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 cap, large lipid pools, and a heavy inflammatory burden. These features are observed with high specificity and sensitivity in patients who died from a cardiovascular event. However, for prediction and diagnostic relevance, it is the predictive value that is more informative than specificity: given the characteristic of the plaque, how often will this characteristic be associated with the future occurrence of an event?

The need for surrogate measures of plaque progression with sufficient predictive value is evident. Better insight in the mechanisms leading to natural plaque progression will facilitate the discovery and selection of biomarkers that are required to demonstrate appropriate responsiveness to drug treatment. Furthermore, the search for biomarkers with high predictive value will help identify patients at high risk to reach statistical power in drug studies with lower patient numbers. Finally, for target selection with the objective to find drugs that stabilize atherosclerotic plaques, it is essential to discriminate between genes and proteins that are cause or consequence of the disease: something that is impossible in cross-sectional observational studies.

For these and other reasons, many efforts have been undertaken to select imaging modalities that reflect atherosclerotic disease progression that would allow patient stratification and identify those at high risk. To unravel the sequential events resulting in plaque thrombosis, clinical studies are being executed including multiple imaging modalities simultaneously in patients who underwent coronary catheterization procedures. In the Integrated Biomarker and Imaging Study (IBIS), for instance, the researchers executed serial imaging procedures as part of a randomized placebo controlled study. Imaging, biomarker, and biobank studies such as IBIS and PROSPECT, with multiple samplings and imaging procedures, will become increasingly important for the understanding of the mechanisms underlying natural acceleration of plaque growth toward a clinical syndrome and facilitate the selection of surrogate measures for progression of atherosclerotic disease.

In this issue of Circulation Research, Gonçalves et al used an original approach to understand how quickly atherosclerotic lesions undergo structural remodeling. They assessed $^{14}$C content in different regions of 5 atherosclerotic plaques. The technique of radiocarbon dating was developed by Willard Libby in 1949. Libby estimated the steady-state radioactivity concentration of exchangeable carbon-14 and was awarded the Nobel Prize in chemistry for this work. The $^{14}$C fraction is taken up by plants and declines after plants die or are consumed by other organisms (eg, humans or other animals); the decline, after being consumed, is at a fixed exponential rate because of the radioactive decay of $^{14}$C. In archeology, comparing the remaining $^{14}$C fraction of a sample to that expected from atmospheric $^{14}$C allows the age of the sample to be estimated. In medical science, $^{14}$C dating is also applied making use of the fact that nuclear testing took place during the cold war in the 1950s and 1960s. These nuclear tests resulted in a fast increase in $^{14}$C in the atmosphere and, because of diffusion, the concentration of $^{14}$C decreased rapidly. Thus, whereas in archeology, one makes use of the half-life of $^{14}$C and a near constant value of $^{14}$C in the atmosphere, medical scientists such as Gonçalves et al make use of the rapid increase and decline of $^{14}$C concentrations in the atmosphere to age human biological specimen: the same tool but different concepts to age a material of interest.

Based on the $^{14}$C levels in different parts of the atherosclerotic plaques, the authors describe that the average turnover of the different plaque compartments may take many years. They found a younger age for caps of the plaques compared with the core of the plaque and calcified regions.

The approach is original and, although the patient numbers are small, the observations are of interest. However, before
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 pharmaceutical 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.

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