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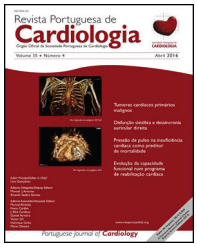

COMMENTARY

Challenges in patients living with HIV: The sudden cardiac death conundrum

Desafios em doentes com HIV: o problema da morte súbita cardíaca

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Early in the epidemic of human immunodeficiency virus (HIV), opportunistic infections related to acquired immune deficiency syndrome (AIDS) inevitably led to death and palliative care was the rule. Fortunately, effective therapy emerged during the so-called highly active antiretroviral era, leading to improved survival. Nowadays, the long-term care of people living with HIV/AIDS (PLWHA) has led to increased focus on the chronic management of comorbidities, particularly those related to the aging of the HIV-infected population and to cardiovascular disease (CVD). While acute life-threatening cardiac manifestations (especially infective endocarditis, myocarditis and pericarditis) dominated the clinical picture in the early HIV epidemic, premature atherosclerosis and its consequences are currently the leading cardiovascular presentation of PLWHA.[1–3]

Although the survival of well-managed PLWHA on antiretroviral therapy is now comparable to that of healthy controls, deaths due to CVD have been proportionately increasing in the former.[4] Several mechanisms may be responsible, including a higher prevalence of traditional cardiovascular risk factors in HIV-infected patients than in age- and gender-matched controls, a chronic inflammatory state and low-grade systemic inflammation even in patients with apparently controlled HIV infection, atherothrombotic risk factors, and adverse events related to combined antiretroviral therapy.[1] These may account for the pervasiveness of coronary artery disease (CAD), microvascular disease, heart failure (HF) and atrial fibrillation, among others, in PLWHA.

Surprisingly, a large study by Tseng et al.[5] enrolling 2860 consecutive PLWHA showed that, over a median 3.7 years of follow-up, non-AIDS mortality was mostly due to sudden cardiac death (SCD), which accounted for 86% of all cardiac deaths. These patients had a higher prevalence of prior myocardial infarction compared to those who had a non-SCD (17% vs. 1%, p<0.0005). The mean SCD rate reported was 2.6 per 1000 person-years over a 10-year period. Moreover, Mongardon et al.[6] retrospectively assessed 99 PLWHA successfully resuscitated after cardiac arrest, and demonstrated that a third of these were due to a cardiac cause, roughly half of which were clearly unrelated to myocardial infarction. In addition, these authors suggested that outcomes were not associated with HIV status (i.e., CD4 and viral counts), as per propensity-score matching to a control cohort with a similar presentation.

Altogether, the available evidence supports the idea that SCD occurs at a higher rate than expected in PLWHA. This may be due to various factors that are yet to be elucidated,[7] which may include the following:

- Host-related factors: increased atherogenic burden and SCD as a manifestation of CAD and HF. However, it has been suggested that SCD has a higher incidence than would be expected solely as a direct consequence of the aforementioned clinical scenarios; additionally, substance abuse (particularly amphetamines and alcohol) may also play a role;
- HIV-related factors: mechanisms may include systemic inflammation leading to rapidly progressive CAD, featuring vulnerable plaques known to be associated with a higher risk of atherothrombotic events and arrhythmogenic manifestations; in addition, HIV-related rhythm

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disturbances that may be the result of electrical cardiac remodeling and prolonged QTc due to autonomic dysfunction, may also facilitate SCD;
- Treatment-related factors: several drugs used in PLWHA (such as lopinavir-ritonavir, trimethoprim-sulfamethoxazole and methadone) are associated with both metabolic derangements and acquired prolonged QTc interval (hence torsades de pointes); furthermore, hypokalemia, hypomagnesemia and hypocalcemia are frequently found in HIV-infected patients, often as a consequence of drug-related diarrhea, gastrointestinal opportunistic infections and/or HIV enteropathy.

It is indisputable that SCD is worrisome in PLWHA and may account for many (if not most) premature and late deaths. As of now, we lack tools that can predict SCD risk in PLWHA and that may guide effective prevention. Other than systematically measuring QTc interval, particularly when introducing QTc-prolonging drugs, and selecting patients who may benefit from an implantable cardioverter-defibrillator (ICD), no other interventions are known to prevent arrhythmic SCD in HIV-infected patients. Moreover, identification of PLWHA with HF who may benefit from an ICD as primary prevention is done by extrapolating data from HF trials that have not properly addressed HIV-related cardiomyopathy. There are too many unknowns, and there is a need for urgent action in a matter of utmost importance.

The current issue of the *Journal* sees the publication of a single-center prospective case-control study of 89 PLWHA (antiretroviral therapy in 74% and controlled viral counts in 53%) and 62 age and gender-matched healthy controls.[8] Cetina et al. found that PLWHA had significantly increased Tp-e (measured from the peak to the end of the T wave) and corrected Tp-e (Tp-ec) intervals, as well as a higher Tp-e/QT ratio, in comparison to controls. Furthermore, these variables had a moderate but significant inverse correlation with CD4 T-cell counts. These findings add to the known increased risk of SCD in HIV-infected patients,[5] but also extend it to those with apparently controlled infection (as per CD4 T-cell counts and viral loads). Moreover, they unveil a potential role in PLWHA for easily measured electrocardiographic markers known to be linked to arrhythmogenic burden and SCD.

Tp-e interval, Tp-ec interval and Tp-e/QT ratio, indices of repolarization heterogeneity, have been shown to be increased in several clinical scenarios in comparison to healthy controls, such as in pediatric patients with dilated cardiomyopathy,[9] acute myocarditis[10] and sleep apnea,[11] to name a few, and it has been suggested that they may indicate increased SCD risk. Future investigations should focus on large studies with long-term follow-up to elucidate whether these markers may aid in arrhythmogenic stratification of PLWHA and, ultimately, facilitate interventions to further improve management in a population already at higher risk of both atherogenic and SCD events. In addition, the question whether QTc prolongation due to HIV treatment and known pathophysiological mechanisms shared with premature CAD play a major role in SCD is worth investigating further.

In conclusion, the shift of HIV from a life-threatening acute condition to a chronic manageable disease, in parallel with the aging of PLWHA, has led to a new paradigm of increased need to focus on treating related comorbidities and to draw on a wide range of medical specialties, especially cardiology, oncology, and geriatric medicine. Finally, the role of the cardiologist caring for PLWHA not only includes prevention of cardiovascular risk factors to mitigate atherogenic burden but may also extend, in the future, to SCD prevention once suitable tools are available to enable appropriate risk stratification to be integrated into clinical practice. The present study[8] adds a small but important piece to the puzzle of SCD in PLWHA.

Conflicts of interest

The authors have no conflicts of interest to declare.

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