Cold War Battle Against Hot Atherosclerotic Plaques

Gerard Pasterkamp, Dominique de Kleijn

Atherosclerotic disease develops over decades, which makes it difficult to study the temporal changes in remodeling processes during initiation, progression, and destabilization of vascular lesions. The mechanisms and current concepts of atherosclerotic plaque stabilization and destabilization in literature have mainly been based on human pathological observations. The natural history of advanced atherosclerotic disease progression is still unknown, although studies in genetically modified animals that spontaneously develop atherosclerosis have revealed new insights in the pathogenesis of the disease. We have to appreciate, however, that in these animal studies, the definition of the dependent variable (eg, plaque phenotype, stable or unstable) is often based on the concepts that have been obtained from postmortem human research.

There is a growing interest in the sequential events that result in the formation of an atherosclerotic plaque that is likely to rupture and acute luminal thrombosis. The plaque-related features that reflect progression and complication of atherosclerotic lesions could serve as surrogate measures for hard clinical endpoints in interventional studies. Based on the cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous cross-sectional pathological studies, plaques that are considered vulnerable are characterized by having a thin fibrous...
making inferences, the chosen methodology and patient selection merit careful consideration of which some have been discussed by the authors.

First, the outcome of the $^{14}$C assessment provides an average for the tissue that is being studied. The different compartments of the atherosclerotic tissues consist of cellular and noncellular material. Sometimes the cap overlying an atheroma consists of collagen fibers with a limited number of smooth muscle cells, whereas the latter cell type may be dominating in others. Also, inflammatory cells may be present or absent in different parts of the plaque. The cellularity of a plaque is likely to reflect the degree of fast tissue turnover and may influence the average aging of a tissue. Recent intraplaque bleeding may also have a strong impact on the average age of different plaque components. Therefore, the authors made the appropriate choice to consider the outcome of the $^{14}$C as a measure of tissue turnover and not just “age.”

Secondly, inferences from this study may be applicable to a specific patient domain. This study has been executed in a low number of samples and the older plaques, based on $^{14}$C levels, originated from patients who previously experienced amaurosis fugax or who were asymptomatic. It has been established that plaques obtained from symptomatic patients have different characteristics compared with asymptomatic plaques. Moreover, within the symptomatic group, plaques that give rise to amaurosis fugax share the same phenotypic characteristics as asymptomatic plaques, eg, are more fibrous and have lower levels of inflammatory cells and cytokines. Tissue turnover is expected to be accelerated in tissues where inflammation, intraplaque bleeding, and plaque rupture is likely to occur. Indeed, in the study by Gonçalves et al, plaque aging showed different results in the younger patient who had experienced stroke. We have previously demonstrated that the time between an event and surgery strongly affects plaque characteristics specifically in stroke patients compared with patients suffering from amaurosis fugax. Stroke is associated with significant plaque thrombosis that will accelerate local tissue repair and hence tissue turnover. For the understanding of natural developmental changes in plaque destabilization, it may therefore have been an advantage that asymptomatic patients were studied since after a thrombotic event it may not be possible to distinguish aged plaque components that are a cause or consequence of the acute event.

It is difficult to estimate the relevance of this study for the research field. The authors discuss that their results could explain why regression of atherosclerotic plaque size is rarely observed in cardiovascular intervention trials since a pharmacological intervention may not affect tissue components with a low level of remodeling. However, it could be argued that those components that most strongly affect plaque composition may not have a similar relative impact on the plaque mass and will therefore have less effect on plaque aging by measuring radiocarbon. For instance, the relative contribution of macrophages and proteases on plaque volume may be limited but they may still dominate a future phase of plaque destabilization. Theoretically, a relatively small difference in age between plaque components may originate from very recent subtle changes in destabilizing components.

The report by Gonçalves et al is one of the first that provides insight in temporal aspects of arterial plaque remodeling within humans. Their observations provide supportive evidence that, on average, plaque constituents are being rebuilt and restructured: a process that may take many years. To draw further conclusions, the results need to be reproduced in a larger study group.

Sources of Funding
Research performed by the authors is funded by the University Medical Centre Utrecht, Interuniversity Cardiology Institute of the Netherlands, EU KIP7, and public/private partnerships such as the Center for Translational Molecular Medicine initiative.

Disclosures
Both authors are consultants for Cavadis.

References

Key Words: natural history ■ atherosclerosis ■ vulnerable plaque ■ $^{14}$C
Cold War Battle Against Hot Atherosclerotic Plaques
Gerard Pasterkamp and Dominique de Kleijn

Circ Res. 2010;106:1017-1018
doi: 10.1161/CIRCRESAHA.110.217794

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/106/6/1017

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/