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Comprehensive Exercise Stress Echocardiography: a Pathophysiological Prism Dissecting the Spectrum of Hypertrophic Cardiomyopathy

Ph.D. Thesis Booklet

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Publications related to the thesis

1) **Pálinkás ED**, Re F, Peteiro J, Tesic M, Pálinkás A, Torres MAR, Dikic AD, Beleslin B, Van De Heyning CM, D'Alfonso MG, Mori F, Ciampi Q, de Castro Silva Pretto JL, Simova I, Nagy V, Boda K, Sepp R, Olivotto I, Pellikka PA, Picano E. Pulmonary congestion during Exercise stress Echocardiography in Hypertrophic Cardiomyopathy. Int J Cardiovasc Imaging. 2022 Dec;38(12):2593-2604. doi: 10.1007/s10554-022-02620-0. Epub 2022 Nov 2. PMID: 36322266; PMCID: PMC9708780.

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2) **Pálinkás E**, Nagy V, Varga A, Ágoston G, Kákonyi KM , Szűcsborus T, Somfay A, Badó A, Sepp R, Czakó L, Pálinkás A. A Látens Bal Kamra Kiáramlási Pálya Obstrukció Vizsgálata Kerékpáros Stressz Echokardiográfiával Hypertrophiás Cardiomyopathiás Betegeken. Medicina Thoracalis (Budapest). 2019 Feb;72: 3–11.

3) Ciampi Q, Olivotto I, Peteiro J, D'Alfonso MG, Mori F, Tassetti L, Milazzo A, Monserrat L, Fernandez X,

Pálinkás A, **Pálinkás ED**, Sepp R, Re F, Cortigiani L, Tesic M, Djordjevic-Dikic A, Beleslin B, Losi M, Canciello G, Betocchi S, Lopes LR, Cruz I, Cotrim C, Torres MAR, Bellagamba CCA, Van De Heyning CM, Varga A, Ágoston G, Villari B, Lorenzoni V, Carpeggiani C, Picano E, The Stress Echo Study Group On Behalf Of The Italian Society Of Echocardiography And Cardiovascular Imaging Siecvi. Prognostic Value of Reduced Heart Rate Reserve during Exercise in Hypertrophic Cardiomyopathy. J Clin Med. 2021 Mar 24;10(7):1347. doi: 10.3390/jcm10071347. PMID: 33805111; PMCID: PMC8037369.

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4) **Pálinkás ED**, Ciampi Q, Picano E. The Expanding Role of Stress Echocardiography in Hypertrophic Cardiomyopathy. Cardiologia Hungarica. 2019 Nov;49:330–337. doi: 10.26430/CHUNGARICA.2019.49.5.330

Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common inheritable myocardial disease characterized by heterogeneous clinical expression, distinctive pathophysiologic features, and diverse natural history. In HCM patients who do not exhibit left ventricular outflow tract (LVOT) gradient ≥50 mm Hg during standard echocardiographic evaluation and are symptomatic, exercise stress echocardiography (ESE) should be performed to detect and quantify provocable LVOT obstruction (LVOTO) and mitral regurgitation. In asymptomatic patients without inducible LVOT obstruction ≥50 mm Hg on standard transthoracic echocardiography, it can be beneficial to perform ESE, considering that it provides a comprehensive understanding on their individual pathophysiology, especially if the presence of LVOT obstruction is relevant to lifestyle advice and decisions on medical treatment. Of note, regardless of symptomatic status, LVOT assessment during exercise should be performed in every HCM patient without resting obstruction (>50 mmHg) who has positive history of syncope. Despite that ESE examination

plays a central role in the management of HCM patients, current HCM guidelines recognize LVOTO as the utmost parameter to look for during exercise stress. However, with this approach, the etiology of symptoms can be overlooked and the opportunity for individualized care can be missed. In fact, numerous other guidelines and consensus statements recommend the evaluation of other ESE parameters for HCM patients. Furthermore, several studies have pointed out lately other SE imaging variables that might aid in improving risk stratification for individuals with HCM. In the Stress echo 2020 (NCT03049995) international, multicenter, prospective, effectiveness study, a novel multiparametric stress echocardiography perspective was used for the first time. The study started in 2016 and more than 100 quality-controlled, high-volume SE labs adhered for its clinical, laboratory and imaging data collection. As a result, a new approach for functional testing was developed, verified, and widely used in coronary artery disease and other diseases, comprising HCM. The study protocol includes 5 basic steps, feasible in all patients with all stress modalities: A: regional wall motion abnormalities

(RWMA), B: B-lines, C: left ventricular (LV) contractile and preload reserve, D: Doppler coronary flow velocity reserve in the left anterior descending coronary artery and E: ECG-based assessment of heart rate reserve (HRR). This procedure provides comprehensive information on the different vulnerabilities of HCM patients as it makes possible to uncover easily and systematically concealed myocardial ischemia (step A), pulmonary congestion (step B), preload reserve and contractile reserve impairment (step C), coronary microcirculatory dysfunction (step D) and cardiac autonomic dysfunction (step E). Step G (LVOT gradient) and step F (flow of mitral regurgitation) are two additional steps that are crucial for the HCM-specific subproject.

Aims

In the frame of the Stress echo 2020 (NCT03049995) international observational study, 3 investigations were carried out to evaluate the clinical value of ABCDE-related ESE parameters in patients with HCM, with the following goals:

1) To assess the clinical, anatomical and functional correlates of pulmonary congestion elicited by exercise in HCM.
2) To evaluate latent LVOTO during semi-supine ESE .
3) To determine the value of HRR in predicting prognosis in HCM.

Methods

Consecutive HCM patients were enrolled from the Stress echo 2020 study and the corresponding multicenter database built over the last 30 years. All patients underwent symptom-limited dynamic echocardiographic examination according to the referring physician's indications as part of the routine workup. All echocardiographic measurements were measured at rest and with stress by experienced cardiologists according to standard criteria of execution and interpretation recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Upstream to patient recruitment, each participant in Stress Echo 2020 study had passed the quality control procedures of reading examinations with

inter-observer variability <10% in quantifying B-lines and estimating LV area by planimetric method. the wall motion score index was calculated by applying the four-point score system ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the left ventricle. New RWMA were defined as an increase of at least one grade in at least two LV myocardial segments at peak stress. HRR was calculated as the peak/rest heart rate from 12-lead ECG. Stroke volume (SV) was calculated as the difference between end-diastolic volume and end-systolic volume. Cardiac output was computed using the following formula: SV x heart rate. Cardiac output and SV were normalized to body surface area to obtain SV index and cardiac index. Preload reserve impairment was defined as peak stress end-diastolic volume is less than baseline end-diastolic volume. Lung ultrasound acquisition was performed at rest and peak (or immediately after) stress with the 4-site simplified scan at the third intercostal space on the anterior and lateral hemithoraces, using the same probe employed for the cardiac scan. B-lines were defined as hyperechoic reverberation artifacts rising from the pleural line to the bottom of the screen moving

synchronously with lung sliding without fading. After scanning the 4 chest sites, the cumulative B-line score was obtained by summing the number of detected B-lines at each site. B-lines were considered present if at least 2 B-lines could be detected.

Summary of results

Our investigation on exercise pulmonary congestion revealed that lung ultrasound during ESE is feasible and simple in HCM, with 100% success rate for B-lines and only a minimal increase in imaging time. We found B-lines in about 10% of HCM patients at rest and in about 30% during ESE. HCM patients presenting B-lines at stress were diagnosed later in life and had higher sudden cardiac deaths risk scores. They showed higher pulse pressure at rest, with similar heart rate and cardiac output compared to patients without stress B-lines, suggestive of a stiff aorta contributing to abnormal ventricular arterial interactions during stress and eventually favouring myocardial fibrosis and dysfunction. Stress B-lines were associated with worse rest and stress diastolic function, greater rest and stress estimated systolic pulmonary arterial pressure and

larger increment in mitral regurgitation during stress. Furthermore, HCM patients with stress B-lines had lower cardiac index and cardiac index reserve at comparable heart rates and they exhibited more often abnormal blood pressure response to exercise, compared to those without stress B-lines.

According to the results of our study on latent LVOTO, in almost a quarter of unselected Hungarian HCM patients without baseline LVOTO, latent LVOTO could be identified during ESE. In our study, regardless of their clinical symptoms, we examined all HCM patients without resting LVOTO. Based on our results, HCM patients with latent LVOTO have higher baseline LVOT gradient and smaller resting LVOT diameter compared to non-obstructive HCM patients.

In our HRR study, we revealed that a reduction of HRR is associated with worse survival in patients with HCM. Furthermore, we demonstrated that the prognostic value of HRR is independent of other established predictors such as age and LV maximal wall thickness. HRR outperformed LVOT gradient and exercise-induced hypotension for predicting survival and was independent

and additive to RWMA. Notably, the prognostic value of HRR was observed in patients off and on beta-blockers at the time of testing. Not only high heart rate at rest but also poor exercise tolerance and low heart rate at peak exercise are associated with a reduced HRR, and both contribute to its capability to stratify outcome.

Conclusions

Albeit stress echocardiography is included in current guidelines for the management of HCM, mostly it is considered only a tool to evaluate peak LVOT gradients. However, ESE is a powerful multi-purpose tool with far-reaching clinical implications also in non-obstructive patients and provides much broader information for clinical practice.