대한기계학회 2001년도 춘계학술대회논문집 E pp. 17~24

강연10

# The Future Prospect of Biomedical Engineering

## - An Angiologist's View-

이병붕 (성균관대학교 의과대학, 삼성서울병원)

As lamented by my close respectable colleague, Professor Solomon Victor of the Heart Institute at Chennai, India, half of humanity is still worried about their next meal while the other half is simply ignoring the virtue of life and only engrossed in the pursuit of fame and fortune only to make human life more miserable. But thank goodness, still there are a few fighting against this ignorance and pondering over the wonders of creation including life and life forms in the belief that all the lives on earth are anticipated, planned, designed and documented, so that it can never be ignored.

Prof. Victor urges us to fight to overcome this perpetual cycle of "ignorance" to get out from our ever-condemned unnerving attitude of ignorance. Alexis Carrel of the last century broke the century-old ignorance through the proper verification of simple but critical cause of failure of vascular anastomosis. His overcome of the ignorance to this crucial fact was ever appreciated as major contribution to mankind through the novel prize in 1902. My mentor, David Hume of Richmond, Virginia also overcame the serious ignorance in traditional concept of immunology and made historical major breakthrough in the field of clinical organ transplantation to achieve world first successful clinical renal transplantation in 1951 during his tenure at Harvard and Brigam Hospital, though his untimely death allowed his partner Joseph Murray alone to receive the Novel prize later for their contribution to mankind to overcome another nightmarish ignorance in human history.

Recently my colleague, Charles Witte of Tucson, Arizona offered ignorance map as road map to help us to fight it, as following;

First, you should know exactly all the things that you know you don't know (known unknowns), and then your should try your best to know more about all the things that you don't know you don't know (unknown unknowns).

At the same time, you have to make yourself clear for your stance from a few more issues, that is all the things you think you know but actually you don't know (errors);

Also you should try to learn all the things you thought you don't know but indeed you know (unknown known); and also

all the things you are too painful to know so that you actually don't know though you were able to know (denials); and of course,

all the things you want to know but you were forbidden to know because you were told to be dangerous and/or polluting, etc. (taboos).

If we do understand properly all these six crucial facts of the ignorance of ignorance map, the future prospect of the biomedical engineering will be more brighter than ever on my opinion as one of angiologists committed to fight this ever-challenging ignorance problem.

In order to make proper strategy against this ignorance, we ought to gain precise understanding of ever-shifting domains of the ignorance to the uncertainty and also to the unknown first, and then to improve the skills to recognize and deal this ignorance to uncertainty and unknown productively and also precisely. In order to do so you have to question yourself critically and creatively focusing on proper raising, listening, analyzing, prioritizing and answering from many different point of views as strategy against ignorance. At the same time, you have to communicate clearly with different people and other resources in order to collaborate effectively, constantly reinforcing your positive attitude to the values of curiosity, optimism, humility, self-confidence, and skepticism altogether. With this new strategy against the ignorance we can solve various biomedical engineering problems more effectively and also more efficiently at the same time.

During the last half of century, biomedical engineering has made tremendous contribution in various field of medicine through the close collaboration with clinical medicine. Especially biomedical engineering took the critical role on the rapid development of vascular medicine and surgery though vascular surgery has quite brief history not for more than 50 years as self-contained and distinct specialty (Emerick Szilagy of Detroit, Michigan). However, in spite of tremendous advancement of vascular medicine and surgery for the management of vascular disease through the last three decades, public awareness on the peripheral artery disease (PAD) in particular has been remained in the dark so long for unknown reason even though general awareness on vascular disease has been much increased lately. If the public should have been informed for one critical fact that the disease prevalence of peripheral artery disease (7 to 12 millions) is same as those of diabetes mellitus (10.3 millions), you ought to wonder why there is no public advocacy for the proper diagnosis and management of such an important disease. But the answer is relatively simple, that is due to our ignorance to the critical issue of vascular disease with lack of sense of priority.

When you look at the natural history of peripheral arterial disease among the population of age over 55 years, 10% of this population will be found to have asymptomatic but significant peripheral arterial disease (ABI: Ankle-Brachial Index-lesser than 0.9) already and 5% of the population will develop the intermediate claudication as 5 year outcome with serious consequence of peripheral artery occlusions and significant cardiovascular morbidity/mortality as well. 1% of this population will further progress to the critical limb ischemia. Furthermore, the natural history of peripheral arterial disease (PAD) with intermediant claudication on 5 year outcome among the population of age 55 or more, shows more progress of the disease to worsening claudication in 16% and 7% requires leg bypass surgery while 4% requires major amputation, though the majority (73%) will remain in stable claudication. However, one serious aspect we can not afford to continue to ignore is the fact that, this intermittent claudication group will develop non-fatal cardiovascular event (e.g. myocardial infarction-MI/stroke) in 20% and its mortality will reach to good 30% in general. In spite of our very aggressive attitude lately toward the ideal clinical treatment goal to improve symptoms, functional status, exercise capacity and quality of life; to preserve the limb and decrease the needs for the re-vascularization; to prevent progression of the atherosclerosis; and to reduce cardiac and cerebral vascular morbidity and mortality, the relative five year mortality rates of this PAD still remains at 28%. This crucial fact has never received same kind of serious attention colon

and rectal cancer (5 year mortality 38%*), breast cancer (-15%*), or Hodgkins disease (-18%*) received, mostly because of our serious ignorance to the importance of proper public attention to get their critical support as well.

* American Cancer Society in 1997 on Cancer Facts and Figures.

If this PAD is such a common but serious problem to threaten the public health but remains largely neglected by the physicians, bioengineers and patients besides the public in general for such high rates of cardiovascular ischemic events as deadly disease, whatelse would be more urgent and important than our multidisciplinary approach as a fully integrated team of various related clinicians and bioengineers to tackle this vascular disease together as new venture of new millennium!

In order to establish our common strategy among many different specialties of biomedical engineering particularly in the field of circulatory disease, the angiopathy (vascular disease) should be understood together properly from all the different views based on anatomy, etiology, histopathology and also mechanical/hemodynamic physiology at the same time, as following;

1. Anatomical & physiological view: artery, vein, lymphatic, arterio-venous communicating (fistula) structure, and venolymphatic combined structure
2. Etiological view: degenerative change (e.g. artery-atherosclerosis) and non-degenerative change (e.g. inflammation-vasculitis)
3. Anatomo-histopathological view: endothelial, medial, and pan-vascular change
4. Mechanical/hemodynamic view: occlusion (stenosis to obstruction) and dilatation (ectasia to aneurysm)

Classical concept of angiopathy based on anatomy, etiology, physiology and histopathology has been well accepted for its value through centuries with proper analysis. However, new mechanical/hemodynamic (physiologic) view of angiopathy has never been properly accepted for its value and ignored for the proper assessment until lately, which become the base of the crucial role to the biomedical engineer involved into the field of circulatory disease.

Therefore, proper awareness of known-unknown in the field of hemodynamics through the proper analysis and review will be most crucial issue before taking the next step to tackle the unknown-unknown area to minimize our ignorance to avoid mistake as much as we can. For example, one thing we know to be sure is the fact that the obstruction (stenosis) of arterial system reflects the interference with efficient transport of blood to the peripheral capillary bed, resulting in clinically serious "peripheral ischemia" on hemodynamic point of view, regardless of the various etiologies like atherosclerosis, fibromuscular dysplasia, thrombus, emboli, dissection, trauma, and external compression, etc. And also we know to be sure this extent of the interference of blood flow will be totally depending on the degree of the narrowing (stenosis) of the vessel lumen, which will be determined only by the strict hemodynamic principles. However, the symptoms and signs of this obstructive lesion of arterial system will reflect the restriction of the arterial blood flow to the capillary bed and the actual capillary flow deficit is quite complex form depending upon various factors involved, like the severity and location of obstruction, compensatory ability of the cardiac work, collateral channels, and dilatation of peripheral arterioles and precapillary sphincters. And therefore hemodynamic information of atherosclerosis has to be prioritized as very essential

knowledge for the proper understanding of angiopathy in general.

Atherosclerosis is the most important and popular disease to affect vascular system. It is generalized degenerative disease process mainly affecting large and medium sized artery and characterized by the accumulation of cells, matrix fibers, lipid and tissue debris in the intima. However, the morbidity of the atheroscleorosis is resulted from the localized (focal) plaque deposition on the limited area of vessel wall, and not from the diffuse disease nature involving entire vessel wall. Hemodynamic variables accountable for this selective distribution of the plaque as focal (localized) lesion on the vessel wall are shear stress, flow separation and stasis, oscillation of shear stress vectors, and turbulence. These variable distribution of shear stress and tensile stress by different geometry and flow will enhance the effect of the clinical risk factors of atherosclerosis.

Another word, alterations in the field flow to potentiate the plaque formation through the increased/decreased velocity, high-wall/low-wall shear stress, flow separation and turbulence, departures from unilaminar flow patterns, and high/low mural tensile stress will affect the metabolism, thickness and compliance of the arterial wall in various degree.

Wall shear stress is the tangential drag force produced by blood moving across the endothelial surface as the function of velocity gradient and therefore it is directly proportional to the blood flow and blood viscosity, but this shear stress is inversely proportional to the cube of radius which is so critical on hemodynamic point of view. Atherosclerotic plaques, therefore will localize preferentially in the region of low shear stress since low shear rates retard the transport of atherogenic substances away from the vessel wall, interfering with normal endothelial surface turnover of essential substances.

Turbulence may develop in association with stenosis and irregularity of the flow surface caused by the plaques but the turbulence develops distal to the lesion and not at the lesion itself. Therefore, turbulence per se is not an initiating factor in atherogenesis but it might play an important role in plaque disruption or thrombogenesis, which has increasing meaning to the clinicians.

Wall Tension (T) is the circumferential stretching force exerted in a direction tangent to the arterial wall following the law of Laplace (T=Pr r: radius P: pressure). The increasing wall tension is counterbalanced by the increase in the wall thickness to maintain a constant wall tensile stress; S=Tr/d (d: wall thickness), as physiologic response of vessel.

Velocity is naturally greatest in the center of stream when the vessel is straight and declines symmetrically toward the lumen surface due to the friction resistance and therefore it will maintain the symmetrical parabolic state in the straight vessel. However, the direction of the high central velocity will proceed, toward the outer (convex) portion of the vessel at the bend and when it reaches to the branching area, the flow divider will intercept high velocity along the inner wall at branching point which is so crucial for the focal plaque formation of the atheromatous plaque along the outer wall of vessel.

Flow separation and stasis increase the residence time of atherogenic particles prolonging their exposure to the vessel wall to allow the interaction and further facilitate the plaque formation. It increases the deposition, adhesion, and diapedesis into the vessel wall by blood cellular element.

Birectional oscillation of the shear stress vector by pulsatile blood flow during the cardiac cycle

also increases endothelial permeability by direct mechanical effect in the cell junction (e.g. outer wall of carotid bifurcation), in comparison to the uni-directional shear stress which favors mechanical integrity of endothelial cells to make orderly and tight line up without gap between cells. Accordingly, atherosclerosis is systemic disorder but characterized with localized plaque deposition in selected sites on arterial tree and low or oscillatory wall shear stress or both and increased particle residence time due to the flow stasis are the critical hemodynamic condition associated with localized plaque deposition in atherosclerosis. Alteration in this local hemodynamic condition will be responded by adaptive change of the vessel wall through the compensatory enlargement of artery and/or sequestering of the plaque in certain degree in order to minimize the effect of focal stenosis in earlier stage. Clinical complications, however occurs in its later stage when this normal adaptive and compensatory mechanism should fail and proceed to the stenosis with subsequent ulceration, embolization and thrombosis.

The rheologic differences and their hemodynamic consequences between high pulsatile arterial flow and low fluctuating venous flow, however are largely left alone for the further clarification.

The dilatation (aneurysm) of the vessels either artery or vein, as one of two major components of the hemodynamic (mechanical) classification of angiopathy is as critical issue as the obstruction (stenosis) to the clinician and angio-engineer but in the different aspects. Dilatation of arterial system will have perpetual risk of the expansion leading to the eventual rupture but it seldom produces symptoms of obstruction except for the thrombus formation and occasional dissection and it usually does not give adequate information to let us predict the outcome of the progressive expansion properly to prevent disastrous rupture. The stresses to lead to the rupture of arterial aneurysm however, has not been understood properly except a few critical factors and mostly limited to the vague concept based on the information obtained from the deficiency of proper elastic component of arterial wall (e.g. Ehrler-Danlos syndrome; Marfan's syndrome).

On the contrary, this dilatation (aneurysm) problem in venous system with low functioning pressure brings entirely different issues with perpetual risk of development of new thrombus and its bi-directional extension besides undeniable risk of distant migration of separated thrombus to the pulmonary artery bed either in acute condition (e.g. pulmonary embolism) or chronic condition (e.g. chronic cor pulmonale), rather than the risk of rupture, like arterial aneurysm.

Therefore, what we should know more on this aneurysm (or dilatation) issue of angiopathy in terms of angio-rheology point of view will be the critical rheologic factors related to the progress of aneurysm either in arterial or venous system.

And therefore for the arterial aneurysm, the relationships among various critical (minimal) factors of the rupture that is the diameter, length, thickness and pressure of the aneurysm have to be thoroughly assessed besides unknown role of intraluminal thrombus to the risk of rupture. For the venous aneurysm, critical (maximum) factors besides size to develop new thromboembolism also has to be investigated with different concept based on new venodynamics.

Rheological significance of the contour of the aneurysm (eg. saccular versus fusiform) can not be over-emphasized especially from the rupture point of view.

Accordingly, what we believe we do know in most now is the major issues of the rheological aspect

of stenosis in arterial system mainly related to this atherosclerosis due to high pulsatile pressure condition. Also we believe we know the critical part of major issues of the rheological aspect of the aneurysm in arterial system, and perhaps less of the rheological aspect of arteriovenous fistula at the present time. However, what we don't know sufficiently now is many critical issues of the rheological aspect of the stenosis in venous system which is strikingly different from the arterial stenosis since venous system reflects the low fluctuating pressure condition.

Rheological aspect of the stenosis in lymphatic system based on peristaltic pressure condition is another matter with more confusion than venous dynamics.

The knowledge in rheological aspect of aneurysm in venous and lymphatic system is much far behind and further limited.

One characteristic aspect of the obstruction (thrombosis) in venous system is it will exert dual effects as acute consequence of the venous thrombosis; systemically with acute pulmonary embolism, and regionally and locally with acute venous hypertension in various degrees up to the venous gangrene as the consequence of acute impact to artery-capillary-venous microcirculatory system. Subsequently following the acute consequences of venous obstruction, chronic consequences of venous thrombosis also exert its dual effects as the obstruction and reflux phenomena due to the natural response to the blocked vein lumen mostly with partial recanalization in its later stage, and will result in chronic venous insufficiency (CVI) due to the combined effect of initial obstruction condition and subsequently added reflux condition by valvular damage at the same time locally and regionally.

However, the venous system has been proven to be very energy-efficient system on hemodynamic point of view. That is, elliptical cross section of vein lumen reflects partly collapsed state but it has far more resistance than circular cross section of vein, but when the vein is distended this high resistance falls immediately to respond to the rapid increase of blood volume within the lumen with little increase in the energy gradient at the same time.

The venous system is very peculiar, rather paradoxical system in terms of pressure, volume and flow relationship in contrast to the arterial system. The venous pressure and venous volume will change inversely proportional to the venous flow, that is venous pressure and venous volume may decrease when venous flow increases but the venous pressure and volume may increase when venous flow decreases or reverses. In contrast, arterial system maintains proportional change of these three components, pressure, volume and flow together in the same direction. That is, when arterial pressure and arterial volume should increase, arterial flow will also increase together, and when decrease, decreases together. This paradoxical relationship of venous pressure and volume to its flow is partly resulted from the collapsible nature of the vein. This collapsible nature of the vein is responsible for the great variation in venous capacity with little change in venous pressure to maintain its critical role as major storage facility of the blood, allowing energy-efficient status.

Depending upon the change of transmural pressure of the vein wall, which is the balance of the differences in pressure between intraluminal pressure acting to expand the vein outward and tissue pressure acting from outside to collapse the vein inward. The contour of the vein will change from the elliptical shape during the low transmural pressure to the circular shape in high transmural

pressure to meet the necessity. Such a vast change of venous volume with energy efficient minimal pressure change in venous system is largely due to the fact related to the cross-section of the venous lumen; elliptical contour at low transmural pressure and circular contour at high transmural pressure. For example, minor increase of the transmural pressure from 0 to 15mmHg will allow huge increase of the volume of vein for more than 250%. Little increase in pressure in venous system is required at this time to convert low-volume elliptical tubes into high-volume circular tube. But much more pressure is required to stretch this vein wall further, once the circular configuration is easily reached from collapsed elliptical status

Accordingly, the hemodynamics in venous system has to be aware of for its striking difference from the arterial hemodynamics first and then the proper interpretation of many different informations of venodynamics in various venous condition (e.g. obstruction and reflux) has to be made from many different views before proper clinical applications to three different aspects; thrombosis and pulmonary embolism, reflux originated venous insufficiency, and obstruction originated venous insufficiency.

On the basis of what we do know and what we don't know in most in angiopathy, we can tell more clearly about what we should know next in this field. For this, the answer should come first to clear the difference between fluid dynamics and angiodynamics, and then the difference between hemo(arterial and venous)-dynamics and lymphodynamics, and after all the differences between arterial dynamics and venous dynamics. Dynamics of lymphatic system is newly developing area with recent establishment of the new concept of normal physiolgy and pathophysiology of lymphatics.

"Lymphangion" - based new concept of lymphodynamics finally allowed correct interpretation of chronic "lymphedema" for the first time in decades, which is known for centuries as old enigma of medicine and still remains as the last frontier of vascular disease. But we still have such a limited knowledge and technology to assess lymphodynamics with too much known- unknown area and also too much unknown-unknown area even through the latest turn of the century is representing highly sophisticated biomedical technology.

Partly due to our ignorance, there are over 140 million patients of chronic lymphedema throughout the world, that is one among 20 persons on earth is known to suffer from chronic lymphedema; e.g. 30 millions of primary lymphedema and 20 million of post-mastectomy lymphedema according to WHO data (John Casley-Smith-1993). However, at least we learned lately that lymphedema is not as one dimensional problem of simple clinical manifestation of the mechanical failure of lymphatic system to transport protein-rich interstitial fluid out of tissue but it is three dimensional problems of progressing chronic degenerative and inflammatory process of the skin, lymphatics and lymphnodes with fibrotic change of soft tissue during the episode of dermatolymphoadenitis (DLA). Lymphedema should be no longer considered as simple phenomenon of accumulation of fluid (old concept) but considered as whole process of dermatolymphoadenitis (new concept; W. Olszewski-1997).

Lymphatic system is fine adjuster of tissue micro-environment, helping the maintenance of the fluid, protein and osmotic equilibrium around the cells and aiding the absorption and distribution of

various nutrients and disposal of their waste.

Lymphangion is such an important functional unit to become the base of the new concept of lymphodynamics to carry on this critical lymphatic function. Lymphangion is a lymphatic segment between well-developed intraluminal valves as functional unit and maintains spontaneous intrinsic segmental contraction for the proper lymph propulsion as normal physiologic function of the lymphatic system. Therefore, there would be no continuity of fluid column in normal lymphatic vessel in contrast to the venous system, as far as this lymph propulsion is properly carried. In the normal flow-pressure lymphodynamics, pumping capacity of lymphatics can overcome high resistance (impedance) of tissue by generating intraluminal pressure of 30-50 mmHg and peripheral lymp flow is regulated primarily by this spontaneous contraction of lymphatics and it is not affected by the skeletal muscle contraction like venous return. However, once normal flow-pressure dynamics should become abnormal in chronic lymphedema, lymphodynamics will become abnormal and eventually become same as venodynamics. Lymphatic obstruction with persistent lymphostasis due to the failure of normal lymphatic truncal contraction will change this unique dynamic status of the lymphatic system to the similar static one of venous system so that fluid column in lymphatics will become continuous like venous system and skeletal muscle or external compression becomes effective pumping mechanism as in venous system, to aid lymph transport at this late stage of lymphedema. Accordingly, lymphangion as a unit is essential for lymphodynamics and the lymph flow is running from low resistance condition to high resistance condition by this lymphatic contractibility in contrast to the venous flow which is running from high to low resistance system.

Conclusion: The comprehensive approach, therefore based on the multidisciplinary coordination among clinicians and biomedical engineers as a team, should be the first step against the ignorance in the investigation of hemodynamic characteristics of these three different vascular structure arterial, venous, and lymphatic system. And the relationship between known-unknowns area and unknown-unknowns area in vascular disease should be further clarified only to make the future prospect of biomedical engineering brighter than ever, providing the last missing piece of complex puzzles we lost long by the ignorance.