JOINT EFFECTS OF HIGH SENSITIVE C-REACTIVE PROTEIN AND CHARACTER OF ULTRASOUND MORPHOLOGY IN CAROTID RUPTURE-PRONE PLAQUES

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Specific Aims

In most industrialized countries, stroke has become the third most common cause of death and many patients surviving a stroke often suffer permanent disabilities with regard to work or even need help for daily activities. There is mounting evidence that the sudden and often catastrophic nature of stroke is a result of embolization arising from degenerative breakdown or thrombotic occlusion of complex plaques located in the extracranial vessels which are readily accessible to ultrasound imaging. However, histological studies examining the relationship between carotid plaque morphology and clinical outcome have reported conflicting findings. Several studies found plaque components (the lipid core, the necrotic core, or calcification, etc) and complications (for example, intraplaque hemorrhage) are frequent in cases with stenosis and that most of them apparently heal without giving rise to symptoms [1,2]. Thus, not all plaque complications in B-mode ultrasonography are necessarily harmful and develop clinical events, and carotid plaque components and complications in B-mode ultrasonography for unstable plaque alone may present limited evidence to guide carotid endarterectomy or other medical therapy. Recently more and more growing evidence shows that the inflammatory mechanism may play an important role in initiating, advancing, and destabilizing human atherosclerotic lesions; hs-CRP has been a more sensitive indicator in the process. Therefore, we will discuss the evolving hypothesis regarding the association between inflammatory markers hs-CRP and the characteristic morphology of carotid plaque in B-mode ultrasonography, and the joint effect that may guide us to better describe and analyze the orientation, stability, and quantification of plaques. The findings may supply adequate evidence for clinical study in the prevention of ischemic stroke.

Principal Findings

CHARACTER OF B-MODE ULTRASOUND MORPHOLOGY OF CAROTID PLAQUE

With the advance of B-mode ultrasound technique and clinical pathology, several studies showed promise and exciting findings in the characteristic morphology of carotid plaque; and some new digital imaging processing and videodensitometric analysis could provide better qualitative analysis characterization of plaque, and reduce subjective analysis of plaque morphology in the early stages of B-mode ultrasound. For example, densitometric evaluation allows differentiation of the carotid plaque components. The determination of plaque composition, based on density measurement, may provide information about its potential for thromboembolization [3-5] (Figure 1). However, discrepant results were found in a few trials. For example, the disruptive processes that underlie plaque instability appear to be closely associated with plaque size and stenosis rather than plaque composition [1]; using the Honeywell Ultra Imager, the presence of ulceration,
intraluminal and intramural thrombus, fibrous intimal thickening and necrosis are not related to the echogenic appearance of internal carotid stenoses [2], etc. Fortunately, most new high-resolution, real-time B-mode ultrasonic imaging techniques combined with clinical pathology demonstrated that echo-lucent plaques were associated with a higher content lipid and hemorrhage, and therefore more prone to rupture, whereas echo-rich plaques contained more calcification and fibrous tissue and were more prone to stabilization [4,6-8].

Figure 1. (A) mixed plaque           (B) soft plaque                 (C) hard plaque

Data are from our study (carotid plaques occurred in 444 subjects of 1,392) with High-Resolution Ultrasound (Medical Diagnostic Ultrasound System, Model Aspen, Acuson Corporation); “soft” plaques: homogeneous plaques with low echogenicity had a high lipid content; “hard” plaques indicate homogenous plaques and were highly reflective, those with shadowing were found to be calcified; and “mixed” plaques of nonhomogeneous echogenicity had high and low reflecting areas, sometimes with shadowing.

OCCURRENCE AND RUPTURE OF PLAQUE

Atherosclerotic lesions result from a series of highly specific cellular and molecular responses to various endogenous risk factors and potential exogenous antigens. These responses are mediated by endothelial cells, monocyte-derived macrophages, smooth muscle cells, and specific subtypes of T lymphocytes. Activation of these cells leads to the release of a wide spectrum of inflammatory hydrolases, cytokines, and growth factors followed by cellular lipid accumulation and proliferation of smooth muscle cells as well as formation of fibrous tissue [9].

Destabilization of the fibrous cap likely results from not only decreased collagen production by vascular smooth muscle cells, but also increased collagen and matrix degradation, primarily by monocytes/macrophages. Similarly, destabilization of plaque may attribute to results of multiply highly specific cellular and molecular responses to various endogenous risk factors and potential exogenous antigens interactively, for example, matrix metalloproteinase [10], triglyceride-rich lipoproteins [11], macrophage Myeloperoxidase (MPO) [12], PAPP-A & free IGF-1 [13], CD-40 ligand [14], P-selectin [15], IL-6 [16], TNF-alpha [17], and Cellular adhesion molecules (CAMs) [18], etc. It seems that destabilization of plaque may be a complicated process related to inflammation activity.

HIGHER CRP IS AN IMPORTANT RISK FACTOR FOR RUPTURE OF PLAQUE

CRP may be an important risk factor for the rupture of plaque and intraplaque hemorrhage. Pathophysiologically, CRP has been suggested to be involved in the immobilization and binding
of low density lipoprotein cholesterol, and the fact that foam cells in the early lesion stain positively for CRP may provide evidence for the hypothesis that CRP participates in foam cell formation by opsonizing lipid particles in the arterial wall [19,20]. Recently, one study suggested that CRP may also be involved in the accumulation of lipoproteins in early atherosclerotic lesions, and in cytolysis in advanced atherosclerotic lesions which may be a major prerequisite for the enlargement of the necrotic core of the plaque [21].

Atherosclerotic intra-plaque CRP mRNA levels may be seven-to-ten times higher than in normal artery or liver. \textit{In situ} hybridization demonstrates CRP and C4 mRNA in plaque macrophages and smooth muscle cells [22]. These data with both CRP and activated complement in atherosclerotic plaque imply that plaque growth is “autotoxic” and may begin a cascade of events terminating in sudden arterial thrombosis [13]. For example, study evidence show that hs-CRP is also significantly elevated in patients dying suddenly with severe coronary artery disease, both with and without acute coronary thrombosis, and correlates with immunohistochemical staining intensity and numbers of thin cap atheroma [23], and CRP may be a stronger marker of thrombotic risk than that of the degree of atherosclerosis [24].

Although the specifics of hs-CRP diagnostic potential will be further defined, hs-CRP is also the strongest correlative factor for future clinical events due to arterial inflammation in several studies from both the United States and Europe which indicate that elevated levels of hs-CRP among apparently healthy population are a strong predictor of future cardiovascular events [25] (Figure 2).
Figure 2. Prospective studies of high-sensitivity CRP as a risk factor for future vascular disease. Risk estimates and 95% CI are calculated as comparison of top versus bottom quartile within each study population. CHD, coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial; PHS, Physicians’ Health Study; CHS/RHPP, Cardiovascular Health Study and the Rural Health Promotion Project; WHS, Women’s Health Study; PVD, pulmonary vascular disease; CVD, cardiovascular disease; and MONICA, Monitoring Trends and Determinants in Cardiovascular Disease.
(Figure 2 is derived from Ridker PM. Circulation 2001;103:1813-18)

On the methodology of hs-CRP measurement, in several large-scale prospective studies, hs-CRP assay has been shown to reproduce the predictive value of hs-CRP testing for peripheral arterial disease [26], myocardial infarction, and stroke [27]. hs-CRP can be detected in very low circulating levels. Moreover, in the low normal range needed for vascular risk detection, the variability and classification accuracy of hs-CRP is similar to that of total cholesterol [28].

Although cost effectiveness of hs-CRP testing has not been formally evaluated, it is well known that testing of hs-CRP is inexpensive, and thus possibly to prove cost effective, particularly when compared with techniques such as electron-beam calcium scanning or magnetic resonance imaging.

If inexpensive commercial assays for hs-CRP are available, clinicians will need to know the population distribution of hs-CRP, the magnitude of vascular risk that can be expected at each level of hs-CRP, the accuracy of prediction for plaque destabilization in the combination of hs-CRP and B-mode ultrasound, and the utility of preventive strategies to control inflammatory risk. In a word, in clinical practice, the measurement of hs-CRP may be an important method for the prediction of clinical events related to the rupture of plaque.

Conclusions

Our analysis may raise two hypotheses: (1) there is a possible association between the
inflammatory marker hs-CRP and characteristic morphology of carotid plaque in B-mode ultrasound imaging; (2) It may be feasible to join the effects of hs-CRP and characteristic morphology of carotid plaque for destabilization in the potential diagnostic use of B-mode ultrasound (Figure 3). However, we found the discrepancy in the limited reports of association between hs-CRP and the characteristics of carotid plaque. For example, Yamagami et al. examined the relationships of serum IL-6 and hs-CRP levels with carotid plaque echogenicity by integrated backscatter (IBS) analysis, which was a quantitative method to evaluate echogenicity of atherosclerotic plaques, and found that higher IL-6, in addition to hs-CRP levels, appeared to be associated with lower echogenicity of carotid plaques, suggesting a link between inflammation and potential risk of plaques [29]. Similarly, Muscari et al. assessed the bifurcations of carotid and femoral arteries, maximum combined plaque/intima-media thickness (CPIMT max), and mean plaque density by ultrasound with densitometric analysis, and demonstrated that CRP was associated with high density femoral plaques, but no acute phase protein was independently associated with low density, potentially vulnerable plaque [30]. However, Liu et al. used high-resolution ultrasound in combination with evaluation of a scoring system (Crouse method) to detect the plaque score in the carotid artery, and proved that IMT, total plaque score, and soft and hard plaque scores in the carotid artery in the acute coronary syndrome group were significantly increased, and hs-CRP was positively related to IMT, total plaque score, and soft and hard plaque scores in the carotid artery, respectively [31].

The discrepancy may result from the different designs of study, data of population, and measure methods of B-mode ultrasound and hs-CRP; therefore, consistent results will benefit from improved standard measure methods and quality control.

As more and more important investigations address our hypotheses, and more standard measures and high quality controls are performed, the mechanism will be better elucidated and powerful evidence will be found in future.
Embolization arise from degenerative breakdown or thrombotic occlusion of complex plaques located in carotid arteries, and often lead to ischemic stroke.

Destabilization of plaque may attribute to results of matrix metalloproteinase, triglyceride-rich lipoproteins, macrophage Myeloperoxidase (MPO), P-selectin, IL-6, TNF-alpha, Cellular adhesion molecules (CAMs), etc.

CRP may be important to cause rupture of plaque and intraplaque hemorrhage.

Some new vidiodensito-metric analysis of B-mode ultrasound make better qualitative analysis in the characterization of plaque, but present limited evidences of unstable plaque.

Electron-beam calcium scanning or magnetic resonance imaging also make better qualitative analysis in the characterization of plaque, but highly cost.

Screen for highly sensitive and specific markers of vulnerable plaque.

Screen for cost effective examination of carotid plaque.

hs-CRP has better sensitivity in the prediction of plaque stability.

vidiodensitometric analysis of B-mode ultrasound is better cost effective examination of carotid plaque.

(1) there is a possible association between inflammatory markers hs-CRP and character of morphology of carotid plaque in B-mode ultrasound imaging; (2) It may be feasible to joint effects of hs-CRP and characteristic morphology of carotid plaque for destabilization in the potential diagnostic use of B-mode ultrasound.

The advantage of this method may guide us to better describe and analysis of orientation, stability, and quantification of plaques. The findings may supply adequate evidence for clinical study in the prevention of ischemic stroke.

Figure 3. Schematic diagram
References


