



July 1, 2012 Bale/Doneen: Inflammation – our side of the story! – Arteriology and Inflammation.

Understanding the mechanism from which heart attack or ischemic stroke occurs allows for an appreciation of the connection between inflammation, disease and vascular events. Atherosclerotic plaque lesions develop silently within the artery wall, often with minimal luminal encroachment. When an artery wall weakens due to an influx of inflammation, the protective endothelial lining can rupture or erode, thus exposing the plaque to blood flow, creating the potential for thrombus formation. Not all plaque ruptures or erosions result in major CV events, some lead to progression of plaque volume or create microvessel thrombi that cause microvascular disease states such as silent heart attacks, silent strokes which contribute to vascular dementia and peripheral vascular disease. Regardless of the resulting effects of a thrombus, the presence of an atheroma is essentially a condition *sine qua non* for an event.

Knowing that an atheroma is *sine qua non* for an event, CVD prevention must be anchored in a disease treatment platform by determining if an atheroma is present. The Bale/Doneen Method classifies each patient based on the presence or absence of atherosclerosis. If there is an absence of subclinical atherosclerosis, this is true primary prevention and the goal of therapy is to forever prevent the formation of atheroma. Because inflammation appears to be causal of atherosclerosis as indicated by recent genetically based studies, primary prevention requires assessment and management of arterial inflammation. A patient is classified as secondary prevention when subclinical atherosclerosis is identified anywhere in the vascular system. Goal of treatment is to stabilize the atherosclerotic process through appropriate treatment and therefore prevent a plaque rupture or erosion that can cause a CV event. Tertiary prevention is determined when a previous CV event has occurred and the goal of treatment is to prevent a recidivistic event. Understandably, routine inflammatory monitoring is essential in these groups as well. In any of these situations, the goal of therapy is to minimize any opportunity for thrombus development through rupture or erosion. This is accomplished by mitigating the risk of any vascular inflammation.

Evidence supports inflammation as a key player in the development and progression of atherosclerosis. In addition, inflammation is involved in destabilizing the plaque and in promoting thrombosis. Inflammation is a manifestation of underlying pathology such as obesity, stress, hypercholesterolemia, diabetes, and infection. A comprehensive CV wellness program must evaluate each patient for all conditions known to be associated with CV risk or which can stimulate systemic inflammation.

Current genetic research indicates that Inflammation appears to be causal for CHD. Prior to this data, the hypothesis existed that persistent inflammation was a contributor to the various stages of the pathogenesis of CVD, however causality had not been established. Sarwar's recent genetic work demonstrated via the Interleukin-6 receptor (IL-6R) signaling pathway that inflammation has a causal role in the development of CVD. Furthermore, this research can be "used to validate and prioritize novel therapeutic opportunities to treat CVD". With this research, we must embrace the ability to utilize biomarkers of inflammation to assess for arterial wall stability and to validate the impact of therapy.

The Bale/Doneen Method utilizes several biomarkers to assess for vascular inflammation, both in determining risk of an active atherosclerotic disease process that could promote formation of an atheroma or an event



along with evaluating the effectiveness of therapy. We utilize these biomarkers when initially assessing each of our patients and then determine repeat testing based on their diagnosis of primary, secondary or tertiary. Inflammatory biomarkers evaluate the stability of the atherosclerotic process. They are not utilized to determine the presence of atherosclerosis and are not surrogate markers for lumen diameter assessment. The science of arteriology (Bale/Doneen Method) relies on inflammatory assessment to determine risk of erosion or rupture, stability of the atherosclerotic disease process and the effectiveness of treatment.

Currently, we utilize the following biomarkers for initial and routine assessment:

F2 Isoprostane

This test measures oxidative stress formed from the peroxidation of essential fatty acids. Oxidative stress is an imbalance between the formation of free radicals and antioxidant protective mechanisms. Increased oxidation places individuals at risk for aging faster, cancer and CVD. We have nicknamed this test as the “Lifestyle Lie Detector” test because it is maintained at optimal levels by regular exercise, healthy eating, healthy sleep patterns, stress management and smoking cessation. It has importance at three stages of prevention, namely: primary, secondary and tertiary. Since lifestyle is the most effective therapy for CVD prevention, this test should be measured on a routine basis and can help to ensure compliance with healthy living.

Fibrinogen is an acute phase reactant and it contributes to the clotting cascade. High levels of fibrinogen are associated with increased thrombotic events. It is frequently elevated in insulin resistant conditions such as metabolic syndrome. It has significance in any stage of prevention. Elevated levels can be treated by weight loss, smoking cessation and medication.

Microalbumin/Creatinine Urine Ratio (UACR)

Arguably the most important structure in our bodies is the endothelium. Heart attacks and strokes remain the number one cause of death and disability. Those events can only occur when the endothelium fails at least twice. The first failure is when it starts allowing substances like LDL-C to pass through into the wall of the artery initiating the process of atheroma formation. The second failure is when the endothelium ruptures or erodes which leads to either atheroma growth, microemboli or a symptomatic heart attack or stroke. Therefore, the health of the endothelium is extremely important to evaluate in all the stages of CV prevention. Albumin is a huge protein that should not easily pass through the endothelium of capillaries in the kidney allowing it to show up in the urine. How much albumin is getting into the urine is strongly determined by the health and permeability of the endothelium. The Framingham study found UACR to be one of only two independent biomarkers for CV event risk (the other was BNP). A very recent study added to the evidence that changes even within the ‘normal’ UACR range is independently associated with adverse CV outcomes. It was concluded that there is a continuous association between UACR and CV outcomes starting as low as 4.4 mg/g. This simple urine test is extremely valuable in all stages of prevention and should be monitored routinely.

High-Sensitivity C-Reactive Protein (hs-CRP)

Albeit long proven to not be a player in the disease state, hs-CRP may mark increased endothelial inflammation. This acute phase reactant protein, when ≥ 1 mg/dL has been predictive of heart attacks and ischemic strokes. The weakness with this marker is it is not specific for endothelial inflammation. It is well known that any inflammation will cause a rise in hs-CRP. It is very comforting to see a low level of hs-CRP as that indicates the endothelium is not inflamed. When it is elevated one does not know for sure if it is due to arterial inflammation. It can help to couple the result with UACR. If both are elevated, it is more likely to be due to endothelial inflammation. Hs-CRP can be useful in all stages of prevention. It should be monitored routinely in patients who are not known to have other chronic inflammatory conditions. It is very comforting if it is low. When elevated it should always be associated with the UACR.

Lipoprotein Associated Phospholipase A-2 (Lp-PLA2)

Lipoprotein associated phospholipase A-2 (Lp-PLA2) is an enzyme that was FDA approved for coronary heart disease assessment in 2003 and stroke risk assessment in 2005. It is now emerging as not only a marker of arterial wall inflammation, but also as a direct player in the atherosclerotic disease process. A recently published study suggests Lp-PLA2 plays a key role in cholesterol plaque inflammation and vulnerability. The authors note that this supports Lp-PLA2 inhibition as a strategy for the prevention of CVD. Inflammation in the intimal layer is present with an active atherosclerotic disease process that can result in atheroma formation. Inflammation in this layer is also present during destabilization of the atheroma and fibrous cap. It was recently published that Lp-PLA2 is not an acute phase reactant. Most Lp-PLA2 is created within macrophages and foam cells in the intima of the artery. The production of Lp-PLA2 is a driver of inflammation increasing the risk of atheroma formation and or plaque rupture. Therefore, it is important to access the levels at any stage of prevention. Studies have shown a correlation between plasma levels and intimal levels albeit not perfect. Lp-PLA2 should be monitored routinely in any prevention program.

Myeloperoxidase (MPO)

Myeloperoxidase is an enzyme that is normally used by the immune system to fight infection. It is usually only found at elevated levels at the site of an infection. Approximately 4% of individuals are found to have elevated systemic levels. High levels are indicative of CV risk due to numerous potential mechanisms. MPO interacts with hydrogen peroxide to produce hypochlorous acid that can cause erosion of the endothelium. MPO diminishes nitric oxide from direct consumption along with reduced production. Nitric oxide (NO) is the best 'food' for the endothelium. Lowering NO weakens the health of the endothelium which can promote an active atherosclerotic disease process or in those with atheromas, place them at increased risk for a rupture or erosion. Additionally, this enzyme produces numerous reactive oxidants which render all of the cholesterol substances more inflammatory. This includes the 'good' cholesterol HDL including hindering its reverse cholesterol capability. MPO also promotes the activation of MMP-7. In patients with atheroma this will make the fibrous protective cap more prone to rupture. MPO elevation predicts coronary artery disease presence and risk of an event regardless of other known risk factors such as cholesterol, hypertension and diabetes. We have nicknamed MPO the 'joker'. It is elevated in about two out of fifty individuals; if this 'card' gets played, the



game of life might be over. In our opinion, it should be measured initially in all individuals seeking CV prevention. If it is normal, it should be assessed annually in an asymptomatic individual and immediately in any one who has CV symptoms. If it is abnormal, it should be reassessed routinely. It has importance at any stage of prevention, but extreme importance in secondary and tertiary prevention especially in a symptomatic individual.

The Bale/Doneen View on the clinical utility of inflammatory biomarkers:

All stages of CV prevention should involve monitoring arterial inflammation. The above mentioned tests appear adequate to make clinical decisions. These tests, in light of the current evidence of causality, are arguably the most important biomarkers for assessing CV wellness. Definite evidence of arterial inflammation demands a change in medical management whether with lifestyle, OTC or prescription medication. Since we know most events arise from non-obstructing atheromas, evidence of arterial inflammation in an asymptomatic individual is not a call for non-medical interventions.

Ordering inflammatory biomarkers: Myeloperoxidase (MPO) and F2 Isoprostane (F2 Iso) are proprietary to the Cleveland HeartLab (CHL). All other markers discussed can be ordered at various laboratories around the country. CHL is the only lab that offers these labs in one panel (with the exception of fibrinogen). They label this biomarker panel as the 'Inflammatory Panel – IT". We call the entire panel of labs discussed in this paper, "The Bale/Doneen Fire Panel" and find its utility critical in our CVD prevention efforts.

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