HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

Scientific Comment

Haemoglobinopathies from the cardiac point of view

Minna Moreira Dias Romano *

Universidade de São Paulo (FMRP-USP), Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article history:
Received 9 May 2019
Accepted 9 May 2019
Available online 23 July 2019

Heart disease is a leading cause of mortality and the main determinant of prognosis in haemoglobinopathies as beta-thalaessemia (βT) and sickle cell disease (SCD). Cardiac involvement is affected not only by the molecular defect causing chronic haemolisis, but also by the therapeutic requirements involving transfusion and chelation therapy.[1] Chronic haemolisis causes anemia and then a high cardiac output state.[2] Repetitive haemotransfusions, on the other hand, leads to myocardial iron deposition, which can evolve to a pattern of Restrictive Cardiomyopathy.

Two geometric patterns of left ventricle (LV) remodeling can be observed although they are not exclusive. High output Cardiomyopathy is characterized by a kind of Dilated Cardiomyopathy (CMP), with left chamber dilatation secondary to overload, eccentric LV hypertrophy, and in general, a preserved LV ejection fraction. Diastolic function of LV can be severely altered in a proportion of patients even before systolic dysfunction.[3] Myocardial ischemia can happen in a subset of patients with this physiopathology and can contribute to further LV systolic dysfunction.

Restrictive Cardiomyopathy secondary to iron overload is associated to chronic transfusions. It is characterized by LV thickness and concentric pattern of hypertrophy, also associated to diastolic LV dysfunction and left atria (LA) enlargement. LV ejection fraction is also usually preserved until a late phase of disease. Two variables can be of particular importance in iron deposition and cardiac alterations: the necessity of transfusion and the combined iron chelation therapy.[1,4,5] These variables can be very difficult to control in scientific studies. Although iron overload CMP is more prevalent in βT patients, an incidence of 2–5% is described in SCD patients.[6]

Detection of CMP in this heterogeneous group of patients can be a challenge. Echocardiography is a very useful image method able to identify geometric and functional changes in all cardiac chambers. However, LV ejection fraction, although being a so robust measurement of systolic LV function, is not a sensitive parameter of incipient myocardial damage. LA volume and LV diastolic parameters as mitral annulus Tissue Doppler are usually early compromised in βT patients.[7,8] LV diastolic dysfunction is also very prevalent in SCD patients, as high as 30%.[8] Right ventricle involvement can also be detected by echocardiography associated or not to pulmonary hypertension.[9–11] Myocardial deformation analysis from bidimensional speckle tracking echocardiography is a very sensitive tool able to detect incipient myocardial

* *Corresponding author at*: Cardiology Division — Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FMRP-USP), AV Bandeirantes, 3.900 - 2° andar, Monte Alegre CEP 14098780, Ribeirão Preto, SP, Brazil.
E-mail address: minna@fmrp.usp.br
https://doi.org/10.1016/j.htct.2019.05.002

damage in several CMP. The technique is based on tracking of bidimensional speckles and is relatively independent of load conditions. Although it is not really a measurement of myocardial contractility it is very close to it. Few studies have tested global longitudinal strain (GLS) in patients with haemoglobinopaties. Whipple et al. in 2018 studied a large number of children with SCD evaluating myocardial deformation of both ventricles. Although there was no significant difference in LV GLS from controls, RV GLS of SCD patients (and not of controls) decreased with aging and it was associated with LA enlargement and LV volume increase.[12] In another study of strain echocardiography, applied to patients with βT, Odoardo et al. compared LV global indexes of deformation with the cardiac magnetic resonane (CMR) index T2*, a marker of myocardial iron deposit. Significant reductions of strain indexes were found in βT patients compared to controls. However, no correlation of strain parameters and T2* was demonstrated, reinforcing the concept that iron deposition is not the only determinant of myocardial damage.[13]

CMR has been established as the only non-invasive method of detection of myocardium iron deposit. T2* technique, which is based on heterogeneity of magnetic field imposed by iron deposition on tissues, was validated to myocardium decades ago. It was also demonstrated as a strong predictor of myocardial dysfunction at evolution of patients with haemoglobinopathies.[14] The CMR ability to measure both cardiac function and iron deposition and further to evaluate liver deposition in the same scan has revolutionized the understanding of iron storage disease. Introduction of routinely CMR evaluation for patients with haemoglobinopathy, specially those with βT, has changed prognosis of this group of patients.[15]

Regardless of this complex diagnosis scenario, there is a group of patients with a double heterozygosity of SCD and βT, which leads to the clinical expression of a variant of SCD. This condition has a considerable prevalence in Brazil and cardiac alterations of a sample of these patients were studied by Benites et al.[16] and presented at this journal. There were no cardiac geometry alterations neither differences in LV systolic function between SCD variant patients and controls when evaluated by conventional echocardiographic indexes. Results probably reflect what was pointed before about the difficulties to demonstrate early myocardial damage in this group of patients with conventional echocardiographic measurements. New techniques able to detect myocardial damage as strain echocardiography may play an important role in this so special disease.

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

1. Farmakis D, Triposkiadis F, Lekakis J, Parissis J. Heart failure in haemoglobinopathies: pathophysiology, clinical phenotypes, and management. Eur J Heart Fail. 2017;19(April (4)):479–89.
2. Hammoudi N, Lionnet F, Redheuil A, Montalescot G. Cardiovascular manifestations of sickle cell disease. Eur Heart J. 2019;(April), http://dx.doi.org/10.1093/eurheartj/ehz217 [Epub ahead of print].
3. Niss O, Quinn CT, Lane A, Daily J, Khoury PR, Bakeer N, et al. Cardiomyopathy with restrictive physiology in sickle cell disease. JACC Cardiovasc Imaging. 2016;9(March (3)): 243–52.
4. Stakos DA, Margaritis D, Tziakas DN, Kotsianidis I, Chalikias GK, Tsatalas K, et al. Cardiovascular involvement in patients with beta-thalassemia major without cardiac iron overload. Int J Cardiol. 2009;134(May (2)):207–11.
5. Ballas SK, Zeidan AM, Duong VH, DeVeaux M, Heeney MM. The effect of iron chelation therapy on overall survival in sickle cell disease and beta-thalassemia: a systematic review. Am J Hematol. 2018;93(July (7)):943–52.
6. Ginwalla M, AlMasoud A, Tofovic D, Alin T, Al-Kindi S, Oliveira G, et al. Cardiovascular evaluation and management of iron overload cardiomyopathy in sickle cell disease. Am J Hematol. 2018;93(January (1)):E7–9.
7. Rodrigues A, Guimaraes-Filho FV, Braga JC, Rodrigues CS, Waib P, Fabron-Junior A, et al. Echocardiography in thalassemic patients on blood transfusions and chelation without heart failure. Arq Bras Cardiol. 2013;100(January (1)):75–81.
8. Vogel M, Anderson LJ, Holden S, Deanfield JE, Pennell DJ, Walker JM. Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial dysfunction related to myocardial iron overload. Eur Heart J. 2003;24(January (1)):113–9.
9. Mancuso L, Vitrano A, Mancuso A, Sacco M, Ledda A, Maggio A. Left ventricular diastolic dysfunction in beta-thalassemia major with heart failure. Hemoglobin. 2018;42(January (1)):68–71.
10. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, et al. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. 2010;3(May (3)):451–8.
11. Chiadika S, Lim-Fung M, Llanos-Chea F, Serauto Canache A, Yang W, Paruthi C, et al. Echocardiographic parameters to identify sickle cell patients with cardio-pathology. Echocardiography. 2018;35(September (9)): 1271–6.
12. Whipple NS, Naik RJ, Kang G, Moen J, Govindaswamy SD, Fowler JA, et al. Ventricular global longitudinal strain is altered in children with sickle cell disease. Br J Haematol. 2018;183(December (5)):796–806.
13. Di Odoardo LAF, Giuditta M, Cassinerio E, Roghi A, Pedrotti P, Vicenzi M, et al. Myocardial deformation in iron overload cardiomyopathy: speckle tracking imaging in a beta-thalassemia major population. Intern Emerg Med. 2017;12(September (6)):799–809.
14. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001;22(December (23)):2171–9.
15. Anderson LJ. Assessment of iron overload with T2* magnetic resonance imaging. Prog Cardiovasc Dis. 2011;54(3): 287–94.
16. Benites BD, Cisneiros IS, Bastos SO, Beppler AP, Lino L, Costa FF, et al. Echocardiografic abnormalities in patients with sickle cell/β-thalassemia do not depend on the β-thalassemia phenotype. Hematol Transf Cell Ther. 2019;41(2):158–63.