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Review

Noninvasive Cardiovascular Imaging: Emergence of a Powerful Tool for Early Identification of Cardiovascular Risk in People Living With HIV

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ABSTRACT

Antiretroviral therapy (ART) has been pivotal in prolonging the lifespan of people living with HIV (PLWH). However, this also simultaneously increases their risk of cardiovascular disease (CVD) either related to ART, aging, hypertension, immunosenescence, inflammation, immune activation, or other comorbidities. Although the use of risk markers has greatly enhanced the field of cardiovascular (CV) medicine and improved the prognosis and early diagnosis in the general population, this strategy has not been clearly elucidated in PLWH. Developing accurate risk algorithms for PLWH requires an innate understanding of mechanistic factors influencing their risks. Early identification of CV risk will significantly enhance the prospects of PLWH living longer and relatively healthily. Herein, we discuss the use of multimodality noninvasive CV imaging as robust markers for ameliorating CV risk. The ability to prognosticate CV risk and hence prevent CV events in PLWH would represent an important advance in CV medicine, allowing precise detection and early institution of preventative strategies. Using novel CV imaging modalities and strategies would have a positive impact on precision medicine in this patient cohort.

RÉSUMÉ

La thérapie antirétrovirale (TAR) joue un rôle central dans la prolongation de l'espérance de vie des personnes vivant avec le VIH. Toutefois, ce traitement a également pour effet d'accroître le risque de maladie cardiovasculaire (CV) dans cette population, que ce soit en lien avec la TAR ou avec le vieillissement, l'hypertension, l'immunosénescence, l'inflammation, l'activation du système immunitaire ou d'autres affections concomitantes. Si le recours aux marqueurs de risques a permis un rehaussement important du domaine de la médecine CV et une amélioration du pronostic et du diagnostic précoce dans la population générale, cette stratégie n'a pas encore fait ses preuves chez les personnes vivant avec le VIH. Pour élaborer des algorithmes de risque exacts pour les personnes vivant avec le VIH, il faut avoir une connaissance approfondie des facteurs mécanistiques influençant les risques auxquels cette population est exposée. La reconnaissance précoce des risques CV augmentera de façon marquée la probabilité pour les personnes vivant avec le VIH de vivre plus longtemps et, relativement, en meilleure santé. Dans le présent article, nous abordons l'utilisation de l'imagerie CV multimodale non invasive comme marqueur robuste pour réduire le risque CV. La capacité de pronostiquer le risque CV et, par conséquent, de prévenir les événements CV chez les personnes vivant avec le VIH constituerait une avancée importante en médecine CV, en permettant une détection précise et l'instauration précoce de stratégies à visée préventive. L'utilisation des nouvelles modalités et stratégies d'imagerie CV pourrait avoir des répercussions positives sur la médecine de précision dans cette cohorte de patients.

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See page 267 for disclosure information.

The advent of effective antiretroviral therapy (ART) has dramatically altered the course of the human immunodeficiency virus (HIV) and prolonged life for approximately 37 million people living with HIV (PLWH) globally.[1] Although ART suppresses viremia to undetectable levels and improves immune function, its widespread use has been associated with

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undesirable effects such as dyslipidemia and lipodystrophy.[1] These observed effects have led to higher prevalence of cardiovascular disease (CVD), which is one of the main causes of morbidity and mortality in PLWH. Risk of CVD in PLWH persists even after adjusting for traditional cardiovascular (CV) risk factors.[2] Risks relating to vascular dysfunction, atherosclerosis, coronary artery disease (CAD), heart failure (HF), and hypertension are increased in PLWH compared with the general population.[3] Other mechanistic factors for these observations are likely to be multifactorial and include increased prevalence of comorbidities such as hepatitis C virus, inherent immune activation, and dysregulation of the immune system.[2,3]

Current CV risk algorithms developed for use in the general population may not reflect true CV risk in the HIV population. The performance of Framingham Coronary Heart Disease, Framingham Atherosclerotic Cardiovascular Disease (ASCVD), and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk equations assessed in a male HIV-positive—mostly ART-treated—cohort reported systematic underestimation of CV risk.[4] HIV-specific algorithms have also been developed[5] and recently updated to include $CD4^+$ T-cell counts, exposure to protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTI), and current use of abacavir,[6] although their application in this population has been controversial.[7]

There is a pressing need for novel strategies to identify at-risk patients with HIV accurately and develop effective approaches to CVD risk reduction, with a paradigm shift toward precision medicine. This shift is further buoyed by advances in technology with the arrival of advanced analytics and big data applications in health care with regard to HIV and CVD.[8,9] Cardiac and vascular imaging provides sophisticated measures of many pathological processes related to CV disease including inflammation, the presence and quantification of CAD, identification of "vulnerable or high-risk" plaques prone to rupture, and the presence of microvascular disease.[10]

In this review article, we discuss how multimodality CV imaging can be used as a powerful tool in providing new insights into the pathogenesis of accelerated CVD seen in the HIV-positive population.

Vascular Imaging

Carotid artery imaging

Inherent inflammation due to HIV infection has been implicated in the pathogenesis of atherosclerosis in which interaction of immune mechanisms with metabolic risk factors leads to development and propagation of atherosclerotic lesions. PLWH display persistent inflammation with chronic monocyte activation, which may contribute to vascular dysfunction, modulating the risk of atherosclerosis and subsequent CV events.[11] There is a need to establish specific guidelines for management of CVD in PLWH. Ascertaining surrogate markers of atherosclerosis will allow accurate prediction of future CV events in the HIV-positive population.

B-mode carotid ultrasound is a noninvasive method for measuring surrogate markers of atherosclerosis such as carotid intima-media thickness (CIMT) and carotid plaque.[12] HIV infection has been associated with higher rates of preclinical atherosclerosis as measured by surrogate markers—that is, CIMT and carotid plaque—similar to that observed for smoking.[13] Hsue et al. described a dramatically increased rate of CIMT progression at 1 year in HIV-positive patients compared with HIV-negative age- and sex-matched controls.[14] These results were further confirmed after a median follow-up of 2.4 years; HIV-positive participants without carotid plaque on their baseline scan had significantly higher rates of incident plaque on follow-up when compared with controls (44% vs 2.8%), suggesting that HIV is associated with accelerated atherosclerosis.[13] Furthermore, in HIV-positive patients who did not have histories of clinical atherosclerosis, multivariate adjusted analysis found that over a follow-up period of 13.5 years, baseline CIMT and carotid plaque were independent predictors of all-cause mortality, whereas the ACC/AHA ASCVD risk scores were not.[15] HIV-positive persons followed-up over a period of 7 years were found to have significantly increased risk of new formation of carotid plaque compared with the HIV-negative cohort in a large longitudinal study.[16] Carotid ultrasound is a simple, low-cost, and noninvasive modality that can improve risk stratification in PLWH. However, further work is required because of conflicting results reported in previous studies. A longitudinal matched cohort study of patients with low CV risk profile found that over a 3-year follow-up period, neither HIV positivity nor protease inhibitor use contributed to the progression of CIMT.[17]

Recently, a retrospective study by Janjua et al. used contrast-enhanced computed tomography (CT) to establish the rates and characteristics of carotid plaques (noncalcified) and high-risk plaques (HRPs—defined as plaques with spotty calcification or low attenuation) and their relationship to future CV events in a HIV population compared with HIV-negative controls followed-up over a median period of 3 years.[18] Multivariate analysis demonstrated that, in HIV-positive patients, the presence of any carotid plaque and HRP were associated with approximately 3 times increased risk for CV events. Although all subjects were free of known vascular disease, there were significant differences in the baseline characteristics between groups; 60% of HIV-positive patients had $\geq$ 1 traditional CV risk factors compared with 64% of controls who did not have any identifiable traditional CV risk factors. Similarly, nontraditional risk factors for carotid plaque, such as hepatitis C and exposure to cocaine, were significantly higher in the HIV-positive group compared with the control group.[19] Notwithstanding these limitations, identification of carotid plaque by CT in PLWH is an imaging biomarker that may improve CV risk stratification. The applicability of CT as a general screening tool, however, is limited by its necessary exposure to ionizing radiation and potentially nephrotoxic contrast agents. Accuracy in identification of HRP requires higher resolution acquisitions, equating to increasing exposure to radiation. Consequently, alternative modalities, such as innovative ultrasound techniques and magnetic resonance imaging (MRI), are likely to be more favoured instead. Rose et al. used carotid MRI to compare rates of atherosclerosis between a HIV-positive group on stable ART with suppressed viremia and low traditional CV risk with that of a similar profile HIV-negative control group.[20] The wall/outer-wall ratio (an index of vascular thickening) was found to be significantly elevated in HIV-positive patients compared with controls. Further studies

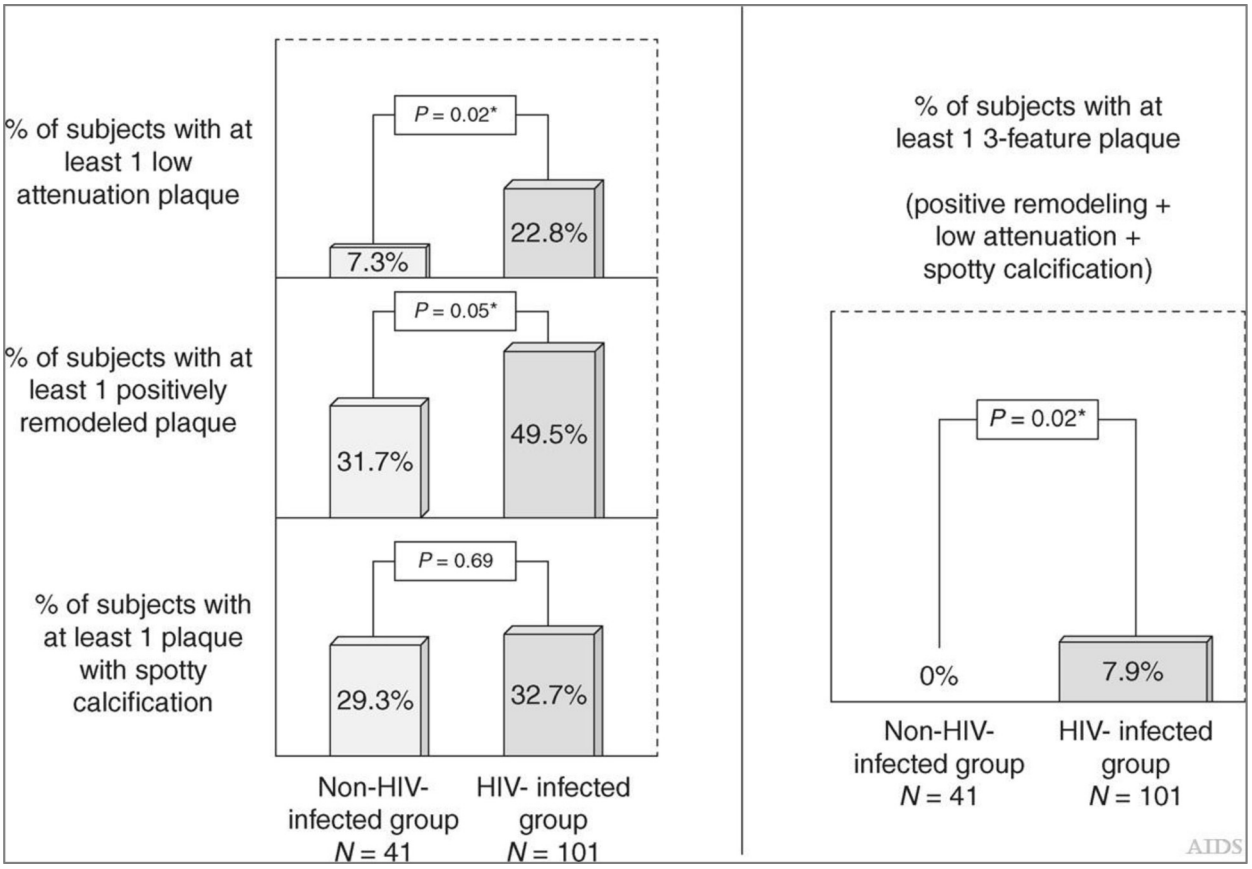

Figure 1. Prevalence of HIV-infected and non—HIV-infected persons with at least 1 coronary atherosclerotic plaque positive for select vulnerability features. Adapted from Zanni et al.[35] with permission from Wolters Kluwer Health, Inc.

are required to determine whether this technique can provide incremental CV risk stratification in PLWH.

Aortic and coronary artery imaging

HIV infection confers approximately 1.5- to 2-fold increased risk of developing CAD in comparison with HIV-negative persons.[2,21-25] Coronary artery calcium (CAC) score on noncontrast CT is a strong predictor of CAD and provides incremental risk stratification over traditional risk factors in general population.[26] Similarly, in PLWH the utility of an increased CAC score to provide incremental risk stratification was demonstrated in a prospective observational study of 843 HIV-positive patients established on ART for at least 6 months. In the HIV cohort, a CAC score $\geq$ 100 was associated with 3.3 times increased odds of myocardial infarction or death—independent of age and gender—over a median follow-up of 2.8 years.[27]

Although the ability of high CAC scores to reclassify HIV-positive patients to a higher CV risk group appears robust and clinically useful, a more contentious issue is the use of low calcium scores to reclassify HIV-positive individuals to lower risk of future CV events. A potential limitation of CAC screening is that, by definition, it does not identify non-calcified plaque (NCP).[28] In the general population, for asymptomatic middle-aged persons, the prevalence of exclusively NCP is approximately 4%, and the risk of future CV events in these people remains very low.[28] However, several studies point toward likely increased rates of NCP in HIV-positive patients compared with HIV-negative persons.[29] For example, Kristoffersen et al. reported that in 105 asymptomatic HIV-positive patients on stable ART without a history of CAD, 18% had evidence of a perfusion defect on myocardial perfusion imaging (MPI), and 42% of these had a CAC score of zero.[30] The prognostic significance of low or zero calcium scores in PLWH is therefore unclear, and further studies are needed in this regard.

Most cases of acute coronary syndrome (ACS) are precipitated by acute plaque rupture,[31] with the precursor lesion typically having a necrotic core covered with a relatively thin fibrous cap, which is infiltrated by large numbers of macrophages, commonly referred to as "vulnerable plaque."[32] Cardiac CT angiography (CCTA) is an established tool for assessing coronary plaque characteristics.[33] CCTA features of vulnerable plaque such as areas of low attenuation, spotty calcification, and positive vascular remodelling are associated with increased risk of ACS.[34] Zanni et al. compared 101 HIV-positive men (95% of whom were on ART with suppressed viremia) with 41 age-matched HIV-negative healthy controls and found that there was an increased prevalence of low attenuation plaque, positively remodelled plaque, as well as "high-risk, 3—feature-positive plaque" (Figure 1).[35] Increased rates of vulnerable NCP could be a mechanism by which PLWH experience increased rates of ACS. A prospective study

outlined that increased levels of soluble CD163 was associated with increased NCP in asymptomatic HIV-positive patients with well-controlled levels of viremia. This relationship persisted even after adjusting for traditional CV risk factors, suggesting that chronic inflammation with resultant monocyte/macrophage activation may have a role in the pathogenesis of NCP formation in PLWH.[36]

The Multicenter AIDS cohort study described, for the first time, the association between HIV infection and increased incidence and progression of high-risk coronary plaque.[37] The authors performed baseline and follow up CCTAs on 253 HIV-positive men and 156 HIV-negative controls with a median interval of 4.5 years between scans. HIV-positive patients demonstrated a higher incidence of NCP, low attenuation, and mixed plaque with higher rates observed in men with viremia compared with those with suppressed viremia. Similarly, HIV-positive patients presenting with plaque at baseline had increased progression of NCP compared with HIV-negative cohort. This study highlights the importance of viremic control to reduce the progression of high-risk coronary plaque in HIV-positive patients. Table 1 is an overview of significant literature that has incorporated the use of CCTA in identifying risk of CVD in PLWH.[16,35,36,38-44]

Molecular imaging of CVD has significant utility in providing insight into the mechanistic factors of atherosclerosis at a cellular level. ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography CT (PET/CT) can be reliably used to evaluate aortic vascular inflammation associated with atherosclerosis.[45] Importantly, arterial inflammation on PET/CT (seen as increased FDG uptake) has been shown to improve risk stratification beyond Framingham risk score,[46] a point that has particular relevance to the HIV population for whom the prevalence of CV disease extends beyond what can be predicted by traditional risk assessment tools.[47] Using FDG PET/CT, Subramanian et al. demonstrated an increased arterial inflammation in the group of relatively young HIV-positive patients with low Framingham risk score and well-controlled disease.[48] The same group subsequently demonstrated that PET evidence of arterial inflammation was associated with high-risk coronary plaque morphology in HIV-positive patients with well-controlled viremia and low Framingham risk score.[49] In a relatively small study of 12 patients with ART-naive HIV, Zanni et al. did not identify a change in the FDG-PET–determined arterial inflammation in the 6 months following commencement of ART.[50] However, any significant inferences from this study has to be cautioned, owing to the low number of subjects followed over a short period. More studies are needed to demonstrate the potential utility of monitoring effects of reducing vascular inflammation in patients with HIV. Nevertheless, arterial inflammation imaging by PET/CT has improved our understanding of factors associated with accelerated atherosclerosis in PLWH.

Although there is a wealth of literature and evidence pertaining to CCTA and FDG PET/CT as screening tools in the general population, attending physicians providing care for PLWH need to be aware of the difficulties with extrapolating evidence derived from the general population. In PLWH, chronic inflammation and immune activation affects their arterial biology, and mechanisms effecting development of atherosclerotic lesions greatly differ from the general population.

Cardiac Imaging

The pattern and frequency of HF in HIV is determined primarily by geographic location and access to ART. Echocardiographic findings that were common in the early years of the HIV epidemic included left ventricular systolic dysfunction and pericardial effusion. Such presentations still occur in sub-Saharan Africa, where availability of ART is limited and progression to advanced AIDS remains a reality.[51] In industrialized nations, where ART availability is widespread, there has been a dramatic shift in the epidemiology of HIV-associated cardiomyopathy where asymptomatic mild left ventricular systolic or diastolic dysfunction now predominates.[51] Indeed, a new paradigm postulates that systemic proinflammatory state induced by comorbidities, such as obesity and diabetes, plays a key role in effecting diastolic dysfunction.[52] Given that HIV infection is characterized by chronic inflammation, considerable efforts have been made to ascertain rates of diastolic dysfunction in PLWH.[53,54] In the Veterans Aging Cohort Study, subjects free from baseline CVD[3] were observed over a median follow-up period of 7.1 years. After adjusting for confounders, HIV-positive patients had significantly increased risk of HF associated with both reduced as well as preserved ejection fraction. Although such large-scale observational studies provide contemporary data on the epidemiology of HF in the post-ART era, determination of the factors associated with the increased rates of diastolic dysfunction warrants further investigation.[55]

Rates of pulmonary artery hypertension in HIV-positive patients are several-fold higher than in the general population; however, the overall prevalence of pulmonary artery hypertension associated with HIV is low in the post-ART era, at approximately 0.46%.[56] Accordingly, recently published guidelines do not advocate for routine screening of asymptomatic HIV-positive patients for pulmonary artery hypertension, whereas comprehensive transthoracic echocardiography is considered to be an appropriate first-line investigation in symptomatic people.[56]

There is a dearth of evidence in the use of stress echocardiography (SE) as a CAD risk-stratification tool in PLWH. Wever Pinzon et al. studied 311 HIV-positive patients with either known or suspected CAD, who underwent either exercise or dobutamine SE.[57] Twenty-six percent of patients had abnormal SE at baseline. Over a follow-up period of 2.9 ± 1.9 years, PLWH with normal SE had a benign prognosis, with an event rate comparable with the general population ($< 1\%$ per year). The same group also showed that the presence of inotropic contractile reserve during dobutamine SE predicted improvement in left ventricular ejection fraction in patients with HIV-associated cardiomyopathy.[58]

PLWH are at increased risk of HF even in the absence of CAD, although the mechanisms for increased risk are incompletely understood.[59] The pathogenesis of this myocardial dysfunction is not yet fully elucidated; however, recent data from cardiovascular magnetic resonance (CMR) studies have proven informative. Comprehensive CMR with novel techniques, such as T1 mapping and magnetic resonance spectroscopy, permit simultaneous evaluation of

Table 1. Overview of current research involving cardiac computed tomography angiography (CCTA) in HIV-positive cohorts

Study	Study design	Population		Imaging technique	Main findings
		HIV positive	HIV negative		
Fitch (2010)[38]	Cross-sectional	2 HIV positive groups (men) • HIV-positive but with presence of MS (n = 27) • HIV-positive without known cardiac disease or MS (n = 87)	n = 40 Without known cardiac disease	64-slice CT-scanner	HIV-positive + MS subjects and HIV-positive controls both demonstrated increased prevalence of plaque and increased number of NCP segments compared to HIV negative group
Lo (2010)[41]	Cross-sectional	n = 78 (men)	n = 32 Similar Framingham 10-year risk	64-slice CT scanner	HIV-positive, compared with controls demonstrated • Higher prevalence of coronary atherosclerosis • Higher coronary plaque volume • Greater number of coronary segments with plaque
Burdo (2011)[36]	Cross-sectional	n = 102 (men) Without known cardiac disease	n = 41 Equivalent CV risk factors	64-slice CT scanner	HIV-positive, compared to controls, had • Significantly increased levels of sCD163 • Increased presence of coronary plaque • sCD163 was positively associated with number of coronary segments with NCP in HIV infected individuals with undetectable HIV RNA levels
Zanni (2013)[35]	Cross-sectional	n = 102 (men) Without known cardiac disease	n = 41 Matched for CV risk factors	64-slice CT scanner	HIV-positive, as compared to controls, had • Higher number of LAP and PR plaque per patient • Higher prevalence of individuals with at least one of: • LAP • PR plaque • High-risk 3-feature* plaque
Post (2014)[43]	Cross-sectional	n = 450 (men) No previous history of cardiac surgery or percutaneous coronary intervention	n = 309	64-slice CT or 320-row multi-detector CT	HIV-positive men, compared to controls, had • Higher adjusted prevalence of NCP • Greater extent of NCP
Miller (2015)[42]	Cross-sectional	n = 453 (men)	n = 311	64-slice CT or 320-row CT	After demographic adjustment, HIV-positive men, compared with controls had • Twice the odds of positive remodelling, which persisted after CAD risk factor adjustment
Lai (2016)[40]	Cross-sectional	n = 787 African American adults	n = 470 African American adults	64-slice or 128-slice CT scanner	• No evidence of an independent association between HIV-seropositivity and subclinical coronary atherosclerosis • Duration of ART use modified the overall association between HIV infection and subclinical coronary atherosclerosis • The magnitude of long-term ART exposure-associated risk depended on cocaine use status
Foldyna (2018)[39]	Cross-sectional	n = 97 (men) n = 48 (women)	NA	64-slice CT scanner	HIV-positive women, compared with HIV-positive men, had • lower prevalence of any subclinical coronary atherosclerotic plaque • Lower number of segments with plaque • Lower prevalence of high-risk PR plaque • Lower number of PR plaque segments

Table 1. Continued.

Study	Study design	Population		Imaging technique	Main findings
		HIV positive	HIV negative		
Tarr (2018)[44]	Cross-sectional	n = 367 (men) n = 61 (women) No documented CAD	n = 219 (men) n = 57 (women) Similar Framingham risk scores	64-slice or 256-slice CT scanner	HIV-positive individuals and HIV-negative controls demonstrated a similar degree of NCP/mixed plaque and high-risk plaque
Post (2018)[37]	Longitudinal	n = 253 (men) 70% of HIV seropositive subjects were aviremic during the interval	n =156	Baseline and follow up CCTA were performed with median intescan interval of 4.5 years	HIV-positive individuals without baseline plaque had greater incidence of NCP, LAP, and mixed plaque compared with controls In individuals with the greatest NCP volume change, the adjusted increases were significantly higher among HIV-positive compared with HIV-negative controls

CAD, coronary artery disease; CCTA, cardiac computed tomography angiography; CT, computed tomography; LAP, low attenuation plaque; MS, metabolic syndrome; NCP, noncalcified plaque; PR, positive remodelling.

*"High-risk 3-feature plaque" defined as: LAP + spotty calcification + PR.

myocardial contractile function and myocardial tissue composition (including myocardial fibrosis, lipid metabolism, and edema) and has excellent utility in the detection of subclinical changes in multiple structural, functional, and biochemical myocardial variables.[60] Holloway et al. performed the first comprehensive study using CMR to establish the prevalence of myocardial abnormalities in an asymptomatic, contemporary ART-treated HIV-positive cohort without a history of CVD.[61] When compared with age-matched controls, HIV-positive patients demonstrated increased rates of cardiac steatosis (associated with diastolic dysfunction) with 47% increased median myocardial lipid levels.[61] The second pertinent finding from this study was that late gadolinium enhancement (LGE) CMR showed evidence of patchy myocardial fibrosis with a basal inferolateral wall predominance in 76% of the HIV-positive group compared with 13% of HIV-negative controls.[61] The authors note that this pattern of fibrosis can be the consequence of previous myocarditis. Of note, the frequency of fibrosis observed on CMR appears similar to results from autopsy studies at the time of the HIV epidemic, which describes focal mild myocarditis as a prevalent finding in patients dying of AIDS.[62] T1 mapping allows the measurement of extracellular volume (ECV) and has advantage over LGE CMR imaging, as the latter can only identify pathology in which there is a regional aggregation of abnormal myocardium.[63] ECV quantification has a close correlation with diffuse interstitial myocardial fibrosis on histology and can be considered to be a CMR biomarker of myocardial fibrosis.[60] Thiara et al. reported that levels of intramyocardial lipid and indices of myocardial fibrosis (as determined by T1 mapping of ECV) were both increased in 95 HIV-positive patients when compared with 30 HIV-negative matched controls.[64] Several studies have corroborated that visceral adipose tissue volume was found to be an independent predictor of intramyocardial lipid levels, suggesting that metabolic effects of visceral fat may modulate altered myocardial lipid composition in HIV-positive patients.[65] Furthermore, the authors reported a positive correlation between myocardial fibrosis and intramyocardial lipid levels but not with duration of ART or degree of viral suppression, suggesting that cardiac fibrosis may be sequelae of metabolic effects of HIV.[65]

A recent small study reported a novel finding of increased CMR markers of myocardial inflammation in 28 asymptomatic well-controlled HIV-positive patients compared with 22 HIV-negative controls.[66] In line with previous larger studies,[61] HIV-positive patients also had evidence of patchy fibrosis on LGE compared with controls, with a preponderance for midventricular and basal inferolateral walls.[66] Ntusi et al. extended Holloway's initial studies[61] in this area by including 66 new HIV-positive patients and added to the growing evidence to suggest that in well-treated HIV infection, there are significant alterations in myocardial tissue characterization as well as structural and functional myocardial changes (Figure 2).[67] Specifically, they reported that in 103 HIV-positive patients, compared with 92 HIV-negative controls, there was 7% increased myocardial mass, 29% lower peak diastolic strain rate, and increased native T1 values. Furthermore, observation of pericardial effusions was much more frequent in HIV-positive patients (more than 50%) compared with HIV-negative controls, suggesting that this increased rate of small pericardial effusions, together with evidence of increased myocardial fibrosis and edema, are likely sequelae of a chronic inflammatory state.[67]

Unabated chronic inflammation from any cause has the potential to cause tissue damage by means of fibrosis. CMR has helped to provide significant evidence that myocardium is also affected by fibrosis in HIV-positive persons. It is becoming increasingly clear from CMR studies that, in addition to viral suppression, strategies to avoid the deleterious effects of chronic inflammation are required to restore health for PLWH. Further insight in this respect is anticipated from the recently announced Characterizing Heart Function on Antiretroviral Therapy Study, which aims to determine mechanistic factors of diastolic dysfunction in HIV-positive patients through analysis of circulating biomarkers for myocardial stress, inflammation, immune activation, echocardiography, and myocardial fibrosis as determined by CMR.[55]

In the asymptomatic HIV population, previous studies have evaluated the prevalence of myocardial perfusion

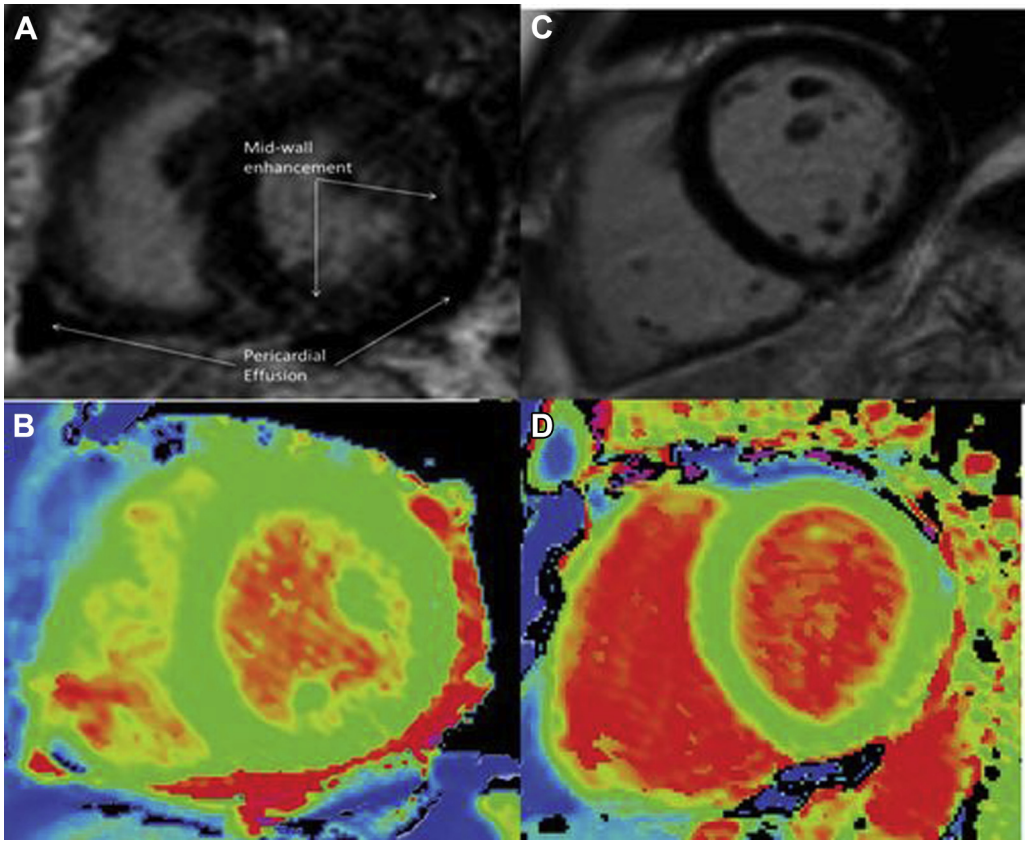

Figure 2. Pericardial effusions, late-gadolinium enhancement, and native T1 mapping in HIV-infected patients and controls. (**A**) Cine image from a patient with HIV, with **arrows** demonstrating mid-wall fibrosis and a small pericardial effusion, compared with a normal control subject (**C**). (**B**) The corresponding T1 map, from a patient with HIV, with associated pericardial effusion (**red**) compared with a normal control subject (**D**). Adapted from Ntusi et al.[67] with permission from Wolters Kluwer Health, Inc.

abnormalities on single-photon emission computed tomography (SPECT). Catzin-Kuhlmann et al. used gated SPECT to compare the myocardial perfusion in 105 young (mean age 37 years) asymptomatic HIV-positive patients—most of whom were on ART—with 105 HIV-negative gender- and age-matched controls, excluding all individuals with previous histories of CAD.[68] There was no evidence of increased risk of abnormal perfusion when the 2 groups were compared. In an older group (age 59 $\pm$ 7 years) of asymptomatic HIV-positive patients, Mariano-Goulart et al. reported 9.6% abnormal myocardial SPECT findings.[69] Notably, in their study, all of the abnormal SPECT scans were in men older than age 52, who had 2 or more additional CV risk factors.[69] From the findings of the 2 studies, it is clear that the prevalence of silent myocardial infarction in HIV-positive patients is very low before the fifth decade. PET can characterize the distribution of an intravenously administered positron emitting radionuclide tracer within the myocardium and can provide an accurate and reproducible measure of absolute myocardial blood flow and myocardial flow reserve following vasodilator challenge. A recent cross-sectional study using ^{82}Rubidium PET in HIV-positive patients showed that, in those with well-controlled viremia, there is no significant impairment of the myocardial microcirculation.[70] The value of screening SPECT/PET perfusion scans in HIV-positive patients remains unestablished, particularly in asymptomatic younger patients, in whom the yield is expected to be low.

Conclusions

Greater longevity in the PLWH population has increased the need for a more accurate assessment of CV risk and identification of effective risk-reduction strategies. The ability to forecast increased risk of CV events in individuals with HIV would represent an important advance in CV medicine, as it would identify those patients who are in most urgent need of earlier institution of preventative strategies. It is indeed an early dawn of application of cardiac and vascular imaging for prediction of risk in HIV and, in its present state, comes with limitations. Caution must be taken, as not all imaging modalities are created equal, with risks associated with increasing radiation for better image resolution, differing prognostic utilities, and rising health costs with more expensive procedures. The challenges for the future include training highly skilled personnel to interpret the imaging data and amassing big data registries of images, which comes at a high financial cost.

CV imaging parameters will have impact on early CV risk identification and stratification strategies in PLWH. Although CV imaging modalities require specialized interpretation, when combined with the use of newer advances in the

field—such as machine learning and automated software—they are likely to change current practices and have a positive effect on current and future long-term health care costs for PLWH. Machine-learning approaches in cardiac and vascular imaging data, combined with HIV-specific inflammatory and immune biomarkers, may allow future development of more accurate risk-reduction algorithms for the HIV population. At present, there is a paucity in research involving machine-learning approaches in CV imaging in the HIV population; thus, research in this area will transform how care is provided to PLWH in the future.

Disclosures

The authors have no conflicts of interest to disclose.

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