International Journal of Cardiology 274 (2019) 257–259

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Exercise testing in hypertrophic cardiomyopathy: A pathophysiological goldmine with protean clinical implications

Iacopo Olivotto *, Niccolò Maurizi

Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy

ARTICLE INFO

Article history:
Received 4 September 2018
Accepted 10 September 2018
Available online 13 September 2018

Long gone are the times when hypertrophic cardiomyopathy (HCM) was considered a major contraindication to exercise testing in cardiology textbooks, due to concerns for hemodynamic catastrophe in patients with severe left ventricular outflow tract obstruction (LVOTO). Scores of studies have consistently shown that the physiologic challenge constituted by exercise is both safe and informative in HCM patients, representing a pathophysiological goldmine in a disease so dynamic [1]. Particularly in young and active individuals, assessing patients in the resting state may lead to inaccurate perception of HCM severity, reflecting poorly the relation between symptoms and objective findings [2]. Thus, exercise testing is key to our understanding of symptoms, stage of disease, effects of treatment and patient outlook [1].

Because HCM is not coronary artery disease, physicians must be fully aware of what they should be looking for. In the early days, the main objective of exercise testing was to evaluate hemodynamic and electrical stability, in an effort to identify HCM patients at greater risk for sudden cardiac death [3]. More recently, with the addition of exercise echocardiography and cardiopulmonary testing (CPET), the landscape has become considerably more complex and rewarding (Fig. 1). A more contemporary approach should consider exercise testing – possibly associated with echocardiography – in virtually all HCM patients [1,2]. In symptomatic individuals, the test is quintessential in defining causes of symptoms, planning therapeutic strategies and evaluating the effects of treatment, whether it be septal reduction intervention for LVOTO, heart failure therapy for end-stage dysfunction (ideally combined with CPET) or identification of associated coronary artery disease [1]. In those who are asymptomatic, exercise testing retains an important role in identifying elements of risk (mostly labile obstruction and nonsustained ventricular tachycardia) and in providing tailored lifestyle and sports recommendations [4,5]. Reduced exercise performance is robustly related to adverse long-term outcome, particularly when expressed in terms of peak oxygen consumption [1].

Among this wealth of information, the clinical relevance of abnormal blood pressure response to exercise (ABPR), defined as *hypotensive*, i.e. a decrease >20 mm Hg from peak systolic blood pressure or any fall below resting values, or *blunted*, i.e. failure to increase >20 mm Hg, remains undefined bordering on controversial. This is hardly surprising, given its multifaceted and dynamic pathophysiology which includes a combination of LVOTO and mitral regurgitation on effort, systemic vasodilatation due to autonomic dysregulation, inappropriate tachycardia, impaired diastolic reserve and subendocardial ischemia [2,3]. ABPR generated considerable interest in the nineties, as a marker of hemodynamic instability, associated with increased risk of sudden cardiac death (SCD) [3,5,6]. The early cohorts were accurately investigated but relatively small, with few arrhythmic events during follow-up, and positive predictive accuracy of ABPR proved consistently low [7]. Based on this evidence, ABPR has been included among the 5 major risk factors for SCD in the ACC/AHA 2011 HCM guidelines, although in a lower tier compared to family history of SCD, extreme hypertrophy and unexplained syncope [8]. Conversely, a handful of additional studies failed to show any association of ABPR with SCD [9], with one suggesting an impact only on overall mortality [7]. The recent metanalysis by Christiaans et al. reported a non-significant SCD hazard ratio for ABPR (1.30, with 95% confidence interval 0.64–1.96). Consistently, ABPR failed to enter the multivariable model originating the HCM-ESC risk score for SCD, based on a large international cohort, and is therefore not included in the algorhythm of the ESC 2014 HCM guidelines [8].

After almost three decades of intermittent and conflicting investigation on the subject, the study by Smith et al. [10] is a welcome attempt to clarify the relation between ABPR and outcome, in a large contemporary HCM cohort. In 589 patients from a prospective institutional HCM registry, the authors found a 30% prevalence of ABPR, more common in females. ABPR was associated with reduced functional capacity, (particularly in patients with the hypotensive type) but not with an increased prevalence of LVOTO (56% vs. 63%, $p = 0.11$). Over 4 years, ABPR purported an increased likelihood of HF-related events, but not of SCD or potentially lethal arrhythmic events. When included in a Cox hazard regression model with the variables currently used in the ESC SCD Risk score, ABPR still was not significantly associated with arrhythmic risk. Of note, the study for the first time assessed the

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.07.110.
* Corresponding author at: Unit Cardiomiopatie, Azienda Ospedaliera Universitaria Careggi, Viale Pieraccini 1, 50134 Firenze, Italy.
E-mail address: olivottoi@aou-careggi.toscana.it (I. Olivotto).

https://doi.org/10.1016/j.ijcard.2018.09.044

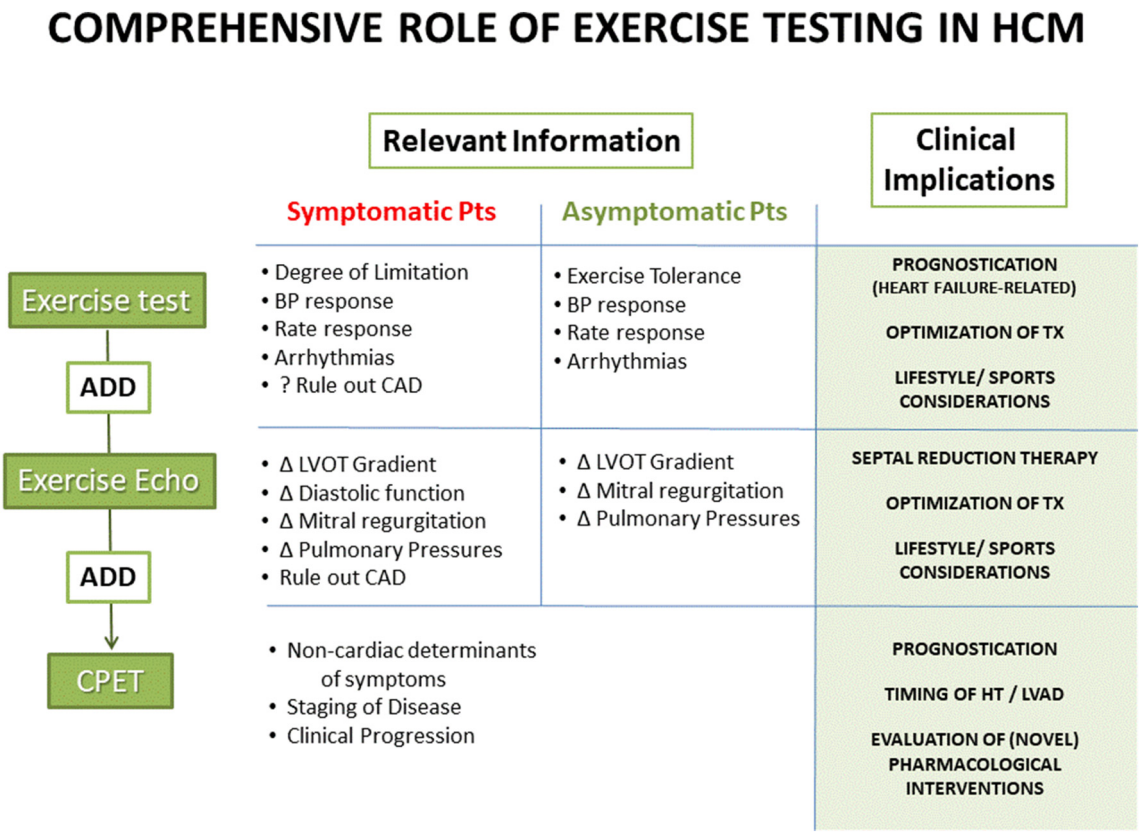

Fig. 1. Comprehensive role exercise testing in patients with hypertrophic cardiomyopathy (HCM). Exercise testing may be adopted in a tiered fashion, by the (not mutually exclusive) addition of exercise echocardiography and cardiopulmonary testing (CPET). Individualizing the most cost-effective and informative approach to each patient may help acquire a wealth of information critical to management, ranging from prognostication to choice of appropriate treatment and evaluation of novel therapeutic options. Both symptomatic and asymptomatic patients benefit from the information obtained by exercise testing, although the focus and clinical impact vary substantially between the two groups. Abbreviations: BP = blood pressure; CAD = coronary artery disease; CPET = cardiopulmonary exercise test; HT = heart transplant; LVAD = Left ventricular assist device; LVOT = Left ventricular outflow tract; Tx = treatment.

reproducibility of ABPR in a subset of 222 patients with repeat exercise tests. Of the 144 with a normal initial response, 19% converted to ABPR on the second test, whereas 52% of 78 patients with an initial ABPR subsequently showed normal blood pressure increase. In the latter subset, only about a fourth of these normalized responses could be attributed to a clear cause, i.e. a successful surgical myectomy – again emphasizing the inconsistent relationship of LVOTO with ABPR. These novel findings suggest that blood pressure response may vary over time in HCM patients – further eroding its value in outcome prediction. Whether patients with consistent as opposed to occasional ABPR encounter different fates deserves further studies in large multicenter registries.

Overall, these novel findings suggest that ABPR is just one of many useful pieces of clinical information obtainable by exercise testing in HCM. Its prognostic power is limited, and probably confined to disease progression and heart failure. Its role in predicting SCD seem less and less convincing over time, and raises questions regarding the opportunity of aggressive interventions based on its occurrence alone. In a broader and probably wiser perspective, individual blood pressure response to exercise should be contextualized, its causes dissected, and its value considered alongside a myriad elements derived from clinical, molecular and imaging-based assessment. That advancing knowledge may defeat prior certainties, by showing greater complexities, should not be seen as frustrating, but as unavoidable towards true understanding.

Acknowledgments

IO was supported by the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement no. 777204: "SILICOFCM - In Silico trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy"; and by the Ministry of Health, Italy "Left ventricular hypertrophy in aortic valve disease and hypertrophic cardiomyopathy: genetic basis, biophysical correlates and viral therapy models" (RF-2013-02356787), and NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy).

Disclosures

None.

References

[1] E.J. Rowin, B.J. Maron, I. Olivotto, M.S. Maron, Role of exercise testing in hypertrophic cardiomyopathy, JACC Cardiovasc. Imaging 10 (2017) 1374–1386.
[2] F. Re, E. Zachara, A. Avella, P. Baratta, M. di Mauro, M. Uguccioni, I. Olivotto, Dissecting functional impairment in hypertrophic cardiomyopathy by dynamic assessment of diastolic reserve and outflow obstruction: a combined cardiopulmonary-echocardiographic study, Int. J. Cardiol. 227 (Jan 15, 2017) 743–750.
[3] N. Sadoul, K. Prasad, P.M. Elliott, S. Bannerjee, M.P. Frenneaux, W.J. McKenna, Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy, Circulation 96 (1997) 2987–2991.
[4] L. Monserrat, P.M. Elliott, J.R. Gimeno, S. Sharma, M. Penas-Lado, W.J. McKenna, Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients, J. Am. Coll. Cardiol. 42 (2003) 873–879.
[5] P.M. Elliott, J. Poloniecki, S. Dickie, et al., Sudden death in hypertrophic cardiomyopathy: identification of high risk patients, J. Am. Coll. Cardiol. 36 (2000) 2212–2218.
[6] S. Maki, H. Ikeda, A. Muro, et al., Predictors of sudden cardiac death in hypertrophic cardiomyopathy, Am. J. Cardiol. 82 (1998) 774–778.

[7] I. Olivotto, B.J. Maron, A. Montereggi, et al., Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 33 (7) (1999) 2044–2051.
[8] P.M. Elliott, A. Anastasakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, A.A. Hagege, A. Lafont, G. Limongelli, H. Mahrholdt, W.J. McKenna, J. Mogensen, P. Nihoyannopoulos, S. Nistri, P.G. Pieper, B. Pieske, C. Rapezzi, F.H. Rutten, C. Tillmanns, H. Watkins, 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy, Eur. Heart J. 35 (2014) 2733–2779.
[9] I. Christiaans, K. van Engelen, I.M. van Langen, et al., Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers, Europace 12 (2010) 313–321.
[10] E.D. Smith, J. Tome, R. Mcgrath, S. Kumar, M. Concannon, S.M. Day, S. Saberi, A.S. Helms, Exercise hemodynamics in hypertrophic cardiomyopathy identify risk of incident heart failure but not ventricular arrhythmias or sudden cardiac death, Int. J. Cardiol. 274 (2018) 226–231.