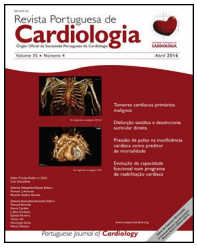
Revista Portuguesa de Cardiologia 40 (2021) 767–769

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org



EDITORIAL COMMENT

Diastolic dysfunction and type 1 diabetes: A sweet link?

Disfunção diastólica e diabetes tipo 1: uma doce ligação?

José Ribeiro

Cardiology Department, Gaia/Espinho Hospital Center, Vila Nova de Gaia, Portugal

Type 1 diabetes mellitus (T1D) is a health challenge; therapeutic measures should be individualized and involve a multidisciplinary approach, but are dependent on the effective administration of insulin, glucose monitoring and decision support. Over the past few years there has been an increasing emphasis on glycemic metrics in addition to glycosylated hemoglobin (HbA1c), its value in the management of T1D patients stems from robust studies that demonstrate a correlation between improved HbA1c levels and fewer diabetes complications. However, despite advances in management, there is still significant morbidity and mortality associated with this condition, of which cardiovascular disease (CVD) is the major complication.[1]

Despite advances in diabetes care and increased life expectancy, adults with T1D have a tenfold increase in the risk of CVD, in addition to early onset of complications and a two to four times greater mortality attributed to CVD compared to the general population.[2] It has been demonstrated in children with T1D that although conventional echocardiography did not reveal differences between patients with T1D and healthy children, tissue doppler echocardiography (TDE) showed dysfunction of both ventricles, with a correlation between diastolic function and HbA1C levels in T1D patients, suggesting that dysfunction may be closely related to the degree of glucose control. These findings support the diagnostic value of TDE in the early detection of cardiac effects in patients with T1D. A correlation was also reported between insulin doses and impaired active diastolic myocardial relaxation.

Endothelial function is altered even at an early stage of T1D. Interestingly, the extent of endothelial dysfunction correlated significantly with blood glucose levels and was inversely related to the duration of diabetes. Hypertension is more common in patients with T1D than T2D and is an important risk factor for CVD.

The term diabetic cardiomyopathy (DCM) was introduced to refer to this cardiac entity, defined as ventricular dysfunction in the absence of coronary artery disease and hypertension. Clinically, the earliest finding in DCM is characterized by cardiac hypertrophy and diastolic dysfunction, which may result in heart failure (HF) with preserved ejection fraction. Diastolic dysfunction not accompanied by any other determinable clinical sign of cardiac disease is categorized as the initial cardiac change in DCM, corresponding frequently to an asymptomatic subclinical phase.

Myocardial damage in T1D patients was demonstrated to affect diastolic function before systolic function as a potential and useful indicator for the prognosis of cardiovascular mortality. Diastolic changes may therefore be the first marker of future myocardial disease and impaired systolic function; however, diastolic dysfunction is not a specific condition of diabetes. Recently, in a systematic review, Ladeiras-Lopes et al. emphasized the prognostic impact and consistent association between diastolic dysfunction and the risk of cardiovascular events and death in community-based

E-mail address: cardiogaia@gmail.com

populations with different risk factors and prevalence of cardiac diseases.[3]

Tissue Doppler imaging echocardiography is an inexpensive non-invasive imaging tool for characterizing cardiac structure and function as well as enabling real time visualization of the cardiac cycle. It is the accepted imaging gold standard for the assessment of systolic and diastolic dysfunction in diabetic patients. It was demonstrated that echocardiography may represent an added value to the standard clinical follow-up in T1D and is a feasible method for detecting early myocardial dysfunction and identifying individuals at particular risk of adverse events.[4] The diagnosis of diastolic dysfunction is itself a challenge in the echocardiographic assessment of these patients. The application of the new 2016 ASE/EACVI recommendations for diastolic function assessment may result in a much lower prevalence of diastolic dysfunction.[5]

In the clinical setting, HF is a common complication of diabetes. The impact of T1D on systolic and diastolic function is less clear compared to type 2 diabetes. Diastolic dysfunction is more common than systolic dysfunction in subjects with T1D, and that myocardial damage in T1D may impair diastolic function before systolic function. It has been shown that T1D negatively impacts echocardiographic parameters of diastolic function, in particular the E/A ratio (ratio of early diastolic filling/late diastolic filling of the left ventricle) and transmitral blood flow velocity, as a sign of premature aging of the heart. In contrast to diastolic function, left ventricular systolic function was not impaired in most studies.[6]

Impairment in global longitudinal strain was described to be controlled by subendocardial longitudinal myofibers which are susceptible to ischemia and fibrosis. Thus, subclinical impairment of longitudinal strain may represent the first anomaly observed in HF. Other studies showed abnormal contractile responses only during exercise and during increased cardiac stress but not at rest. Finally, some studies showed neither a difference in systolic nor in diastolic function between type 1 diabetic patients and a control group. Thus, the true impact of T1D on the heart has still not been fully clarified in human studies. Others discussed that in some studies, echocardiographic parameters of diastolic dysfunction were misinterpreted since absolute values that were significantly different between diabetic and nondiabetic subjects were actually (according to echocardiographic guidelines) within the normal range for healthy people, which would not allow the diagnosis of diastolic dysfunction in the diabetic cohort.[7]

In this recent study, Weber et al. showed, in a case-control study, that echocardiographic evaluation enables the identification of a reduction in diastolic function indexes in T1D, which precedes the initial cardiac lesion in diabetes. This condition may represent a subclinical condition of cardiac impairment. There were no differences in longitudinal strain for left or right ventricles, among T1D patients and controls.[8]

Glycemic control alone is not sufficient to prevent the development of DCM, indicating the need for targeted therapeutic strategies. Some of the newer antidiabetic drugs such as the GLP-1 receptors agonists and the SGLT-2 inhibitors have demonstrated direct protective effects on myocardial tissue.

Therefore, non-insulin antihyperglycemic pharmacological therapy that not only improves glycemic control, reduces insulin requirements, and minimizes the risk of hypoglycemia but also targets bodyweight to improve insulin resistance and cardiovascular risk profile, is what is needed. Not only does it improve glycemic control, but it also decreases glycemic variability and time spent in hyperglycemia, reduced postprandial glucose excursions, and induces remarkable weight loss. These drugs have the most hopeful prospects for the future given their long-term cardiovascular benefits.[9] The potential of SGLT inhibitors as a promising adjunct therapy to insulin in inadequately controlled T1D patients has been studied in several clinical trials and showed additional reduction in HbA1c without the additional risk of hypoglycemia.[10] The knowledge of the signs of cardiovascular involvement in T1D patients, such as diastole dysfunction, may be more than a sweet link and may be an important substrate for future studies into cardiovascular prevention involving new and promising drugs, such as GLP-1 receptors agonists and SGLT2 inhibitors as shown for T2D.[11]

Precision medicine is a rapidly advancing field. Recent studies have demonstrated that RNA-binding proteins (RBPs) play key roles in the development of diabetes and its systemic manifestations. RNA therapeutics delivered using viral vectors have certain advantages such as the ease of generating vectors, highly efficient transduction, and long-term stable gene expression. Thus, RBPs provide another therapeutic option for the prevention of CVD in diabetic patients. Several drugs based on pathophysiological mechanisms including RNA therapeutics are under development.[12]

Thus, newer drugs seem to offer a greatly improved balance of benefits versus risks, and their use in T1D is clearly a thrilling possibility. The key lies in the precise identification of which patients will obtain the greatest benefit with the least risk and how early we should start them. The identification of the early stages of cardiovascular impairment in T1D patients may be crucial.

Conflicts of interest

The author has no conflicts of interest to declare.

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