Heart aging measured with coronary artery calcium scoring and cardiovascular risk assessment algorithms in HIV infected patients

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\begin{abstract}
Many sources have highlighted the high incidence of premature cardiovascular events in HIV infected patients. This raises the suspicion of an accelerated aging of the vascular system in this disease characterized by chronic systemic subliminal inflammation and immune dysregulation. Unfortunately all currently available risk assessment algorithms based on traditional risk factors, and even those containing more HIV-specific factors, fail to accurately predict risk in a large proportion of patients. In the general population several models have implemented imaging data to refine risk assessment, and the concept of vascular aging has been of value in improving the performance of these algorithms. It is expected that HIV patients may benefit from a similar approach as it becomes clearer that vascular imaging provides valuable prognostic information in this patient category.
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\section*{Introduction}

Aging is a relative concept: it progresses at different rates in individuals of different sex and race. One of the principal manifestations of aging is atherosclerosis and its complications. It is reported that Dr. Osler once said: “you are as old as your vessels are.” Hence the vascular age of an individual does not necessarily match the chronological age. Whether HIV infection accelerates or accentuates atherosclerosis development is a matter of debate, but it is a well-known fact that patients affected by HIV suffer a disproportionately higher rate of cardiovascular events compared to their counterparts of similar age and sex.\textsuperscript{1} In this sense, therefore, they age faster than other people of similar social status and with a similar risk profile. Can the process be detected and quantified? And can it be slowed in order to reduce the probability of an event? These questions could also be phrased as: can accurate cardiovascular risk stratification be performed in HIV patients? This is of paramount importance if preventive therapies reduce cardiovascular risk should be implemented in HIV. In this article we review in brief the utilization of computed tomography imaging in the general population and HIV patients to assess vascular age and we discuss the accuracy of risk stratification algorithms in the HIV population.

The concept of vascular age

Computed tomography imaging has been used for almost 3 decades to assess the presence and quantify the extent of coronary artery calcium.\textsuperscript{2} CAC is a reliable marker of atherosclerosis as it is present in approximately 90–95% of the atherosclerotic plaques causing obstruction of the coronary artery lumen, although it is also present in the majority of non-obstructive plaques.\textsuperscript{3} Its utility as a tool to assess risk of cardiovascular events and all-cause death has been extensively studied and validated in the general population and several races.\textsuperscript{3-5} In fact, CAC provides incremental prognostic utility beyond risk factors to predict cardiovascular events.\textsuperscript{6-8} Since cardiovascular disease remains the primary cause of morbidity and mortality among western populations,\textsuperscript{9} the health status of the cardiovascular system of an individual is very likely to affect the outcome of that person. In a seminal publication, Raggi et al.\textsuperscript{10} demonstrated that high CAC score percentiles predicted the occurrence of an acute myocardial infarction better the Framingham risk score and more accurately than the absolute CAC scores. Percentiles of CAC scores were calculated starting from a population of 10,377 asymptomatic subjects from middle Tennessee free of known coronary artery disease. A high percentile in a person submitted to CAC screening suggests that the accumulation of atherosclerotic plaques was accelerated in that person compared to subjects of the same age.
and sex. Hence, by showing that a high percentile is predictive of an event, Raggi et al.\textsuperscript{10} showed that the vascular age of patients suffering a myocardial infarction was greater than their chronological age. In a subsequent analysis Shaw et al.\textsuperscript{11}, demonstrated that a CAC score $> 400$ (Agatston units) conferred a risk as large as 30 y of life loss, while a CAC of 10 or lower reduced the age of a 70 year-old individual by about 10 y. Hence, in a probability estimate, a young person with a CAC score $> 400$ has a life expectancy 30 y shorter than predicted, while an older patient may expect to live 10 y longer than predicted based on her/his chronological age. Furthermore, CAC allowed reclassification of risk (i.e., assignment to a risk category different from the one assessed by means of traditional risk factors) in 45-55% of cases. While over 90% of the 10,377 subjects used to derive traditional risk factors) in 45-55% of cases. While over 90% of the 10,377 subjects used to derive the initial CAC score percentiles were Caucasian,\textsuperscript{10} Bild et al.\textsuperscript{12} and McClellan et al.\textsuperscript{13} published tables of percentiles for patients of different ethnic background based on patients enrolled in the Multi Ethnic Study of Atherosclerosis (MESA). The MESA investigators enrolled 6,814 individuals among 4 different ethnicities: Caucasian, Hispanic, Chinese and Black and performed CT scanning on all of them. This offered an opportunity to derive normative tables of CAC scores to be used in different ethnicities. Sirineni et al.\textsuperscript{14} were able to use these normative tables of CAC to estimate the vascular age of an asymptomatic patient of different ethnic background. Using their calculator a CAC score of 55 corresponds to a vascular age of 63, 72, 75 and 59 for a White, Black, Chinese or Hispanic man. For women of the same ethnic background a CAC score of 55 would bring the vascular age to 76, 81, greater than 85 and 81 y respectively.\textsuperscript{14} The MESA investigators were able to corroborate these assumptions by comparing the utility of chronological and vascular age to predict incident cardiovascular events.\textsuperscript{15} This approach makes the interpretation of the significance of CAC screening results much easier for patients and physicians alike. In this light, a 45 y old Caucasian man with a CAC score of 55 has a vascular system of 63 y of age. This is a very clear message for the patient that can get an immediate appreciation of the impact of his screening results. The concept of vascular age has modernly been imported in algorithms used to model risk of atherosclerotic events in the general population,\textsuperscript{5,16} thus helping to reclassify risk in a substantial number of patients.

**Coronary artery calcium to assess vascular age in HIV**

The utility of CAC as a useful tool to assess cardiovascular risk in HIV infected patients has long been debated, although its validity is slowly emerging. In a recent publication,\textsuperscript{17} both CAC and epicardial adipose tissue, a marker of visceral inflammation,\textsuperscript{18} were independent predictors of hard events (myocardial infarction and death) in a prospective cohort of 843 HIV infected patients. Using concepts similar to those applied in the general population Guaraldi et al.\textsuperscript{19} estimated the vascular age of 400 HIV infected patients without known cardiovascular disease and receiving stable antiretroviral therapy (ART). Among these relatively young patients (mean age 48 years), 162 had an increased vascular age based on extent of CAC, and their biological age was as much as 15 y older than their chronological age. Of interest, there was a positive association between the increased biological age of these patients and the recovery CD4+ count. This suggested a hypothetical implication of CD4+ T-lymphocytes in the pathogenesis of atherosclerosis. In fact, experimental protocols demonstrated that type-1 T-helper lymphocytes are primarily responsible for shuttling messages between inflammatory cells and activating macrophages in the core of an atherosclerotic plaque. The increase in CD4+ induced by ART is also associated with an increase in serum levels of interferon-γ, the principal cytokine released by CD4+. Interferon-γ is also known to be highly atherogenic. It is conceivable, therefore, that reconstituted CD4+ may be dysfunctional or aging prematurely, and develop a pro-atherosclerotic activity rather than defensive functions.

**Other markers of vascular aging**

Telomeres protect against chromosomal end damage and shorten with each cell division. Telomere shortening, therefore, has long been regarded as a marker of aging of human cells.\textsuperscript{20-22} Hunt et al.\textsuperscript{23} performed Southern blot analysis of leukocyte telomere length and chest CT for CAC scoring in 3169 patients enrolled in the National Heart, Lung, and Blood Institute Family Heart Study. They showed a strong association between telomere shortening and CAC, independently of age, race and sex, in rheumatoid arthritis a chronic inflammatory disease for several aspects similar to HIV.

An intriguing observation seems common to both disease states. Ormseth et al.\textsuperscript{25} recently showed an association of leukocytes telomere length and CAC, independent of age, race and sex, in rheumatoid arthritis. Similarly, Zanet et al.\textsuperscript{26} concluded...
that there is no association between telomere length and duration of HIV infection, ART or degree of inflammation. Both authors speculated that factors more strictly related to the disease under analysis other than chronic inflammation may be responsible the shorter telomere length. These may include altered telomerase activity, deficiency of other DNA repair mechanisms and/or genetic factors.

Taken together, it would appear that there is at least a moderately strong association between markers of biological and vascular aging in the general population. There are currently no publications in HIV infected patients to show a relationship between CAC and telomere length. Nonetheless a few parallel observations patients to show a relationship between CAC and telomere length.28 Of note, both an enhanced activation of the immune system, chronic inflammation and greater regulatory cell numbers in the circulation are believed to have any hard events to test the validity of their assertion. Furthermore, they did not compare the algorithms designed for the general population with the DAD algorithm that takes into consideration the contribution of anti-retroviral therapies to cardiovascular disease development specifically in HIV infected patients. In this light, Guaraldi et al.34 compared the ability of all 3 algorithms to predict risk of myocardial infarction, stroke or death in 2550 HIV infected patients followed for an average of 6.5 y from the time of screening. During follow-up the investigators recorded 67 non-fatal myocardial infarctions and 2 cardiovascular deaths for an event rate of \( \sim 4/1,000 \) patient-years. The 3 algorithms performed almost equally in predicting the occurrence of events; about 2/3 of patients who suffered an event during follow-up were classified as high-risk by any of the 3 models. On the other hand, about one third of patients with events were mis-diagnosed as low risk. In a test of net reclassification improvement the ASCVD and DAD algorithms were slightly superior at classifying patients at low-risk compared to FRS, while FRS was marginally better than the other 2 at identifying patients who will suffer an event. In summary, all 3 algorithms performed in an unsatisfactory manner and were disappointingly weak at identifying patients at risk, hence failing their primary purpose. There is a potential small advantage in using the ASCVD or DAD models over the FRS: these models may offer a chance to identify patients intolerant of less noxious ART in whom ART regimen with potential adverse cardiovascular effects could be used. This is obviously a speculation and its formal verification is unlikely to be pursued, although the practicing physician may find it helpful in taking the next therapeutic step. With a similar approach, Crane et al.,35 compared the ability to predict a myocardial infarction using 3 risk score algorithms developed for the general population (FRS, ATP3 and ASCVD) and the HIV-specific D:A:D score in 11,338 HIV-infected patients. They used data collected by the Center for AIDS Research Network of Integrated Clinical System (CNICS) and observed 243 incident myocardial infarctions. Myocardial infarctions were classified as type 1 if they resulted from a spontaneous rupture of an atherosclerotic plaque, and type 2 if they occurred as a result of oxygen demand/supply mismatch due to a variety of causes including sepsis. ASCVD showed a significantly better AUC than other scores for all infarctions and for type 2 infarctions including the D:A:D (p < 0.001), and was non-inferior to the others for prediction of type 1 myocardial infarctions. Once again the D:A:D algorithm was not superior to other non-HIV specific algorithms.

In view of the weakness of the currently available algorithms, atherosclerosis imaging may provide useful applications in risk assessment for both HIV-infected and non-HIV infected patients. Future research should focus on developing more effective risk assessment tools for individuals with chronic diseases such as HIV.
additional information to refine risk stratification. Indeed, this has already been demonstrated and recommended in the general population.36

Several pieces of evidence point at the importance of immunological deregulation and lymphocyte senescence in predisposing HIV infected patients to cardiovascular as well as other non-AIDS related events. A reduction in cardiovascular events was reported in the SMART (Strategies for Management of Antiretroviral Therapy) study, where continuous antiretroviral therapy was used in individuals with a CD4+ cell count below 350/μL.37 In contrast, early implementation of a CD4+ cell count–guided antiretroviral therapy did not reduce cardiovascular events in the START (Strategic Timing of Antiretroviral Treatment) study despite a reduction in AIDS-related events.38 However, relatively few CVD events were observed among antiretroviral therapy-naive individuals.38 Several authors have reported an increased rate of AIDS-related and non-AIDS related events (cardiovascular events among them) in patients with reduced CD4/CD8 counts.39–42 In one case, the CD4/CD8 ratio was associated with an increase in events independent of the current CD4 count.43

Taken together, these data suggest that suppressive antiretroviral therapy based on stricter CD4+ cell count thresholds may result in decreased cardiovascular event rates, particularly as newer antiretroviral regimens with fewer metabolic effects are utilized. However, this prediction awaits further confirmation in future randomized trials. To verify whether statins reduce the elevated risk seen in HIV infected patients, the National Institutes of Health (NIH) recently launched a large trial to assess the efficacy of pitavastatin in primary prevention of cardiovascular disease in this population.44 The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial was launched in April 2015 and will enroll 6,500 HIV-infected patients without prior history of cardiovascular disease. Participants will be randomly assigned to receive pitavastatin 4 mg daily or a placebo for an average of 4 y. The results of the REPRIEVE trial (expected in 5–6 y from today) may greatly affect the approach to cardiovascular risk prevention in HIV-infected patients.

Conclusions

Atherosclerosis is one of the most definitive markers of aging. Imaging has helped define the impact of risk factors on vascular aging in patients from the general population. Currently, CAC scores are being utilized in several models to refine risk assessment of cardiovascular disease in the general population. Although in its early stages of development, atherosclerosis imaging stands to offer a substantial advantage for risk stratification in HIV infected patients as well. In fact, CAC screening has already highlighted the substantial impact of HIV infection with its attendant complications on the vascular aging of these patients. There is a definite need to develop better risk prediction models in HIV patients and vascular imaging may offer the additional necessary information to refine the existing or future models. Other biomarkers of risk can be found in the immune senescence of native and reconstituted lymphocytes. Ongoing clinical trials may provide information of vital importance to improve the cardiovascular outcome of HIV-infected patients.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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