reduced likelihood of rupture.

Several novel imaging modalities have been developed for their potential to screen and identify vulnerable plaque. The "gold standard" – cardiac angiography – demonstrates luminal narrowing extremely well; however, it does not provide information about plaque vulnerability.[5] Intravascular ultrasound (IVUS) provides some detail of the vascular wall and the plaque core, but it is less sensitive in detecting a lipid-rich core as compared to detecting a calcified lesion. Coronary angioscopy utilizes the advancements made with fiberoptic filaments and, through observation of the endothelium surface, lesions are characterized as vulnerable or fibrous based on the endothelial colour. Normal endothelium appears white, while vulnerable plaques appear yellow. However, there are considerable technical and subjective limitations that impact the usefulness of this approach. Other techniques with limited clinical applicability include intravascular magnetic resonance imaging (MRI), spectroscopy, and optical coherence tomography. The various sensitivities for each of these modalities in identifying vulnerable plaque are listed in Table 1.[5] These techniques show promise and, in some cases, have been correlated with future occlusion events; however, they remain in the investigational realm due to their limited clinical applicability. Therefore, other methods must be found in order to limit the rates of vulnerable plaque rupture.

Significant progress has been made in improving primary and secondary prevention strategies to counter the atherosclerotic process involving the coronary tree. Statins and the inhibition of angiotensin-converting enzyme are two major approaches that have demonstrated improvements in major cardiac outcomes.[6-9] Nevertheless, despite the significant benefits associated with these prevention strategies, there is still much ground to cover, as evidenced by the substantial 23% event rate in the aggressive lipid-lowering arm of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial.[10] Other factors must be examined for their potential relevance to the progression of the atherosclerotic process in high-risk individuals.

Paradox of atherosclerosis

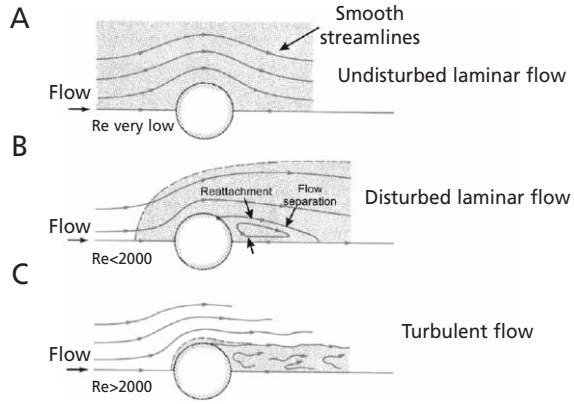
Insights into the mechanisms of atherosclerosis may be found by analyzing the locations of atherosclerotic lesions. Plaques occur at focal points on the inner curvature of vessels and often at bifurcation points, suggesting that possibly local hemodynamic factors are also responsible for

Table 1: Comparison of characteristics of imaging techniques[5]

Comparison of noninvasive and invasive imaging modalities for detection of individual characteristics of vulnerable plaque								
Imaging modality	**Resolution**	**Penetration**	**Fibrous cap**	**Lipid core**	**Inflammation**	**Calcium**	**Thrombus**	**Current status**
IVUS	100 µm	Good	+	++	–	+++	+	CS/CA
Angioscopy	UK	Poor	+	++	–	–	+++	CS/CA*
OCT	10 µm	Poor	+++	+++	+	+++	+	CS
Thermography	0.5 mm	Poor	–	–	+++	–	–	CS
Spectroscopy	NA	Poor	+	++	++	++	–	PCS
Intravascular MRI	160 µm	Good	+	++	++	++	+	PCS

NA indicates not applicable; CS = clinical studies; CA = clinically approved for commercial use; CA* = clinically approved for commercial use in Japan; PCS = preclinical studies; UK = unknown.
+++ = sensitivity >90%; ++ = sensitivity 80% to 90%; + sensitivity 50% to 80%; [en] = sensitivity <50%.

Figure 2: Characterization of flow patterns: turbulent vs laminar flow[11]



Re = Reynolds number

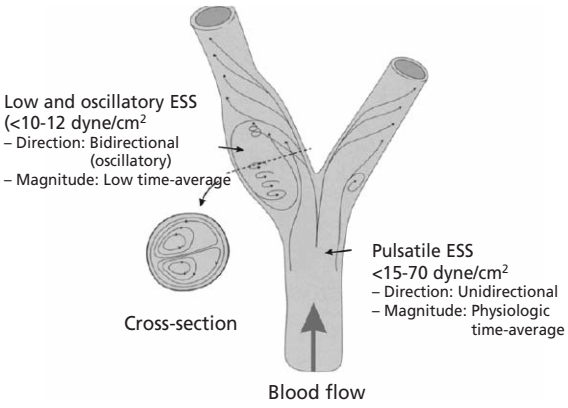
the progression of atherosclerosis, despite the fact that the traditional CV factors exert their influence on all the endothelial cells in the vascular tree. Several sophisticated techniques, including MRI and computational fluid dynamics, have been applied to bifurcation and inner curvature lesions in an attempt to provide further information. These studies reveal that these areas are characterized by low levels of shear stress on the endothelium.[11]

Shear stress

Shear stress is defined as the tangential force derived from the friction of flowing blood on the endothelial surface of the arterial wall.[12] It is expressed in units of force/unit area (N/m^2 or Pascal [Pa] or dyne/cm^2; 1 N/m^2 = 1 Pa = 10 dyne/cm^2).[11,12] Shear stress may be contrasted with radial or expansive stress that exerts its force in a radial manner. Shear stress is dependent both on the viscosity of blood and on the spatial gradient of blood velocity at the artery wall. The importance of the effects of this tangential force on the endothelium has been recognized for more than 40 years, since the first description by Caro et al.[13]

An important determinant of local shear stress is the degree of turbulence exerted by flowing blood. Turbulent flow is differentiated from laminar flow because it exhibits disorganized flow in several directions, whereas laminar flow is organized in the same direction and occurs in layers (Figure 2). A parameter known as the "Reynolds number" is used to identify and predict different types of flow. The Reynolds number is the ratio of inertial forces to viscous forces and it quantifies the relative importance of these 2 types of forces. Laminar flow occurs at low Reynolds numbers when viscous forces are dominant and is characterized by smooth, constant fluid motion. Turbulent flow is dominated by inertial forces and occurs at high Reynolds numbers. Inside an artery, just as in a flowing river, there are areas of laminar flow and areas where eddy currents exist. Analogous to this situation, several areas within the arterial tree may have varying Reynolds numbers and, therefore, varying levels of shear stress. Variable shear stress is a powerful determinant of the progression of atherosclerotic lesions and can have important implications for the remodeling of the vasculature.[11]

Figure 3: Classification of shear stress[11]



Classification of shear stress

Low shear stress: Low shear stress occurs when turbulent flow leads to varying directions of blood flow within an arterial segment. As a result, once all the vectors are added together, the net magnitude is low. This translates into a low shear stress state and is measured in humans at <10-12 dyne/cm^2. This level of shear stress typically occurs upstream of stenoses and at inner curvatures.[11]

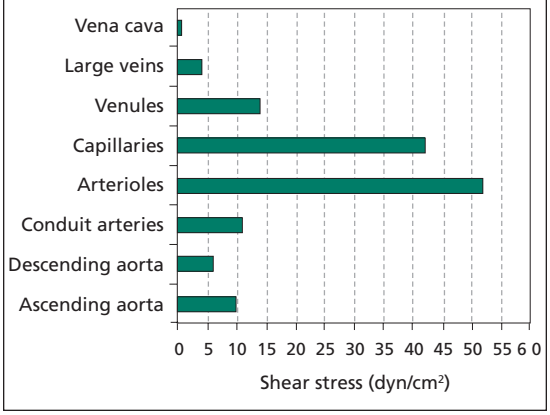
Oscillatory shear stress: In oscillatory shear stress, the overall vector of flow oscillates between 2 major directions within the arterial segment. The resulting overall magnitude of shear stress is low and measured at nearly zero dyne/cm^2. Bifurcation points and the lateral walls of stenoses are usually characterized by oscillatory shear stress.[11]

High shear stress: High shear stress occurs when the net vector of flow is in a single direction, as found in laminar flow. In human physiology, blood flow is pulsatile and referred to as pulsatile shear stress. Values of high shear stress or pulsatile shear stress are in the range of 15-70 dyne/cm^2. Thus, laminar flow corresponds to a high shear stress state (Figure 3).

Typical shear stress values and the implications of alterations

The normal values of shear stress that can be measured within the vasculature tree vary, depending on the location. The highest shear stress is found in arterioles, while the lowest is found in veins. This can have important implications on the use of venous grafts on arterial vessels, because there is a mismatch in the shear forces in the respective vessels leading inevitably to remodeling and potentially the progression of atherosclerosis (Figure 4).[14] Vessels under their respective normal ESS behave in a stable and quiescent manner. Normal shear stress values inhibit atherogenesis by upregulating protective factors such as nitric oxide (NO), prostacyclin, and tissue plasminogen activator inhibitor. Furthermore, normal levels of shear stress promote the longevity of the endothelium.[14]

Figure 4: Classification of shear stress[11]



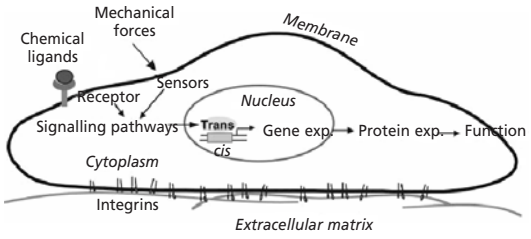
This implies that the endothelium is able to sense changes in shear stress and, in turn, responds by altering rates of gene expression and translation.

Mechanoreception: Tangential shear stress, as well as circumferential shear stress, are capable of influencing endothelial response and homeostasis.[12] This mechanical reception of flow and shear stress by the endothelium is termed "mechanoreception" and is mediated by extracellular proteins interacting with intracellular cytoskeletons. Influence on the genetic control of the cell by varying shear stress is accomplished by several overlapping intracellular pathways and is collectively termed, "mechanotransduction". A major convergence point in this signaling pathway involves the mitogen-activated protein kinase (MAPK) cascade at various levels.[11] The cytoskeleton and various integrin proteins are implicated in the reception of changing values for ESS. Furthermore, surface receptors and ion channels, as well as the glycocalyx itself, have been found to play important roles in mechanoreception of shear stress (Figure 5).[12]

ESS effects on genetic expression: Once ESS is sensed, this message is transmitted via processes of mechanotransduction involving phosphorylation of key enzymes. The process culminates in the binding of transcription factors to shear stress-responsive elements in DNA. Thus, positive or negative regulation of gene expression is achieved via alterations in ESS.[11,12] Regions of the arterial tree that exhibit low ESS are profoundly affected by the progression of atherosclerotic plaques.

Effects of low ESS on elements of atherosclerosis: Several proatherogenic pathways are dramatically stimulated by low shear stress states. NO production is attenuated in areas possessing low shear stress. Physiologic shear stress represents the most potent stimulant for the production of NO by upregulating both gene expression and protein phosphorylation of endothelial NO synthase. Low ESS attenuates prostacyclin production while augmenting the production of endothelin, thus promoting vasoconstriction.[11]

Figure 5: Overview of mechanoreception and mechanotransduction of shear stress[12]



LDL uptake is also facilitated by low shear stress and is mediated by an increased production of the scavenger LDL receptor. Furthermore, monocyte accumulation into the intima is increased when the endothelium senses low levels of shear stress and, under these circumstances, the production of reactive oxygen species is enhanced. Together with the increased uptake of oxidized LDL, the stage is set for the atherosclerotic process. To compound the problem, mediators of inflammation are also elaborated in the presence of low ESS; this includes the production of increased levels of tumour necrosis factor alpha (TNF-α) and chemoattractants such as monocyte chemoattractant protein-1, among others. The vulnerability of the atherosclerotic plaque is also accelerated in the context of low shear stress. This is largely mediated by the production of matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9, which act to degrade extracellular matrix. The "perfect storm" for atherosclerosis is achieved, in large part, due to low ESS.[11]

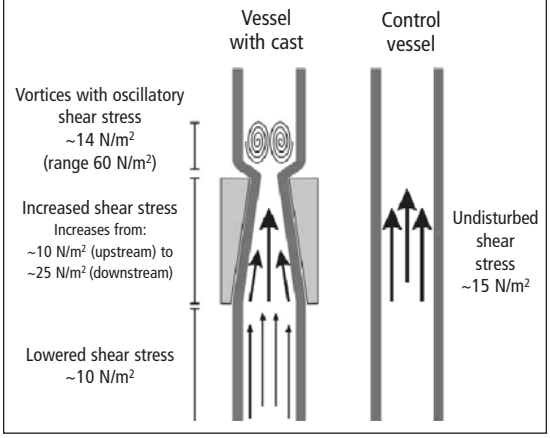
Vascular remodeling in response to shear stress

In addition to changes within the atherosclerotic plaque, varying shear stress levels also have an important impact on the modeling of the vascular tree itself. In normal vasculature, low shear stress induces a compensatory constriction, leading to a narrowing of the lumen, which then causes ESS to turn towards a normal level. However, in vessels with pre-existing atherosclerotic plaques, the interaction with varying shear stress is much more complex. In most cases of atherosclerotic narrowing, a compensatory expansive outward remodeling will occur. This acts to restore the vessel lumen to normal levels and, in the process, leads to a normalization of shear stress levels. However, at other times, for reasons that are currently unclear, this process can become unregulated, leading to excessive expansive remodeling. The result is a vessel lumen that is beyond a compensatory return toward normal. This has been shown to correlate with lower levels of shear stress and increased degradation of extracellular matrix (Figure 1).[11]

In vivo models of varying ESS

The effects of varying ESS have been examined in a prospective fashion, *in vivo*, utilizing an animal model

Figure 6: Alteration of shear stress *in vivo* by a cast[15]



of atherosclerosis and an ingenious device that can modulate shear stress levels. A cast is placed around arteries of apolipoprotein-E deficient mice that induces, within the same vessel, areas of low, high, and oscillatory shear stress (Figure 6).[15] This model clearly demonstrates that areas of low shear stress are characterized by the development of vulnerable plaques, whereas, oscillatory shear stress promotes the development of stable lesions, and high shear stress protects against the development of atherosclerotic lesions.[15]

Clinical correlations

Effect of viscosity and its clinical correlates on shear stress

In addition to the spatial gradient of blood flow on the endothelium, an important contributor to shear stress is viscosity.[11] Viscosity is linearly proportional to shear stress and is chiefly determined by the hematocrit. Consequently, changes in hematocrit due to bleeding can lead to significant changes in the degree of shear stress that is exerted on the endothelial wall. This was demonstrated by elegant experiments in which viscosity was altered by the transfusion of a viscous versus a dilute dextran, utilized as plasma expanders following an induced hemorrhage. This maneuver demonstrated that resultant NO production was clearly influenced by the varying shear stress.[16] Thus, myocardial ischemia and necrosis that occur in the setting of anemia or significant hemorrhage should be seen in a different light, since lowered shear stress potentially leads to vulnerability in an atherosclerotic plaque.

Vascular profiling

The negative consequences of low shear stress are becoming clearer based on *in vivo* and *in vitro* experimentation. However, in order to achieve true clinical significance in the prevention of the adverse outcomes from vulnerable plaques, the identification of early fibroatheromas with the potential of rupture is imperative in the clinical setting. The technique of vascular profiling is beginning to bridge this gap in clinical prediction for vulnerable plaques and may offer significant clinical benefits for early intervention to possibly prevent plaque rupture.[17] In vascular profiling, IVUS and conventional biplane coronary angiography are combined to create a 3-dimensional representation of the coronary tree. From this template, measures of local shear stress and vascular remodeling are made. This technique is both accurate and reproducible, and has been utilized to examine changes in vascular remodeling in humans over periods of time.[18-20] Initial studies have demonstrated a correlation between low ESS in human coronary arteries and progression of atherosclerosis.[19]

An example of the predictive value of low ESS was obtained from a patient enrolled in a prospective study to ascertain the feasibility of vascular profiling. This patient presented with unstable angina 4-months after undergoing angioplasty in the left anterior descending artery. The stent was well-deployed, but a "step-up" phenomenon resulted due to local vascular geometry. This led to an area of flow separation and turbulent flow, resulting in low ESS in that location. On repeat angiogram, areas of highest neointimal formation correlated with areas of low shear stress, indicating that areas of low shear stress can possibly predict adverse vascular remodeling.[21]

If areas of low shear stress are proatherogenic, then it follows that restoration of normal shear stress is protective against atherosclerosis. This was hypothesized and tested in various animal models with special attention to in-stent restenosis. An intra-stent device designed to alter flow toward the endothelial wall, thereby, increasing shear stress, was tested in rabbits prone to developing atherosclerotic lesions. Stents were placed in the femoral arteries and an intra-stent flow divider was placed within one stent. With higher shear stress induced by the flow divider, the rate of luminal loss, inflammation, and injury were significantly decreased compared to the conventional stent.[22] This provides a mechanistic "proof of concept" that modulation of shear stress leads to beneficial outcomes with regard to in-stent stenosis.

Conclusions

The consequences of atherosclerosis are devastating and costly to society in many ways. Prevention strategies aimed at decreasing rates of cardiac adverse events have improved dramatically. However, there is still a subset of the population that does not benefit sufficiently from such measures, primarily because in a substantial proportion of cases, vulnerable plaques do not cause symptoms prior to rupture. Shear stress has important implications for the progression of atherosclerotic plaque, as well as, vascular remodeling. Low shear stress levels can be especially harmful in promoting the vulnerability of atherosclerotic plaques. By beginning to ascertain levels of shear stress clinically,

it is hoped that non-invasive methods of measurement will be developed for screening techniques to prevent the serious consequences of ruptured coronary plaques. Modulation of low shear stress within the coronary tree may be a possible method in the future for manipulating the coronary vasculature.

References

1. Zipes DP, Libby P, Bonow RO, Braunwald E. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 7th Ed. 2005.
2. McGill HC Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 2000;72:1307S-1315S.
3. Fuster V, Fayad ZA, Badimon JJ. Acute coronary syndromes: biology. *Lancet* 1999;353 (Suppl 2):SII5-SII9.
4. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-671.
5. MacNeill BD, Lowe HC, Takano M, Fuster V, Jang IK. Intravascular modalities for detection of vulnerable plaque: current status. *Arterioscler Thromb Vasc Biol* 2003;23:1333-1342.
6. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-1158.
7. Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). *Am J Cardiol* 2007;100:1047-1051.
8. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-153.
9. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-788.
10. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-1504.
11. 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. *J Am Coll Cardiol* 2007;49:2379-2393.
12. Chien S. Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell. *Am J Physiol Heart Circ Physiol* 2007;292:H1209-H1224.
13. Caro CG, Fitz-Gerald JM, Schroter RC. Arterial wall shear and distribution of early atheroma in man. *Nature* 1969;223:1159-1160.
14. Papaioannou TG, Karatzis EN, Vavuranakis M, Lekakis JP, Stefanadis C. Assessment of vascular wall shear stress and implications for atherosclerotic disease. *Int J Cardiol* 2006;113:12-18.
15. Cheng C, Tempel D, van Haperen R, et al. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. *Circulation* 2006;113:2744-2753.
16. Martini J, Cabrales P, Tsai AG, Intaglietta M. Mechanotransduction and the homeostatic significance of maintaining blood viscosity in hypotension, hypertension and haemorrhage. *J Intern Med* 2006;259:364-372.
17. Waxman S, Ishibashi F, Muller JE. Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events. *Circulation* 2006;114:2390-2411.
18. Stone PH, Coskun AU, Kinlay S, et al. Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study. *Eur Heart J* 2007;28:705-710.
19. Stone PH, Coskun AU, Kinlay S, et al. Effect of endothelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans: in vivo 6-month follow-up study. *Circulation* 2003;108:438-444.
20. Stone PH, Coskun AU, Yeghiazarians Y, et al. Prediction of sites of coronary atherosclerosis progression: In vivo profiling of endothelial shear stress, lumen, and outer vessel wall characteristics to predict vascular behavior. *Curr Opin Cardiol* 2003;18:458-470.
21. Thury A, Wentzel JJ, Vinke RV, et al. Images in cardiovascular medicine. Focal in-stent restenosis near step-up: roles of low and oscillating shear stress? *Circulation* 2002;105:e185-e187.
22. Carlier SG, van Damme LC, Blommerde CP, et al. Augmentation of wall shear stress inhibits neointimal hyperplasia after stent implantation: inhibition through reduction of inflammation? *Circulation* 2003;107:2741-2746.

Upcoming meetings

16 – 20 March 2008
The 24th Annual Cardiovascular Conference at Lake Louise
Lake Louise, Alberta
Contact: www.acclakelouise.com/
Carol Cox/ Hallmark Meeting Concepts
Tel. (905) 814-1112
carol151@sympatico.ca

29 March – 1 April 2008
American College of Cardiology Annual Meeting ACC.08
Chicago, Illinois
Contact: www.acc.org

1 – 3 May 2008
European Society of Cardiology (ESC) Euro Prevent 2008
Paris, France
Contact: ww.escardio.org/

30 August – 3 September 2008
ESC Congress 2008
Munich, Germany
Contact: www.escardio.org/

Disclosure Statement: *Dr. Rocca and Dr. Monge have stated that they have no disclosures to announce in association with the contents of this issue.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.