University of Szeged
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USE OF ADVANCED TRANSTHORACIC ECHOCARDIOGRAPHY IN SPECIAL CARDIAC CONDITIONS

PhD Thesis

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2.1.2 Rácz G, Takács H, Kormányos Á, Polestyuk B, Borbás J, Gyenes N, Schvartz N, Németh G, Kincses Zs, Sepp R, **Nagy V**. Screening for Myocardial Injury after Mild SARS-CoV-2 Infection with Advanced Transthoracic Echocardiography Modalities. DIAGNOSTICS 12: 8 Paper: 1941, 13 p. (2022). https://doi.org/10.3390/diagnostics12081941. Független idéző: 8, Q2, IF: 3.6.

2.2 List of citable abstracts related to the thesis

2.2.1 **Nagy V**, Racz G, Takacs H, Polestyuk B, Schvartz N, Vidacs LD, Palinkas A, Kormanyos A, Szucsborus T, Borbas J, Szili-Torok T, Sepp R. Reduction of > 100 mmHg left ventricular outflow tract gradients in obstructive hypertrophic cardiomyopathy during mavacamten treatment already after one week of treatment. EUROPEAN JOURNAL OF HEART FAILURE 27: Suppl 2 pp. 442-442, 1 p. (2025).

2.2.2 Takacs H, **Nagy V**, Racz G, Polestyuk B, Schvartz N, Vidacs LD, Palinkas A, Kormanyos A, Szucsborus T, Borbas J, Szili-Torok T, Sepp R. Temporal changes in echocardiographic parameters of diastolic dysfunction in obstructive hypertrophic cardiomyopathy during mavacamten treatment. EUROPEAN JOURNAL OF HEART FAILURE 27: Suppl 2 pp. 440-440, 1 p. (2025).

2.2.3 Racz G, Sepp R, **Nagy V**, Takacs H, Schvartz N, Polestyuk B, Vidacs LD, Kormanyos A, Borbas J, Szili-Torok T. Changes in global myocardial work indices during mavacamten treatment in obstructive hypertrophic cardiomyopathy. EUROPEAN JOURNAL OF HEART FAILURE 27: Suppl 2 pp. 431-431, 1 p. (2025).

2.2.4 **Nagy V**, Rácz G, Polestyuk B, Takács H, Németh G, Sepp R. Screening for subclinical myocardial injury after mild SARS-CoV-2 infection with extended transthoracic echocardiography modalities. CARDIOLOGIA HUNGARICA 51: Suppl. B pp. B213-B213, 1 p. (2021).

3. ABBREVIATIONS

2D: two-dimensional

AF: atrial fibrillation

AHA/ACC: American Heart Association/American College of Cardiology

ANOVA: analysis of variance

BB: beta-blocker

BMI/BSA: body mass index/body surface area

CAD: coronary artery disease

CCB: calcium channel blocker

CMR: cardiac magnetic resonance

COVID-19: coronavirus disease 2019

CRT: cardiac resynchronization therapy

CYP2C19: Cytochrome P450 2C19

DSC2: desmocollin 2 gene

DSP: desmoplakin gene

e': mitral annulus e' velocity

E: early transmitral inflow velocity

ECG: electrocardiography

EDD/EDV: end-diastolic diameter/end-diastolic volume

EF/LVEF: ejection fraction/left ventricular ejection fraction

EMA: European Medicines Agency

ESC: European Society of Cardiology

ESD/ESV: end-systolic diameter/end-systolic volume

EXPLORER-HCM: Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy

GCW: global constructive work

GLS: global longitudinal strain

GWE: global work efficiency

GWI: global work index

GWW: global wasted work

HCM/oHCM: hypertrophic cardiomyopathy/obstructive hypertrophic cardiomyopathy

HFpEF: heart failure with preserved ejection fraction

ICD: implantable cardioverter defibrillator

IFU: instruction for use

IQR: interquartile range

IVS: interventricular septum

LA/LV: left atrium/left ventricle

LAV/LAVI: left atrial volume/ left atrial volume index

LVH: left ventricular hypertrophy

LVOT/LVOTG: left ventricular outflow tract/ left ventricular outflow tract gradient

MIS-C/MIS-A: multisystem inflammatory syndrome in children/adults

MR: mitral regurgitation

MYBPC3: cardiac myosin binding protein C gene

MYH7: beta myosin heavy chain 7 gene

MYL3: myosin light chain 3 gene

MW: myocardial work

NA: not applicable

NS: not significant

NT-proBNP: N terminal part of B type natriuretic peptide

NYHA: New York Heart Association

PSL: pressure-strain loop

PV: pressure-volume

PW: posterior wall

RV: right ventricle

SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2

SD/SEM: standard deviation/standard error of mean

SR: sinus rhythm

SRT: septal reduction therapy

STE: speckle tracking echocardiography

TDI/TVI: tissue Doppler imaging/tissue velocity imaging

TTE: transthoracic echocardiography

VALOR-HCM: A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy

VTI: velocity time integral

VUS: variant of unknown significance

4. INTRODUCTION

Transthoracic echocardiography (TTE) stands as the foundational, first-line imaging modality in the field of cardiology. As a non-invasive procedure, TTE generates dynamic, real-time images of the heart's anatomy and function. Its widespread availability, cost-effectiveness, and negligible risk profile have established its status as an indispensable tool, offering cardiologists crucial insights into the structural integrity, functional performance, and complex hemodynamics of the cardiovascular system.

The primary importance of TTE lies in its comprehensive assessment of cardiac structure and myocardial function (reviewed in detail in [1]). The technique provides quantitative measurements of all four heart chambers, allowing clinicians to accurately determine chamber size, wall thickness, and geometry. This is critical for diagnosing conditions like ventricular hypertrophy, dilation, and various cardiomyopathies. Furthermore, TTE is the most common method for evaluating left ventricular (LV) systolic function. The ability to visualize the heart's muscle movement in real time helps identify regional wall motion abnormalities, and sophisticated TTE techniques, such as tissue Doppler and strain imaging, allow for the crucial assessment of diastolic function, diagnosing heart failure with preserved ejection fraction (HFpEF), a condition that is otherwise challenging to identify. TTE's utility extends also into the area of valvular heart diseases and complex cardiac hemodynamics, largely through the integration of Doppler technology. Doppler allows clinicians to measure the velocity and direction of blood flow across the valves and within the chambers, transforming the anatomical image into a functional analysis tool. This enables precise diagnosis and grading of valvular lesions. Similarly, colour Doppler mapping visually highlights turbulent flow caused by regurgitation or abnormal communications, making TTE essential for diagnosing congenital heart defects and monitoring pulmonary hypertension. The safety, speed, and low cost of TTE make it perfectly suited for serial follow-up, enabling continuous monitoring of disease progression or the effectiveness of medical and surgical interventions.

4.1 Advanced echocardiography

Advanced echocardiography has shifted the paradigm of cardiac assessment from purely morphological analysis to precise, quantitative evaluation of myocardial mechanics and intracardiac hemodynamics. Modern techniques transformed sophisticated Doppler principles to measure not just blood flow, but the motion of the heart muscle itself, enabling cardiologists to detect subtle dysfunction, calculate pressure gradients, and accurately stage cardiovascular

disease. Three pillars define this quantitative approach: Tissue Doppler Imaging (TDI), comprehensive hemodynamic measurements, and the highly sensitive modality of myocardial strain imaging.

4.1.1 Tissue Doppler Imaging (TDI)

Conventional Doppler echocardiography measures the speed and direction of red blood cells moving within the heart chambers. In contrast, Tissue Doppler Imaging (TDI) focuses on the much lower velocities of the myocardial tissue itself as it contracts and relaxes (reviewed in detail in [2]). TDI is particularly valuable for assessing diastolic function. The primary measurement in TDI is the mitral annular velocity (e'), which, when combined with the early transmitral inflow velocity (E) obtained via conventional pulsed-wave Doppler as the E/e' ratio, becomes a highly reliable, non-invasive indicator of left ventricular filling pressure. This ratio is fundamental for diagnosing and monitoring diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF), a condition often missed by traditional imaging alone.

4.1.2 Echocardiographic hemodynamic measurements

Echocardiography offers a powerful, non-invasive method for calculating pressure differences and volumes, moving beyond visual assessment to provide numerical hemodynamic data. This relies heavily on the Simplified Bernoulli Equation which is widely applied to estimate the severity of valvular heart diseases by calculating gradients across stenotic valves. The integration of Doppler flow patterns and velocity data provides a complete hemodynamic profile, often replacing the need for more invasive catheterization procedures for initial assessment.

4.1.3 Myocardial strain imaging (speckle tracking)

Myocardial strain imaging, most commonly performed using speckle tracking echocardiography (STE), provides the most sensitive measure of ventricular mechanics currently available (reviewed in detail [3, 4]). Strain quantifies the percentage change in the length of a myocardial segment during contraction, essentially measuring the localized deformation of the heart muscle. By tracking the distinct acoustic "speckles" within the myocardium, STE objectively measures three components of strain: longitudinal, circumferential, and radial.

Global longitudinal strain (GLS), which measures the shortening along the long axis of the ventricle, has emerged as the most clinically robust and reproducible parameter. Crucially, GLS is often impaired in cardiac diseases before a change in the traditional measure of ejection fraction (EF) is detected. This capability makes strain imaging indispensable for detecting subtle cardiac alterations, like early identification of cardiotoxicity in cancer patients receiving chemotherapy

or identifying subclinical left ventricular dysfunction in patients with several cardiac conditions. GLS acts as a powerful, incremental prognostic biomarker, refining risk stratification far beyond what EF can achieve alone. These modalities work to diagnose conditions earlier, monitor disease progression more accurately, and provide the essential quantitative data necessary to guide patient care and invasive interventions in contemporary cardiology.

4.1.4 Myocardial work analysis

Global longitudinal strain, derived from speckle tracking echocardiography, offered a significant advance by providing a more objective measure of myocardial deformation. However, GLS is also fundamentally load-dependent; elevated afterload can reduce strain independently of true contractility changes, complicating its interpretation. In response to these limitations, the non-invasive assessment of myocardial work (MW) has emerged as a promising tool, integrating both myocardial deformation and the mechanical load against which the heart contracts, thus providing a more physiological and less load-dependent measure of cardiac performance (reviewed in detail in [5]).

The concept of myocardial work is traditionally derived from the invasive pressure-volume (PV) loop, where the area within the loop represents stroke work. Myocardial work assessment by echocardiography translates this principle to the ventricular wall by creating a pressure-strain loop (PSL). The non-invasive calculation is achieved through a commercially available software package that combines two key inputs: i) GLS: measured via standard 2D speckle-tracking echocardiography from the apical views, this provides the deformation axis of the loop; ii) left ventricular pressure: since direct catheter-based pressure measurements are invasive, the software non-invasively estimates the LV pressure curve: this is accomplished by measuring brachial cuff blood pressure and anchoring an empirically derived, normalized LV pressure curve to key events in the cardiac cycle (aortic valve opening and closure, and mitral valve closure and opening) as timed by Doppler and M-mode echocardiography.

The area of the resulting pressure-strain loop is the global work index (GWI), expressed in mmHg%. The PSL allows for the decomposition of mechanical work into four clinically relevant components:

i) global work index (GWI): the total area of the PSL, representing the total work performed by the LV during the cardiac cycle (from mitral valve closure to mitral valve opening);

ii) global constructive work (GCW): the portion of work that contributes effectively to LV ejection (myocardial shortening during systole and lengthening during isovolumic relaxation).

This represents useful, efficient work.

iii) global wasted work (GWW): the inefficient, non-contributing work (myocardial lengthening during systole and shortening during isovolumic relaxation). GWW often reflects regional dyssynchrony or ischemia.

iv) global work efficiency (GWE): the ratio of constructive work to total work, expressed as a percentage. It is a vital marker of myocardial health, correlating closely with myocardial oxygen consumption.

Myocardial work assessment provides incremental diagnostic and prognostic information beyond LVEF and GLS, particularly in conditions where afterload is a primary determinant of function. In hypertensive heart disease, GWI and GCW are often preserved or even elevated due to increased afterload, but GWE can decline, reflecting the metabolic cost of contracting against high pressure. This provides an earlier sign of maladaptation than changes in GLS alone. In patients with coronary artery disease ischemia immediately causes segmental dysfunction, dramatically increasing GWW in the affected region due to paradoxical lengthening during the ejection phase. MW can thus provide a highly localized and quantitative tool for ischemia detection. Regarding aortic stenosis, MW indices offer a superior estimate of true myocardial contractility than GLS, which may be artificially depressed by severe afterload. MW indices, particularly GWE, are showing promise as highly sensitive, early markers for cardiotoxicity in patients receiving chemotherapy, often preceding changes in LVEF or even GLS, allowing for timely modification of treatment. Furthermore, segmental analysis of wasted work can help identify segments that require correction for dyssynchrony, optimizing lead placement and predicting response to CRT.

Thus, the non-invasive assessment of myocardial work by echocardiography represents a significant paradigm shift in the quantitative analysis of LV function. By combining the sensitivity of speckle-tracking strain with the physiological context of pressure, MW indices offer a robust, less load-dependent, and highly interpretable measure of cardiac mechanics and energetic efficiency.

4.2 Hypertrophic cardiomyopathy and direct myosin inhibitors

Advanced echocardiography is especially useful in the assessment of complex cardiac disorders, like hypertrophic cardiomyopathy (HCM), with intricate morphological and hemodynamic alterations. Hypertrophic cardiomyopathy is a common inherited cardiac disease, defined by the presence of left ventricular hypertrophy (LVH) in the absence of other causal

cardiac or systemic conditions. It is the most frequent inherited cardiac disorder, with prevalence estimated as between 1:200 and 1:500 individuals. On genetic grounds, HCM is an autosomal dominant Mendelian disease, characterized by variable expressivity and penetrance. The first HCM-causing gene, the beta myosin heavy chain gene (*MYH7*) was identified in 1989, and further seven causative sarcomeric genes (*MYBPC3, TNNT2, TPM1, MYL2, MYL3, TNNI3, ACTC1*) were detected throughout the 1990s. Since then more than one thousand variants in these eight sarcomeric genes have been linked to HCM. Sarcomeric gene mutations lead to profound alterations in myocardial contraction and relaxation. At the cellular level, pathophysiological hallmarks of the disease include hypercontractility, impaired relaxation, increased energy consumption and myocardial wall stress, which are caused by excess cross-bridge formation and dysregulation of the super-relaxed state of myosin heads. These cellular abnormalities result in organ-level morphological and functional alterations, including myocardial hypertrophy, left ventricular outflow tract obstruction, diastolic dysfunction, small vessel disease, and myocardial ischemia.

The selective and reversible cardiac myosin inhibitor mavacamten was developed for the treatment of hypertrophic cardiomyopathy (HCM) [6]. By modulating the number of available myosin heads mavacamten promotes an energy-sparing, super-relaxed state of the myosin molecule, thereby reducing the force-producing systolic and residual diastolic cross-bridge formation [7],[8]. The clinical efficacy of mavacamten was evaluated in the EXPLORER-HCM [9] and VALOR-HCM [10] clinical trials which proved the beneficial effects of mavacamten. The EXPLORER-HCM trial showed in 251 symptomatic adult patients with obstructive HCM (oHCM) that a larger proportion of patients met the primary endpoint of the study comprising a change at week 30 in exercise capacity (measured by pVO2) and symptoms (measured by NYHA functional classification). Mavacamten treatment was also associated with a significant improvement in all secondary endpoints, including reduced LVOT gradient, increased pVO2, and improved symptoms. Decreases in cardiac biomarker levels were similarly rapid and sustained while changes in baseline systolic function associated with mavacamten were small. In the VALOR trial mavacamten was shown to be superior in meeting the primary composite endpoint at week 16 which was a composite of patient decision to proceed with septal reduction therapy (SRT) or patients who remain SRT eligible (LVOT gradient of $\geq$ 50 mmHg and NYHA class III-IV, or class II with exertional syncope or near syncope). Long term extension studies revealed that treatment with mavacamten over 180 (EXPLORER-HCM) [11] and 128 weeks

(VALOR-HCM) [12] showed a sustained decrease in resting and Valsalva LVOT gradients, NT-proBNP levels, as well as improvements in NYHA class.

Based on these landmark trials, mavacamten was approved for clinical use [13],[14]. In addition to regulatory approval, the 2023 Guidelines for the management of cardiomyopathies by the European Society of Cardiology (ESC) [15] and the 2024 Guideline for the management of hypertrophic cardiomyopathy by the American Heart Association/American College of Cardiology (AHA/ACC) [16] introduced recommendations for the use of mavacamten as a second-line therapy for oHCM, in addition to a beta-blocker or non-dihydropyridine calcium channel blockers to improve symptoms in adult patients with resting or provoked LVOT obstruction.

4.3 SARS-COV-2 infection and cardiac complications

Advanced echocardiography is equally suitable to detect subtle cardiac alterations like that of caused by coronavirus disease 2019 (COVID-19). COVID-19, caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was an ongoing pandemic with —as of 22 May 2022— over 522 million cases and over 6 million deaths reported. While the disease most noticeably manifests as a respiratory infection it can cause a number of cardiac complications, which are not only common, affecting as much as 20–25% of those infected, but are major contributors of disease burden and mortality as noted in several studies [17, 18]. This highlights the need to consider COVID-19 as a multi-system disease with an important focus on the circulatory system.

The involvement of the cardiovascular system has been proven in all stages of the illness, although exact pathomechanisms and incidence remains uncertain. Cardiac involvement of COVID-19 infection may be due to multiple factors, the most important ones include myocardial damage due to acute systemic inflammatory response; hypoxia secondary to acute respiratory failure; microvascular and macrovascular thrombosis due to systemic inflammation and endothelial dysfunction; and possibly direct viral infection of the myocardium [19]. The most common forms of cardiac involvement were reported as myocardial damage, cardiac failure, acute coronary syndrome, and thromboembolic episodes [19]. Cases of fulminant myocarditis with both atrial and ventricular arrhythmias have also been previously described in the setting of COVID-19 [20].

It is of major importance to investigate the degree of residual cardiac involvement several weeks or months after recovery, due to the very high number of patients affected. This is especially true for patients with mild COVID-19, not hospitalized for the disease. Several cardiac magnetic resonance (CMR) studies have shown that, independent of overall course of the acute illness, a large part of patients showed signs of ongoing inflammation, oedema, fibrosis, and decreased functional parameters [21-24]. As cardiac MR has limited accessibility, especially for follow-up studies, two-dimensional (2D) echocardiography is the most preferred imaging modality for the assessment of most cardiovascular diseases. Among echocardiographic modalities, speckle tracking echocardiography (STE) has emerged as an echocardiographic technique providing novel parameters for the evaluation for myocardial function. The latter includes strain parameters and myocardial work parameters, that evaluates LV work estimated by employing blood pressure and left ventricular global longitudinal strain [25]. These parameters are more sensitive for predicting left ventricular myocardial injury and future cardiac events [26].

5. AIMS

5.1 As mavacamten has been recently introduced for the treatment of oHCM, data on the real-world use and efficacy of the drug are relatively scarce.

Therefore, in my PhD work **I aimed to assess the real-world effectiveness of mavacamten in a patient cohort with oHCM**, with a special attention on:

- effectiveness of mavacamten in oHCM patients with extreme (>100 mmHg) LVOT gradients;

- the short-term effects of the drug after one week of treatment;

- the effect of mavacamten on advanced transthoracic echocardiography parameters, including that of global longitudinal strain and myocardial work.

5.2. Echocardiographic alterations indicating myocardial involvement of the heart are frequent and widely reported in patients hospitalized for acute COVID-19 infection [27, 28], however, there are much fewer data in non-hospitalized, mildly symptomatic COVID-19 patients, especially regarding advanced echocardiographic parameters.

Therefore, another aim of my PhD work was **to screen for myocardial alterations after mild SARS-COV-2 infection with advanced transthoracic echocardiography modalities**, with special attention on:

- to address whether cardiac alterations, characterized by parameters provided by advanced echocardiographic techniques, e.g., strain and myocardial work, are present in patients recovered from mild COVID-19 infection.

6. PATIENTS AND METHODS

6.1 Assessing the real-world effectiveness of mavacamten in patients with obstructive HCM

6.1.1 Patients

A total of twenty-nine oHCM patients were treated with mavacamten. Of these, twenty-five patients [15 men (60%), mean age: 55±11 years] had a resting or provoked LVOT gradient of >100 mmHg and comprised the study population. Their clinical, demographic, and echocardiographic data are presented in *Table 1*. The same data for all 29 oHCM patients are presented in *Supplementary Table 1*.

The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177). The study was approved by the Hungarian Medical Research Council (8489-2/2018/EÜIG, 08783-2/2023/EÜIG, 628-1/2018/EKU ETT TUKEB) and the Institutional Research Ethics Committee of the University of Szeged (148/2024-SZTE IKEB). All subjects participating in the study gave prior written informed consent to participate in the study.

6.1.2 Mavacamten titration

Mavacamten titration was performed according to the instruction for use (IFU) of mavacamten [29], approved by the European Medicines Agency (EMA). Patients were genotyped for CYP2C19 to determine appropriate mavacamten dose. There were two patients with the poor metabolizer phenotypes, the other 23 patients had intermediate, normal, rapid or ultra-rapid metabolizer phenotypes. Starting dose was 2.5 mg in patients with CYP2C19 poor metabolizer phenotype, and 5 mg with CYP2C19 other metabolizer phenotypes. Titration of mavacamten was based on follow-up echocardiographic measurements, recommended in the IFU [29]. At W08 visits, all patients were on the 2.5 mg or 5 mg starting doses. In the 7 patients completing W48 visits, 2, 2 and 3 patients received 5 mg, 10 mg and 15 mg mavacamten, respectively. Disopyramide was stopped before initiating mavacamten treatment in all patients.

6.1.3 Methods

In addition to recording the main demographic, clinical and laboratory parameters, complete standard and 2D-speckle tracking echocardiographic examination was performed in the patients after 1 week (W01) of treatment and in four-week intervals thereafter until 24 weeks and in 12-week intervals until 48 weeks. All patients completed the W08 visit, and 7 patients completed the W48 visit.

Table 1. Clinical, demographic and echocardiographic characteristics of the hypertrophic cardiomyopathy patient cohort with >100 mmHg LVOT gradient treated with mavacamten (n=25).

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS	
Age, years	
Mean (SD)	55 (11.3)
Median (IQR)	55 (50-61)
Female, n (%)	10 (40)
BMI, mean (SD), kg/m^2	30.0 (4.3)
Genetic testing	
genetic testing results available, n (%)	20 (80)
carrier of pathogenic/likely pathogenic (P/LP) variant, n (%)	4 (20)
identified P/LP variants	*MYBPC3* p.Phe1159TyrfsTer9, *MYBPC3* p.Tyr1136del, *MYBPC3* p.Ser25fs, *MYH7* p.Pro307Ser
carrier of VUS (variant of unknown significance), n (%)	3 (15)
identified VUS variants	*DSP* p.Arg1537Cys, *MYL3* p.Pro23His, *DSC2* p.Ala452Val
no variant, n (%)	13 (65)
Baseline NYHA class, n (%)	
Class II	9 (36)
Class III	16 (64)
Duration since HCM diagnosis, mean (SD), years	8 (4.6)

ECHOCARDIOGRAPHIC AND CLINICAL CHARACTERISTICS	
Transthoracic echocardiographic parameters, mean (SD)	
LVEF, %	65.1 (6.0)
Maximal LV wall thickness, mm	24.2 (3.6)
Resting LVOT peak gradient, mmHg	121 (36.1)
Valsalva LVOT peak gradient, mmHg	167 (36.9)
Cardiac rhythm, n (%)	
Sinus rhythm	24 (96)
Comorbidities, n (%)	
Hypertension	18 (72)
Paroxysmal atrial fibrillation	4 (16)
Coronary artery disease	3 (12)
Prior attempted septal reduction therapy, n (%)	
Septal myectomy	0 (0)
Alcohol septal ablation	10 (40)
Background HCM medical therapy prior to mavacamten start, n (%)	
BB monotherapy	5 (20)
Non-dihydropyridine CCB monotherapy	0 (0)
BB and non-dihydropyridine CCB	0 (0)
BB and disopyramide	20 (80)
Prior device therapy, n (%)	
ICD	4 (16)

Data are expressed as mean (standard deviation, SD), median (interquartile range, IQR) or number (percentage). BMI: body mass index, *MYBPC3*: cardiac myosin binding protein C gene, *MYH7*: beta myosin heavy chain 7 gene, *MYL3*: myosin light chain 3 gene, *DSC2*: desmocollin 2 gene, *DSP:* desmoplakin gene, VUS: variant of unknown significance, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, BB: beta-blocker, CCB: calcium channel blocker, ICD: implantable cardioverter defibrillator.

Resting blood pressure was measured in the supine position immediately before the echocardiographic examination. All patients underwent comprehensive echocardiography, including 2D speckle tracking echocardiography for the left and right ventricles and the left atrium, as well as non-invasive myocardial work analysis. All measurements included in this study were assisted or gated with electrocardiogram. Standard measurements of dimensions of the left- and right-side of the heart were carried out with indexing for body surface area (BSA) where necessary. Left ventricular systolic function was assessed comprehensively, including ejection fraction measurement using the biplane Simpson's method and hemodynamic parameters derived from Doppler measurement of the left ventricular outflow tract (LVOT) velocity time integral (VTI) and the size of the LVOT, and well as the resting heart rate. Left ventricular outflow tract gradient was assessed at rest and during the Valsalva manoeuvre to determine peak instantaneous and provoked gradients, respectively. Echocardiographers carefully adjusted the Doppler angle from the left atrium to the LVOT to differentiate mitral regurgitation from LVOT flow. Diastolic function was evaluated according to current guidelines, incorporating tissue velocity imaging (TVI). Left heart speckle-tracking strain analysis included global longitudinal strain (GLS) measurement from apical 2-, 3-, and 4-chamber views. From these data, the following global myocardial work parameters were derived: global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE). Left ventricular peak pressure, used in the GWI, GCW, GWW, and GWE calculations, was determined as previously described [30]. The investigation of the systolic function of the right ventricle included tricuspid annular plane systolic excursion, and the peak systolic velocity of the tricuspid annulus measured by TVI. The right ventricular longitudinal free wall strain was also measured with the dedicated right ventricular speckle-tracking software. All examinations were carried out with a GE Vivid E95 R4 (GE Healthcare, Horten, Norway) cardiac ultrasound system.

6.1.4 Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range, IQR) as appropriate. Normality for the distribution of continuous variables was tested by the Kolmogorov–Smirnov or the Shapiro-Wilks test.

Temporal change in parameters in the mavacamten treated patients was assessed by a mixed model repeated measures ANOVA using autoregressive covariance structure. Assumption of normality of residuals was graphically checked, in case of skewed distributions logarithm transformation was used. Pairwise comparisons were performed on estimated marginal means

using Sidak correction for multiple comparisons. Differences between groups were analysed with the Student's T test, in case of normally distributed continuous variables, and with the Mann–Whitney U test, in case of non-normally distributed continuous variables. For categorical variables the Chi-square test and Fisher's exact tests were used.

Statistical analysis was done with MedCalc® Statistical Software version 20.106 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). A $p<0.05$ value was considered as statistically significant.

6.2 Screening for myocardial alterations after mild SARS-COV-2 infection with advanced transthoracic echocardiography modalities

6.2.1 Patients

Patients recovered from mild COVID-19 infection (defined as not requiring hospital treatment or requiring <5 days hospital treatment) and having residual symptoms were entered into the study. Initially 102 patients were assessed because of residual symptoms such as chronic fatigue, difficulty of carrying out previously undemanding physical activity, and palpitations. Out of the initially assessed subjects, 16 patients were ruled out due to suboptimal image quality, known diabetes and previously known coronary artery disease.

Of the remaining 86 patients [30 (34.9%) males, avg. age: 39.5±13.0 yrs (age range: 13–67 yrs; 90% of patients and 77% of the patients being <55 and <50 yrs old, respectively)] a few had well controlled hypertension, and 1 patient had mixed connective tissue disease which was not active immunologically at the time of examination. Most patients had mild symptoms during their acute illness with COVID-19, with only 4 patients requiring short (<5 days) hospitalization for moderate symptoms, none having troponin T elevation or requiring intensive care unit treatment.

The number of patients receiving any type of specific anti-viral treatment was negligible, with 2 patients having received remdesivir, and 1 patient having received favipiravir.

At the time of assessment (59±33 days after COVID-19 diagnosis; 84% and 90% of the patients were examined within 93 and 100 days, respectively), no patient had elevated troponin T levels or >200 pg/mL NT-proBNP levels. No major ECG changes were detected in the patients apart of >100 bpm sinus tachycardia which was present in 2 patients.

Table 2. Baseline clinical characteristics of study patients.

	control group (*n*=60)	post-COVID group (*n*=86)	relative difference (%) †
age, year	40.3±11.0	39.5±13.0	NA
male sex	24 (40.0)	30 (34.9)	NA
BSA, m^2	1.9±0.3	1.9±0.3	NA
systolic blood pressure, Hgmm	130.3±12.8	132.2±15.8	NA
diastolic blood pressure, Hgmm	75.0 (67.0–82.0)	78.0 (67.8–86.0)	NA
previously treated/diagnosed hypertension	7 (11.7)	10 (11.8)	NA
heart rate, bpm	**70.9±10.8**	**75.6±13.4***	**9.5**

Values are given as mean±SD, median (interquartile range) or *n* (%). Values are considered statistically significantly different at $p < 0.05$ (*), compared with the control group. Significant differences are marked with asterisk and printed in bold. † Relative difference is given only for parameters showing statistical difference compared to controls. BSA: body surface area; NA: not applicable.

An age- and sex-matched group of 60 ostensibly healthy subjects [24 (40.0%) males, avg. age: 40.3±11.0 yrs] served as a control group. None of the subjects had a history of any illness or was on any medication. The control group either did not have COVID-19 infection or had COVID-19 infection >1 year apart of the examination. The baseline clinical characteristics of the study and control patients did not differ statistically (*Table 2*).

6.2.2 Methods

In addition to recording the main demographic, clinical and laboratory parameters, advanced echocardiography was performed as described in section 6.1.3.

6.2.3 Statistical analysis

Statistical analysis was performed as described in section 6.1.4. In addition to the methods described above, for assessing Covid-related changes, the Pearson's or Spearman's correlation analysis was used to analyse correlations between continuous variables. We performed multivariable linear regression analyses to examine the independent correlates between GLS and myocardial work parameters and standard and advanced echocardiographic parameters. To characterize the magnitude of changes, relative difference regarding parameters between the study and the control groups were calculated and were expressed as the relative percentage difference between the median of the parameters (to exclude the effect of outlier values).

7. RESULTS

7.1 Assessing the real-world effectiveness of mavacamten in patients with oHCM

7.1.1 LVOT gradient of >100 mmHg decreased significantly even after one week of mavacamten treatment

After only one week of mavacamten therapy, the resting peak LVOT gradient decreased by an average of -34 mmHg (95% CI: -53 to -14), from 121 to 87 mmHg (p<0.001); which decreased further to 56 mmHg at W08 (p<0.001). The LVOT gradient provoked by the Valsalva manoeuvre decreased by -38 mmHg (95% CI: -60 to -17) at W01, from 167 to 129 mmHg (p<0.001), with a further decrease to 80 mmHg at W08 (p<0.001) (*Table 3* and *Figure 1*). In the 7 patients completing W48 visits, the resting peak LVOT gradient decreased further to 7 mmHg (p<0.001), and the Valsalva peak LVOT gradient decreased to 9 mmHg (p<0.001).

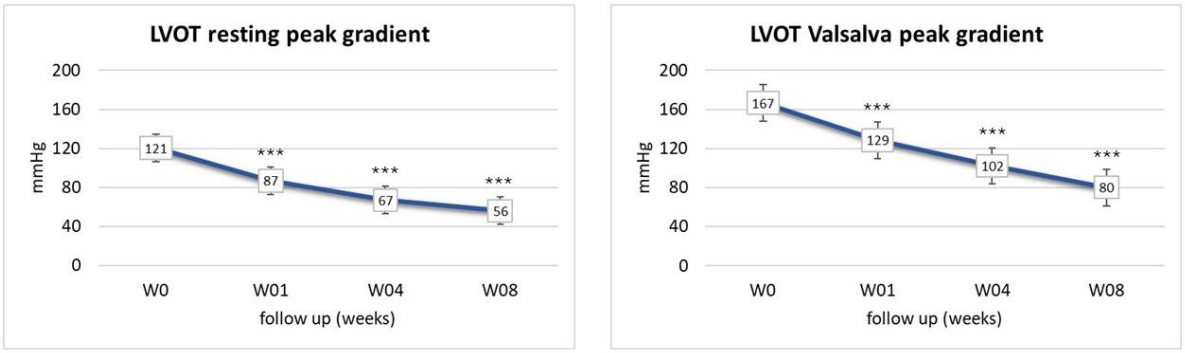

Figure 1. Change in resting and Valsalva left ventricular outflow tract peak gradients after 1 (W01), 4 (W04) and 8 (W08) weeks of mavacamten treatment. *** denotes significant difference vs. baseline values at the p<0.001 level. LVOT: left ventricular outflow tract.

7.1.2 Increase of LVOT gradient with mavacamten withdrawal and restoration of gradient decrease with mavacamten re-initiation

A 58-years-old (Patient No. 2.) and a 56-years old (Patient No. 6.) female patient developed atrial fibrillation (AF) after 36 days (Patient No. 2.) and 188 days (Patient No. 6.) of mavacamten initiation. During mavacamten treatment the LVOT gradient showed a substantial decrease in both cases (resting LVOT gradient from 100-173 to 94-76 mmHg at W1, and to 30-10 mmHg at the time of mavacamten stop; Valsalva gradient: from 195-198 to 132-95 mmHg

Table 3. Change in clinical, echocardiographic and biomarker parameters after one week (W01), 4 weeks (W04) and 8 weeks (W08) of mavacamten treatment in oHCM patients with >100 mmHg left ventricular outflow gradient (n=25).

	baseline	W01	W04	W08
LVOTG, resting peak (mmHg)	121±9	**87±9*** **	**67±9*** **	**56±9*** **
LVOTG, resting peak, mean difference (mmHg)		**-34 (-53 to -14)*** **	**-54 (-78 to -29)*** **	**-64 (-91 to – 37)*** **
LVOTG, Valsalva peak (mmHg)	167±10	**129±10*** **	**102±10*** **	**80±10*** **
LVOTG, Valsalva peak, mean difference (mmHg)		**-38 (-60 to -17)*** **	**-64 (-91 to -38)*** **	**-87 (-116 to -57)*** **
NT-proBNP (pg/ml)	2952±602	**1485±604*** **	**1217±604*** **	**904±615*** **
NT-proBNP, mean difference (pg/ml)		**-1467 (-2379 to -556)*** **	**-1735 (-2951 to -520)*** **	**-2048 (-3491 to -606)*** **
Troponin T (ng/l)	35±10	36±10	30±10	**24±10***
6-minute walk distance (m)	408±18	**434±18***	**466±18*** **	**462±18*** **
EF (%)	65±1	65±1	63±1	64±1
GLS (%)	-13.7±0.6	-13.6±0.6	-13.5±0.6	-13.5±0.6
GWI (mmHg%)	2098±98	1898±99	**1747±98** **	**1659±101** **
GCW (mmHg%)	2622±112	2404±113	**2206±111** **	**2093±115** **
GWW (mmHg%)	310±25	305±26	278±25	278±26
GWE (mmHg%)	85±1	84±1	86±1	85±1
LAV (ml)	132±5	126±5	119±5	120±5
LAV-index (ml/m^2)	66±2	64±2	61±2	61±2
e' lateral (cm/s)	6.8±0.5	7.2±0.5	7.2±0.5	7.9±0.6
E/e'	18±1	18±1	17±1	14±1
mitral insufficiency ≥3, n/n (%)	15/25 (60%)	11/25 (44%)	**4/25 (16%)** **	**3/25 (12%)*** **
mitral insufficiency ≥2, n/n (%)	21/25 (84%)	17/25 (68%)	**13/25 (52%)***	**7/25 (28%)*** **
LV EDD (mm)	46±0.8	46±0.8	47±0.8	46±0.8
LV ESD (mm)	29±0.9	30±0.9	30±0.9	30±0.9
LV EDV (ml)	106±6	101±6	94±6	101±6
LV EDV-index (ml/m^2)	52±3	51±3	48±3	51±3
LV ESV (ml)	37±2.6	35±2.6	35±2.6	37±2.6
LV ESV-index (ml/m^2)	18±1	17±1	18±1	19±1
IVS (mm)	24±0.7	23±0.7	23±0.7	23±0.7
PW (mm)	13±0.5	13±0.5	13±0.5	13±0.5
maximal LV wall thickness (mm)	24±0.7	24±0.7	24±0.7	24±0.7

Data are expressed as mean±SEM or mean (95% confidence intervals). Values are considered significantly different at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Significant changes are highlighted in bold. SEM: standard error of mean, LVOTG: left ventricular outflow tract gradient, EF: ejection fraction, GLS: global longitudinal strain, GWI: global work index, GCW: global constructive work, GWW: global wasted work, GWE: global work effectiveness, LAV: left atrial volume, LAVI: left atrial volume index, LV: left ventricular, EDD: end-diastolic diameter. EDV: end-diastolic volume, ESD: end-systolic diameter, ESV: end-systolic volume, IVS: interventricular septum, PW: posterior wall.

at W01, and to 74-25 mmHg at the time of mavacamten stop). A successful electrical cardioversion was performed in both cases with restoration of sinus rhythm. Although LV ejection fraction was not compromised (EF: 62 and 58%) mavacamten was withhold for precautionary reasons for one month. Without mavacamten therapy the LVOT gradient rose again (resting gradient: from 30-10 to 130-98 mmHg; Valsalva gradient: from 74-25 to 143-127 mmHg). After mavacamten re-initiation LVOT gradients fell again rapidly (resting gradient: from 130-98 to 12-15 mmHg, Valsalva gradient: from 143-127 to 25-22 mmHg) (see gradient changes in Patient No. 2. in *Figure 2*).

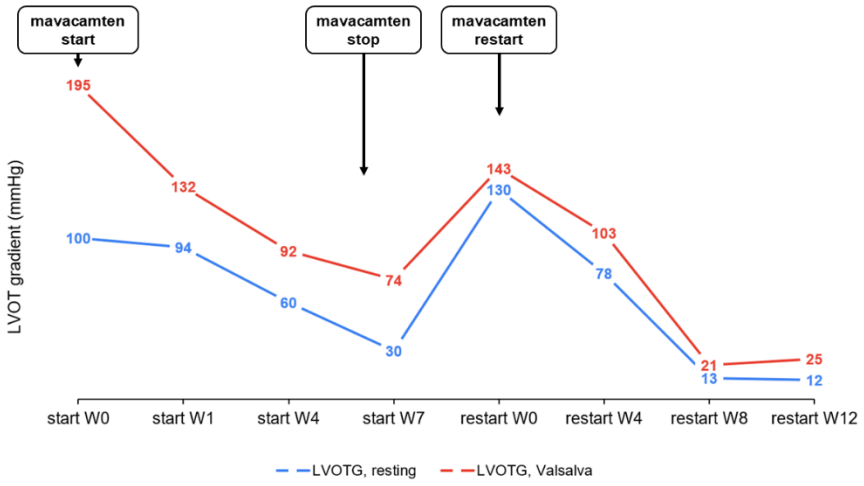

Figure 2. Increase of LVOT gradient in Patient No. 2. with mavacamten withdrawal and restoration of gradient decrease with mavacamten re-initiation. The start, stop and re-start of mavacamten therapy is marked with arrows. See details in text. LVOT: left ventricular outflow tract.

7.1.3 The decrease in the LVOT gradient was paralleled by a decrease in laboratory biomarker levels

Parallel to the decrease of the LVOT gradient, NT-proBNP levels significantly decreased at W01 by -1467 pg/ml (95% CI: -2379 to -556), from 2952 to 1485 pg/ml ($p<0.001$), which further decreased at W08 to 904 pg/ml [mean difference: -2048 pg/ml (95% CI: -3491 to -606); $p<0.001$] (*Figure 3* and *Table 3*). In the 7 patients completing W48 visits the mean NT-proBNP levels decreased to 269 pg/ml ($p<0.001$). Changes in troponin T levels were not significant at W01; however, it showed a significant decrease at W08 (from 35 to 24 ng/l; $p=0.021$) (*Figure 3* and *Table 3*). In the 7 patients completing W48 visit the mean troponin T levels decreased to 12 ng/l ($p=0.021$).

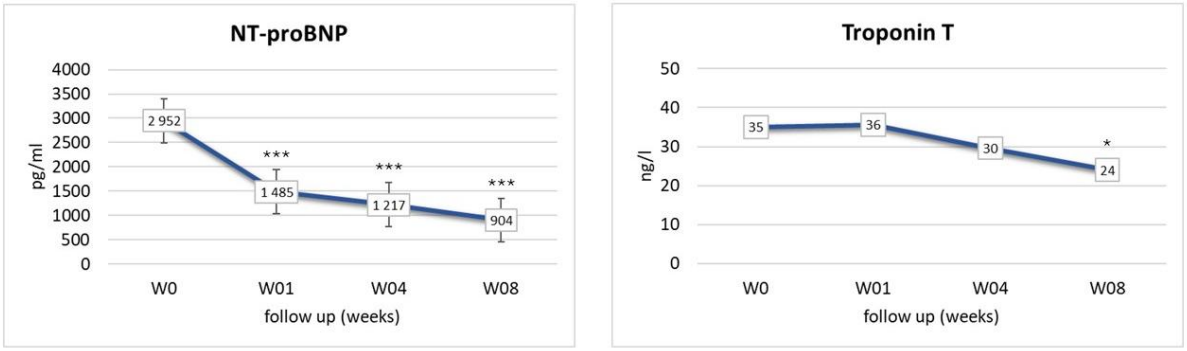

Figure 3. Change in NT-proBNP and troponin T levels after 1 (W01), 4 (W04) and 8 (W08) weeks of mavacamten treatment. *** and * denotes significant difference vs. baseline values at the p<0.001 and the p<0.05 level, respectively.

7.1.4 Significant improvement in NYHA functional class and 6-minute walk distance

There was no significant change in NYHA functional class observed at week 1. The earliest significant improvement regarding NYHA class occurred at week 4 (W04). At this point, the percentage of patients with NYHA class I increased from 0% to 8%, those with NYHA class II increased from 36% to 64%, and those with NYHA class III decreased from 64% to 28% (p=0.0237). NYHA class showed further improvement by week 8 (W08), with the percentages of patients in NYHA class I, II, and III being 20%, 64%, and 16% respectively (p=0.0008) (*Figure 4*). At week 48 (W48), 71% of the patients were in NYHA I, and 29% of the patients were in NYHA II class.

Parallel to improvement in NYHA functional class, 6-minute walk distance significantly improved at the W01 visit [median difference 26 m (95% CI: 5-48), p=0.01] and further improved at the W04 visit [median difference 59 m (95% CI: 33-85), p<0.001] and W08 visit [median difference 54 m (95% CI: 23-86), p<0.001] (*Figure 4* and *Table 3*). Further improvement was observed in patients completing W48 visits [median difference 92 m (95% CI: 2-182), p=0.043].

7.1.5 No significant change of LV diameters, LV volumes, LV ejection fraction or global longitudinal strain

Left ventricular diameters, volumes, ejection fraction and global longitudinal strain did not change significantly neither at W01 nor at W08 visits (*Figure 5* and *Table 3*). No further significant decrease was seen in the 7 patients completing W48 visits.

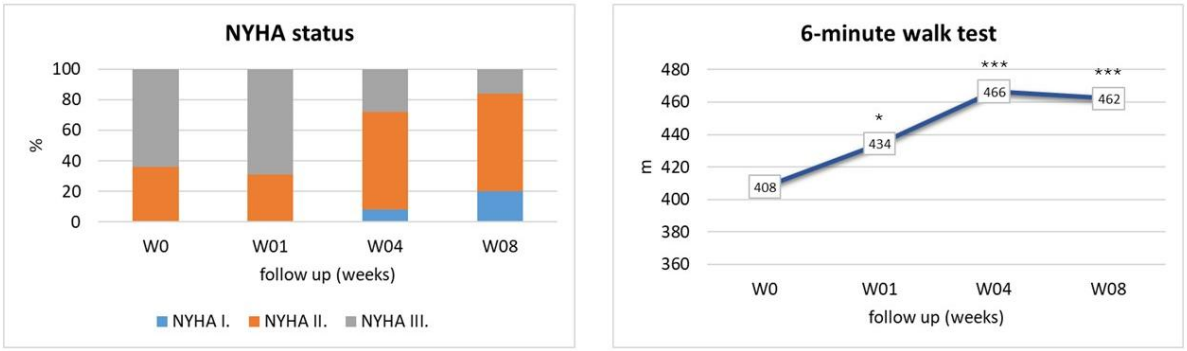

Figure 4. Change in NYHA status and 6-minute walk distance after 1 (W01), 4 (W04) and 8 (W08) weeks of mavacamten treatment. *** and * denotes significant difference vs. baseline values at the p<0.001 and the p<0.05 level, respectively.

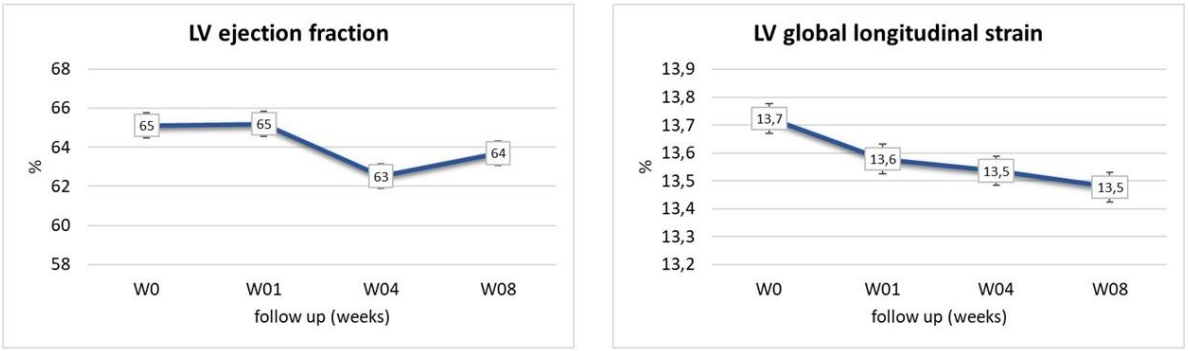

Figure 5. Change in left ventricular ejection fraction and global longitudinal strain after 1 (W01), 4 (W04) and 8 (W08) weeks of mavacamten treatment. For global longitudinal strain absolute values are given. LV: left ventricle.

7.1.6 Despite of no change in global longitudinal strain, myocardial work parameters showed favourable significant changes

As the LVOT gradient decreased, the global work index (GWI) continuously decreased through W08 (2098 vs. 1898 at W01, p=0.100; vs. 1747 at W04, p=0.009; vs. 1659 mmHg% at W08, p=0.003). Global constructive work showed similar changes (GCW: 2622 vs. 2404 at W01, p=0.163; vs. 2206 at W04, p= 0.009; vs. 2093 mmHg% at W08, p=0.002). Global wasted work (GWW) and global work efficiency (GWE) didn't show significant changes (GWW: 310 vs. 305 at W01, p=0.996; vs. 278 mmHg% at W08, p=0.695; GWE: 85 vs. 84% at W1, p=0.998; vs. 85% at W8, p=0.984) (*Figure 6* and *Table 3*).

As values for normal ranges are available for all MW parameters [31], we were able to compare the number of patients with abnormal MW values at the different visits. GWI (normal range: 1292–2505 mmHg%) and GCW (normal range: 1582–2881 mmHg%) was abnormal only in 26% and 39% of patients at W0, respectively, which percentage decreased to 9% regarding both

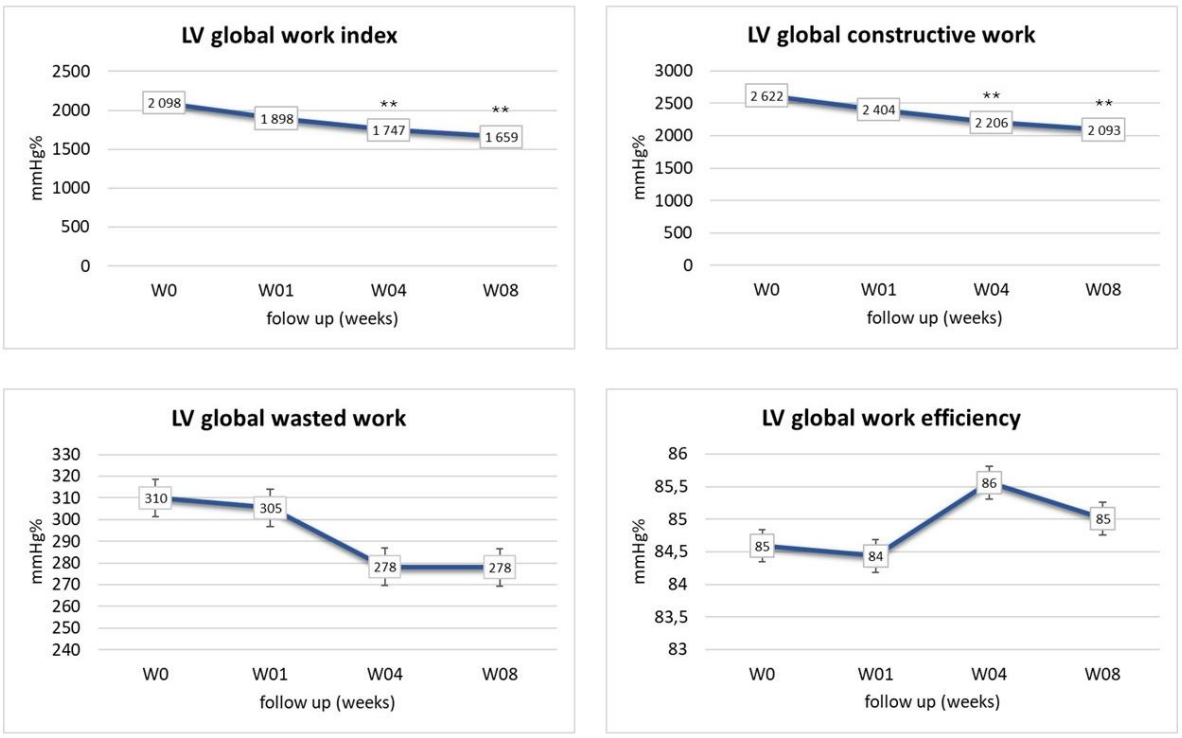

Figure 6. Change in left ventricular global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE) after 1 (W01), 4 (W04) and 8 (W08) weeks of mavacamten treatment. ** denotes significant difference vs. baseline values at the p<0.01 level. LV: left ventricle.

GWI (p=0.124) and GCW (p=0.017) at W08. All patients completing W48 visits had a normal GWI (p=0.127) and GCW (p=0.030). GWW (upper limit of normal: 226 mmHg%) was abnormal in 74% of patients at W0, which percentage decreased to 48% at W08 (p=0.073). All patients completing W48 visits had a normal GWW (p=0.0009). Finally, GWE values (lower limit of normal: 91%) were abnormal in 87% of the patients at W0, which did not change at W08 (78%, p=0.442), but was recorded only in 29% of patients completing W48 visits (p=0.003).

7.1.7 Favourable changes in the degree of mitral regurgitation, diastolic function and left atrial volumes during mavacamten treatment

The degree of mitral regurgitation (MR) showed significant changes with decrease of ≥3 grade MR from 60% to 44% at W01 (p=0.297), to 16% at W04 (p=0.0015) and to 12% at W08 (p=0.0005); and decrease of ≥2 grade MR from 84% to 68% at W01 (p=0.260), to 52% at W04 (p=0.0164) and to 28% at W08 (p=0.0001) (*Table 3*).

Left atrial volume and volume index values showed a favourable non-significant regression trend through W08 (LAV: 132 vs. 120 ml; p=0.175; LAVI: 66 vs. 61 ml/m^2; p=0.492) (*Table 3*), the changes were significant in the 7 patients completing W48 visits (mean difference, LAV:

-46 ml; p=0.001; LAVI: -23 ml/m^2; p=0.001). Lateral e' and E/e' displayed non-significant changes through W08 (lateral e': 6.8 vs. 7.9 cm/s, p=0.230; E/e': 18 vs. 14, p=0.093) (*Table 3*), the changes were significant in the 7 patients completing W48 visits regarding E/e' (mean difference: -7, p=0.035).

7.1.8 The entire cohort of 29 oHCM patients showed similar changes across all assessed parameters

Across the entire cohort of 29 oHCM patients, the temporal change and the magnitude of changes were similar across individuals for all the assessed clinical, echocardiography, and biomarker changes (*Supplementary Table 2*).

7.1.9 Safety profile and adverse events

Three patients developed atrial fibrillation (AF) during mavacamten treatment (a 58-years-old, a 56-years old female, and a 50-years old male), all with a previous history of AF. AF occurred after 36, 188 and 21 days after mavacamten treatment initiation. All patients were converted into sinus rhythm (SR) and remained in SR until last follow up. No hospitalization for heart failure, no major arrhythmia or EF<50% occurred.

7.2 Screening for myocardial alterations after mild SARS-COV-2 infection with advanced transthoracic echocardiography modalities

Altogether, variables from eleven echocardiographic categories representing morphological or functional echocardiographic parameters showed statistical difference between the post-COVID patient group and the control group. The magnitude of change was subtle or mild in case of these parameters, ranging from 1–11.7% of relative change (either increase or decrease in the parameter). Detailed comparison of the echocardiographic parameters regarding dimensions and function of the left-and right-side of the heart is given in *Tables 4–7*.

7.2.1 Dimensional parameters of the left-side of the heart

Among parameters representing dimensions and volumes of the left-side of the heart, the LV end diastolic diameter (46.2 vs. 47.9 mm; p=0.020), the LV end systolic volume index (15.5 vs. 17.1 ml/m^2; p=0.013) and the LV posterior wall thickness (8.5 vs. 9.0 mm; p=0.042) showed significant difference between the post-COVID and the control group (*Table 4*). However, the relative difference was <10% in the case of all the different parameters, indicating only a mild dilatation of the LV in the post-COVID group.

Table 4. Echocardiographic parameters of the left atrium and left ventricle in the study groups.

	control group (*n*=60)	post-COVID group (*n*=86)	relative difference (%) †
left atrial volume, ml	50.0 (42.3–60.8)	50.0 (40.0–60.0)	NA
left atrial volume index, ml/m^2	26.0 (23.0–31.0)	27.0 (22.0–32.0)	NA
left ventricular end diastolic diameter, mm	**46.2±4.2**	**47.9±4.2***	**3.2**
left ventricular end systolic diameter, mm	30.0 (27.5–33.0)	30.0 (27.0–33.0)	NA
left ventricular end diastolic volume, ml	91.5 (72.0–118.5)	97.0 (81.0–114.0)	NA
left ventricular end diastolic volume index, ml/m^2	49.5±11.2	51.9±12.8	NA
left ventricular end systolic volume, ml	32.0 (24.0–36.5)	32.5 (27.0–41.0)	NA
left ventricular end systolic volume index, ml/m^2	**15.5 (13.3–18.6)**	**17.1 (15.2–21.0)***	**9.9**
interventricular septum, mm	9.0 (8.0–9.5)	9.0 (8.0–10.0)	NA
posterior wall, mm	**8.5 (8.0–9.0)**	**9.0 (8.0–10.0)***	**5.9**

Values are given as mean±SD, median (interquartile range) or n (%). Values are considered statistically significantly different at p<0.05 (*), compared with the control group. Significant differences are marked with asterisk and printed in bold. † Relative difference is given only for parameters showing statistical difference compared to controls.

7.2.2 Functional parameters of the left-side of the heart

Parameters representing the systolic function of the LV, including LV ejection fraction (68.0 vs. 66.0%; p=0.031], stroke volume (75.5 vs. 70.5 ml; p=0.004) and stroke volume index (41.6 vs. 37.4 ml/m^2; p=0.0003) were all significantly, but mildly decreased in the post-COVID patient group (*Table 5*). Here again, the relative decrease in these parameters was 10% the most. Interestingly, despite the mild decrease in stroke volume, cardiac output and cardiac index were not different between the groups, as heart rate was significantly increased in post-COVID patients (70.9 vs. 75.6 bpm; p=0.029) presumably compensating for the decrease in stroke volume.

Among parameters representing contractile function of the LV, global longitudinal strain showed one of the most significant differences between the two groups [-20.3 vs. -19.1 %; p=0.0007], with a relative decrease of 5.9% (*Figure 7* and *Table 5*). The decreased GLS values correlated with many parameters of LV dimension and function in univariate correlation

analysis (*Table 7*) but correlated only with LV stroke volume index (partial correlation coefficient, $r_{partial}$: −0.284; p=0.029), and the left atrial volume index ($r_{partial}$: −0.343; p=0.008) in the multivariate regression analysis.

Parameters representing LV diastolic function did not differ between the study and the control group.

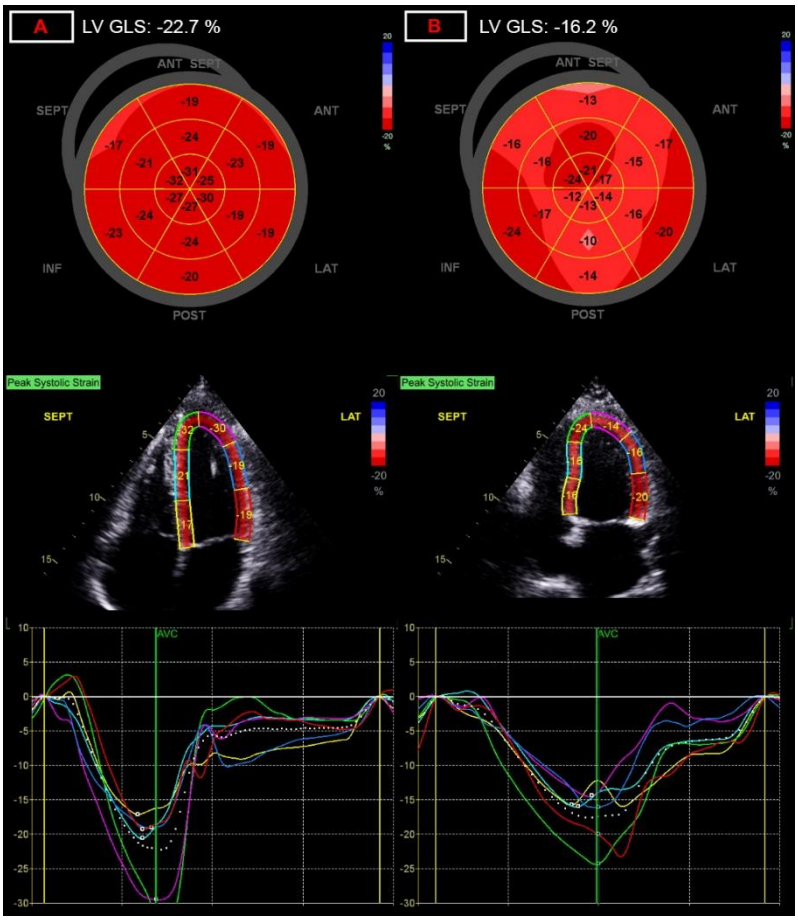

Figure 7. Representation of alterations of global longitudinal strain (GLS) measurement. (A) panel: normal left ventricular global longitudinal strain of −22.7%; (B) panel: decreased left ventricular global longitudinal strain of −16.2%, after COVID-19 infection.

Table 5. Echocardiographic parameters of the systolic and diastolic function of the left atrium and left ventricle in the study groups.

	control group (*n*=60)	post-COVID group (*n*=86)	relative difference (%) †
LV ejection fraction, %	**68.0 (65.0–70.0)**	**66.0 (60.0–70.0)***	**2.9**
LVOT velocity time integral, cm	23.0 (21.2–24.5)	22.2 (20.2–24.9)	NA
LV stroke volume, ml	**75.5 (70.0–87.0)**	**70.5 (61.0–78.0)****	**6.6**
LV stroke volume index, ml/m^2	**41.6 (38.9–43.7)**	**37.4 (33.5–41.8)*****	**10.0**
LV cardiac output, l/min	5.5±1.1	5.4±1.2	NA
LV cardiac index, l/min/m^2	2.9±0.5	2.9±0.6	NA
LV global longitudinal strain, %	**−20.3 (−21.1–−19.0)**	**−19.1 (−20.4–−17.6)*****	**5.9**
LV global work index, mmHg%	**1975 (1789–2105)**	**1829 (1656–2057)****	**7.4**
LV global constructive work, mmHg%	2383 (2226–2577)	2341 (2094–2559)	NA
LV global wasted work, mmHg%	99 (63–129)	107 (77–151)	NA
LV global work efficiency, %	**96 (94–97)**	**95 (93–96)***	**1.0**
transmitral E velocity, cm/s	82.0 ± 13.5	82.21 ± 15.7	NA
transmitral A velocity, cm/s	59.0 (51.3–70.5)	61.0 (54.0–76.0)	NA
E/A	1.35 (1.15–1.63)	1.31 (1.07–1.63)	NA
mitral annulus e' velocity, cm/s	14.5 (12.0–16.0)	13.0 (11.0–17.0)	NA
mitral annulus a' velocity, cm/s	9.0 (8.0–12−0)	10.0 (8.0–12.0)	NA
mitral annulus s' velocity, cm/s	11.0 (10.0–13.0)	10.0 (9.0–12.0)	NA
E/e'	5.6 (4.9–6.8)	6.0 (5.2–7.3)	NA

Values are given as mean±SD, median (interquartile range) or n (%). Values are considered statistically significantly different at p<0.05 (*), p<0.01 (**), p<0.001 (***), compared with the control group. Significant differences are marked with asterisk and printed in bold. † Relative difference is given only for parameters showing statistical difference compared to controls. LV: left ventricle; LVOT: LV outflow tract, LA: left atrium.

7.2.3 Myocardial work parameters

With regard to myocardial work parameters, global myocardial work index (GWI) values (1975 vs. 1829 mmHg%; p=0.007) (*Figure 8* and *Table 5*) and global work efficiency (GWE) values (96 vs. 95 %; p=0.0389 were significantly decreased, and the other two myocardial work parameters, LV global constructive work (2383 vs. 2341 mmHg%; p=0.080) and

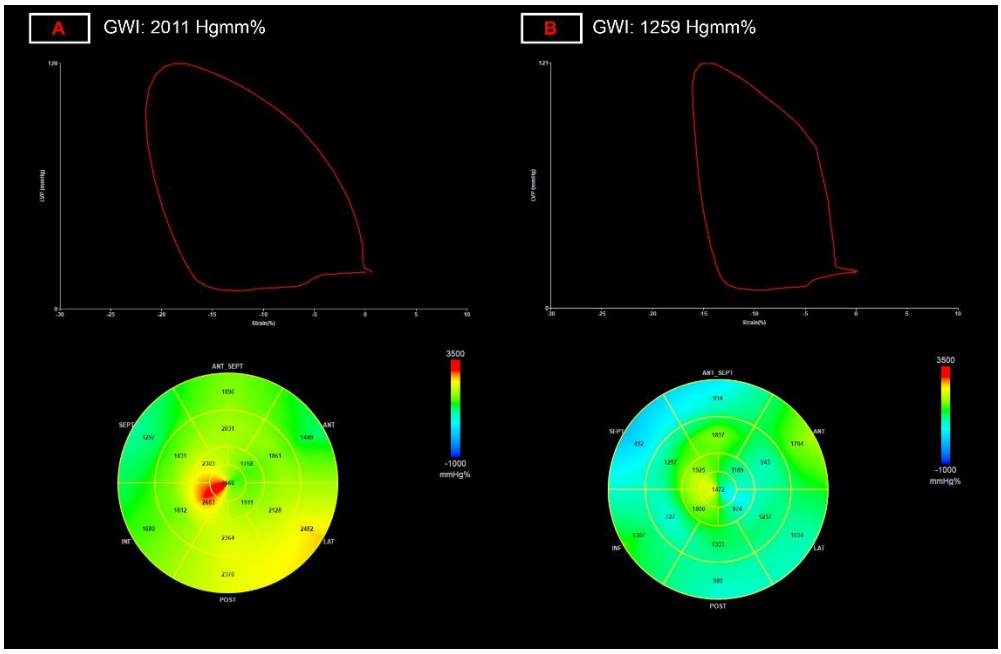

Figure 8. Representation of alterations global myocardial work index (GWI) measurement. (A) panel: normal left ventricular myocardial work index of 2011 Hgmm%; (B) panel: decreased left ventricular myocardial work index of 1259 Hgmm%, after COVID-19 infection.

LV global wasted work (99 vs. 107 mmHg%; p=0.088) also showed marked differences, close to significancy (*Table 5*). The decreased GWI and GWE values correlated with many parameters of LV dimension and function in univariate correlation analysis (*Table 7*) but correlated with none of the parameters in the multivariate regression analysis (apart of GLS and systolic RR which they are derived from).

7.2.4 Dimensional and functional parameters of the right-side of the heart

Dimensions of the right heart did not show statistical difference between the two groups. Among functional parameters, tricuspid annular plane systolic excursion values were significantly decreased in post-COVID patients (23.75 vs. 22.5 mm; p=0.039), while tricuspid annular s' velocity values were similar. However, right ventricular free wall strain values (−26.6 vs. −23.8%; p=0.0003; *Figure 9*) were significantly decreased in post-COVID patients, showing the most significant change, and showing the largest relative difference between the two groups at 11.7% (*Table 6*).

Table 6. Echocardiographic parameters of dimension and function of the right atria and right ventricle in the study patients.

	control group (*n*=60)	post-COVID group (*n*=86)	relative difference (%) †
right atrial area, cm^2	14.0 (11.0–16.4)	14.0 (12.0–16.7)	NA
right ventricular basal diameter, mm	35.0±4.5	35.6±5.6	NA
right ventricular diameter at the level of the papillary muscles, mm	29.0±5.1	29.7±4.7	NA
tricuspid annular plane systolic excursion, mm	**23.75±2.8**	**22.5±3.4***	**5.3**
tricuspid annular s' velocity, mm	14.0 (13.0–15.0)	13.0 (12.0–15.0)	NA
right ventricular free wall strain, %	**−26.6±3.80**	**−23.8±4.0*****	**11.7**

Values are given as mean±SD, median (interquartile range) or n (%). Values are considered statistically significantly different at $p<0.05$ (*), $p<0.001$ (***), compared with the control group. Significant differences are marked with asterisk and printed in bold. † Relative difference is given only for parameters showing statistical difference compared to controls.

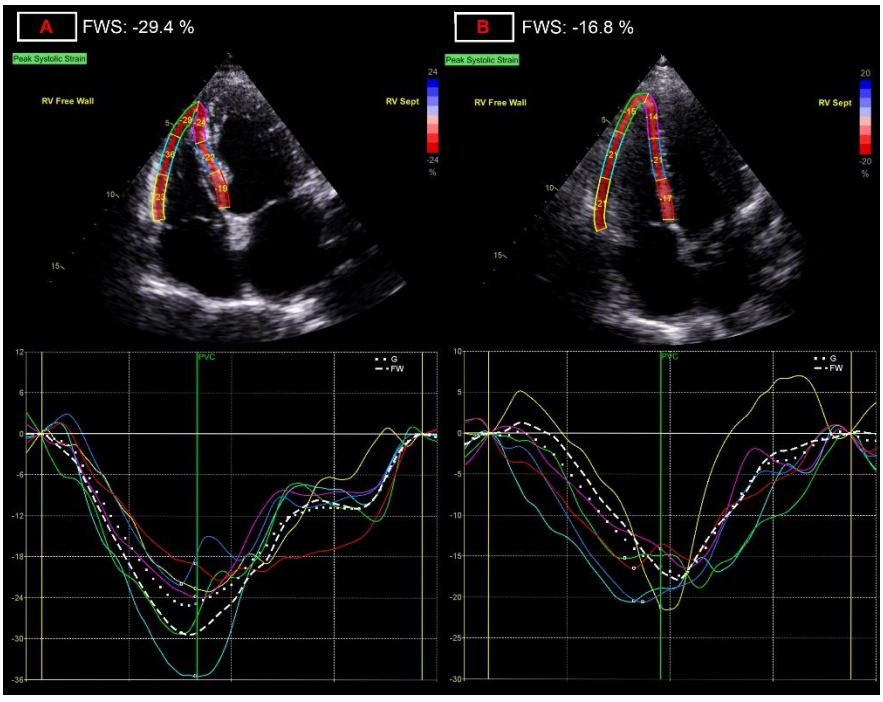

Figure 9. Representation of alterations of right ventricular free wall strain (FWS) measurement. (A) panel: normal right ventricular free wall strain of −29.4%; (B) panel: decreased right ventricular free wall strain of −16.8%, after COVID-19 infection.

Table 7. Univariate and multivariate correlation analysis of advanced echocardiographic parameters.

	GWI		GWE		GLS	
	uni-variate	**multi-variate**	**uni-variate**	**multi-variate**	**uni-variate**	**multi-variate**
LV ejection fraction, %	**0.220***	NS	**0.214***	NS	**−0.252***	NS
LVOT velocity time integral, cm	**0.336****	NS	NS	NS	NS	NS
LV stroke volume index, ml/m2	**0.336****	NS	NS	NS	**−0.387*****	**−0.284***
LV cardiac index, l/min/m2	NS	NS	NS	NS	**−0.262***	NS
LV global longitudinal strain, %	**−0.551******	NA	**−0.561******	NA	NA	NA
LV global work index, mmHg%	NA	NA	NA	NA	**−0.551******	NA
transmitral E velocity, cm/s	NS	NS	**0.326****	NS	**−0.267***	NS
E/A	NS	NS	NS	NS	**−0.252***	NS
mitral annulus e' velocity, cm/s	NS	NS	**0.381*****	NS	**−0.328****	NS
mitral annulus s' velocity, cm/s	NS	NS	**0.240***	NS	**−0.219***	NS
E/e'	**0.247***	NS	NS	NS	NS	NS
left atrial diameter, medio-lateral, mm	**0.334****	NS	NS	NS	NS	NS
left atrial height, mm	**0.248***	NS	NS	NS	NS	NS
left atrial volume, ml	**0.249***	NS	**0.233***	NS	NS	NS
left atrial volume index, ml/m2	**0.321****	NS	**0.286****	NS	**−0.263***	**−0.343****
left ventricular end systolic volume, ml	NS	NS	NS	NS	**0.242***	NS
systolic blood pressure, mmHg	**0.614******	NA	NS	NS	NS	NS
diastolic blood pressure, mmHg	**0.479******	NA	NS	NS	NS	NS

Values represent Pearson's or Spearman's correlation coefficient (r), or partial r in case of multivariate analysis. Values are considered statistically significantly different at $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***), $p<0.0001$ (****). Significant differences are marked with asterisk and printed in bold. GLS: global longitudinal strain; GWE: global work efficiency; GWI: global work index; LV: left ventricle, NS: not significant; NA: not applicable.

7.2.5 Valvular alterations

No hemodynamically significant stenotic valvular disease has been found in either group. Mild aortic (4 patients, 4.65%), mitral (13 patients, 15.1%), pulmonary (28 patients, 32.6%), tricuspid (8 patients, 9.3%) regurgitation was found (data not shown), however, we considered all these hemodynamically not significant.

8. DISCUSSION

8.1 Assessing the real-world effectiveness of mavacamten in patients with obstructive HCM

As mavacamten has been just recently introduced for the treatment of oHCM, data on the real-world use and real-world efficacy of the drug are relatively scarce. Beyond the two pivotal mavacamten clinical trials, EXPLORER-HCM [9] and VALOR-HCM [10], real world data are available from the long-term extension of the above clinical trials [11, 12] and from small, usually single-centre patient cohorts, reporting data on 6-66 patients [32-36] (with the only exception of one report from the Cleveland Clinic reporting data on 150 patients [37]). To expand the real-world data on the clinical use of mavacamten in this work we showed that mavacamten effectively reduced even extreme (>100 mmHg) LVOT gradients and led to significant gradient reduction already in one week. Besides favourable changes in LVOT obstruction, structural and functional echocardiographic parameters, functional capacity, and cardiac biomarkers, it has also led to significant changes in myocardial work parameters.

A novel observation of our study is that mavacamten significantly reduces both resting and provoked LVOT gradients already after one week of treatment. The effect of mavacamten on gradient reduction in clinical trials was assessed at 4 weeks the earliest in both the EXPLORER-HCM [9] and VALOR-HCM [10] trials, and studies reporting real-world data in HCM patient cohorts also assessed gradient reduction only after 4 weeks [32, 33]. As mavacamten is readily absorbed with a median t_{max} of 1 hour after oral administration with an estimated oral bioavailability of approximately 85% [29], this relatively rapid action of the drug and rapid onset of clinical response is not surprising. This observation raises the possibility that mavacamten can be used in situations where relatively rapid (i.e., within a couple of weeks) LVOT gradient reduction is needed in oHCM patients.

Another novel finding of our study that mavacamten is also effective in oHCM patients with >100 mmHg LVOT gradients. In the EXPLORER-HCM study the resting and the Valsalva gradient was 52 mmHg and 72 mmHg, respectively [9]; while in the VALOR-HCM study the resting and the Valsalva gradient was 51 mmHg and 75 mmHg, respectively [10]. In the reported real-world oHCM cohorts treated with mavacamten, the resting LVOT gradient was 41-56 mmHg, and the Valsalva gradient was 72-104 mmHg [32, 33, 37]. In our patient cohort the resting and the Valsalva gradient was 121 mmHg and 167 mmHg, respectively, more than

double, than in the clinical trials. Beyond the LVOT gradients the severity of the clinical status of our patient group is also well demonstrated by the increased level of biomarkers. The NT-proBNP levels in the EXPLORER-HCM and VALOR-HCM trials were 777 pg/ml and 724 pg/ml, respectively [9, 10]; while it was 2952 pg/ml in our patient group. The troponin levels in the EXPLORER-HCM and VALOR-HCM trials were 12.5 ng/l and 14 ng/l, respectively [9, 10], while it was 35 ng/l in our patients. As mavacamten treatment was associated with a rapid and significant gradient reduction also in this patient group, according to our data, the use of mavacamten seems to be equally effective and safe in this very severe group of oHCM patients, like ours.

We were also able to demonstrate that beyond the reduction of gradient, improvement in diastolic function and no change in systolic function, novel echocardiographic measures of myocardial function, parameters of myocardial work (MW), were also reduced rapidly and significantly. As mavacamten directly affects myocardial contractility, the characterisation of change in myocardial work parameters seems to be a primary interest. MW parameters constitute a group of novel parameters which uses pressure-strain loops to estimate myocardial performance [25, 31]. MW has been found to be a more sensitive index of segmental and global LV performance compared to EF and GLS. The additive value of detecting MW alteration has been shown for many cardiac diseases including cardiac dyssynchrony, heart failure, cardiomyopathies, coronary artery disease and valvular heart disease [25, 31]. The non-invasive estimation of left ventricular systolic peak pressure and therefore the possibility to calculate myocardial work in oHCM has been recently reported [30]. Using this estimation, we observed, that many MW parameters showed favourable changes as the LVOT gradient decreased, with changes in GWI and GCW becoming significant already at W04. As calculation of MW parameters incorporates the estimated LV systolic pressure (which is derived from the systolic aortic pressure and the LVOT pressure gradient) there is a strong correlation between the LVOT gradient and GWI and GCW (but less with GWW and GWE [38]). Therefore, it is not surprising that, with a decrease in the LVOT gradient, GWI and GCW also decrease, which, per se, likely reflects a change in left ventricular pressure due to the gradient reduction rather than a presumed direct effect on contractility. As a consequence, in patients with oHCM, changes in GWI and GCW may not be informative, as these parameters may be in the normal range as GLS is reduced but left ventricular pressure is increased due to the LVOT gradient. However, their favourable change was evident, and abnormal GWI and GCW values returned to normal in all patients. On the other hand, GWW (global wasted work, an index of energy loss) and GWE

(global work efficiency) are less correlated with the LVOT gradient [38]. Therefore, their numerical change is not as strongly affected by LVOT gradient reduction as the changes in GWI and GCW. The beneficial changes in GWW and GWE are most clearly demonstrated by the reduction in the proportion of patients exhibiting abnormal values. At baseline, abnormal GWW was present in 74% of patients and abnormal GWE in 87%; these proportions continuously decreased throughout mavacamten treatment. In this context, myocardial work parameters may offer additional discriminative power compared to GLS in patients with oHCM, particularly when examining specific aspects of mavacamten treatment, such as response to therapy, treatment failure, or effects in specific patient subgroups (e.g., sarcomeric mutation carriers or patients with pronounced fibrosis). Predicting which patients will develop systolic dysfunction during mavacamten treatment is a particularly important aspect of this issue. However, identifying predictors for this adverse event is challenging due to the relatively low number of patients experiencing LVEF <50% during mavacamten therapy. Of particular interest, in the VALOR-HCM trial, the mean baseline GLS in the subgroup of 12 patients who required mavacamten interruption was lower than that of the overall study population, with no significant improvement (or worsening) during follow-up. On exploratory logistic regression analysis, a baseline GLS worse than −14.6% was only weakly associated with the likelihood of developing LVEF <50%. As myocardial work (MW) parameters may offer additive sensitivity over GLS, their value in predicting the development of systolic dysfunction should be further tested.

As for safety profile and adverse events, patients did not experience hospitalization for heart failure, and no major arrhythmia or EF<50% occurred during the observational period. Although an increase in the rate of new onset atrial fibrillation (AF) after the initiation of mavacamten has been reported [39], we had no case with new-onset AF. Three patients (12%) developed recurrent atrial fibrillation, all with a previous history of AF. This rate is lower or equals to reported AF occurrence rates (both new-onset AF and recurrent AF) after mavacamten initiation which was reported to be 32% [39], 24% [40], and 11% [41] in real-world case series and to be 14 % [11] and 10.2% [12] in mavacamten long-term extension studies. All of our patients were converted into sinus rhythm (SR) and remained in SR until last follow up.

In conclusion, we observed that the direct myosin inhibitor mavacamten effectively reduces even extreme (>100 mmHg) LVOT gradients and has a significant effect even after one week of treatment. Beyond its beneficial effects on structural and functional cardiac parameters it also favourably impacts myocardial work parameters. While long-term results of mavacamten therapy are available from the long-term extension (LTE) studies of the EXPLORER-HCM [6] and

VALOR-HCM [7] trials, demonstrating the treatment's long-term efficacy and safety, these promising results derive from the original study populations and are therefore potentially subject to selection bias. Consequently, "real-world" data, preferably from large-scale, multicentre datasets, are greatly needed, with a particular focus on outcome and safety parameters, such as the risk of atrial fibrillation, heart failure, and sudden cardiac death.

8.2 Screening for myocardial alterations after mild SARS-COV-2 infection with advanced transthoracic echocardiography modalities

Although echocardiographic alterations in acutely ill patients with COVID-19 infections are well characterized [27, 28], there are still few data regarding the long-term cardiac consequences of the disease, especially in the young and affected by a mild form of the disease. In our study we provided data that subclinical cardiac alterations, characterized by parameters provided by advanced echocardiographic techniques, are frequent following mild SARS-CoV-2 viral infection. This subclinical myocardial injury after mild SARS-Cov-2 infection cannot be detected with laboratory tests, ECG or standard LV echocardiography parameters, however, advanced echocardiographic modalities may provide parameters, such as global longitudinal strain or myocardial work parameters, that indicate subtle LV or RV functional injury.

The occurrence of cardiac alterations is an important aspect of COVID-19 infection. Cardiac involvement due to COVID-19 infection is thought to be multifactorial; that includes myocardial damage due to acute systemic inflammatory response; hypoxia secondary to acute respiratory failure; microvascular and macrovascular thrombosis due to systemic inflammation and endothelial dysfunction; and possibly direct viral infection of the myocardium [42]. Multiple autopsy studies showed that viral presence with active inflammation, and even myocardial inflammatory storm is often present, along with endothelial damage and microthrombi. It is generally hypothesized that both a direct organ damage, and a secondary damage due to the inflammatory response plays a role in cardiac involvement [43]. Pellegrini et al. reported that the most common cause for cardiomyocyte necrosis appears to be of thrombotic origin in SARS-CoV-2 infection, microthrombi being by far the most common [44]. This is caused by direct endothelial infection through ACE2 receptors, but perhaps more importantly secondary to endothelial activation caused by excessive immune system activation. This hyperinflammatory state plays a major role in the course of the infection and its pulmonary involvement, but its cardiac effect must be equally emphasized [45]. Especially this

pathomechanism can lead to severe illness in both children (Multisystem Inflammatory Syndrome in Children, MIS-C) and adults (MIS-A) weeks after initial infection [46]. Both NT-proBNP and hs-Troponin has been described as an independent predictor for adverse outcome in patients requiring hospitalization. Importantly in the case of NT-proBNP, this appears to be unrelated to the development of acute heart failure [47]. Elevated troponin levels on admission were similarly found to be associated with increased 30-day mortality. Interestingly such risk was more robustly predicted in less severe waves of the pandemic [48].

Echocardiographic alterations indicating myocardial involvement of the left- or right-side of the heart are frequent and widely reported in patients hospitalized for acute COVID-19 infection [27, 28, 49]. These alterations include measures of left ventricular systolic and diastolic function, multiple parameters of right ventricular systolic performance as well as pulmonary artery flow acceleration time. In several studies, decreased LVEF was found to be associated with clinical deterioration and mortality [50, 51]. Elevated NT-proBNP and troponin levels were predictive of reduced stroke volume, cardiac output, and cardiac index, which were in turn associated with adverse outcome [51]. However, in contrast to non-invasive hemodynamics, elevation of troponin-I and reduction in LVEF were not significantly related. Not only systolic but diastolic function of the left ventricle is affected, and elevated E/e' is independently associated with mortality [51]. Remarkably, impaired LV global longitudinal strain is not only associated with increased mortality, but a cut of value of ≤15.20% was even showed to have a predictive value with a sensitivity of 77% and a specificity of 75% [52]. Janus et al. also demonstrated that a reduction in GLS is a powerful predictor of mortality in COVID-19 patients [53].

On the contrary to the above findings in hospitalized patients, data on echocardiographic changes in patients with mild (requiring no hospitalization) COVID-19 infection are scarce. Studies have shown that absolute value of left ventricular global longitudinal strain is lower in patients suffering from mild COVID-19 symptoms on initial evaluation, without significant difference in more traditional parameters compared to a healthy control group [54]. In a preliminary report, Uzieblo-Zyczkowska et al. found no difference in GLS after mild COVID infection in post-COVID patients and controls, although assessing only 31 patients [55]. It is reported that LV GLS has some value in detecting subclinical left ventricular dysfunction in patients recovered from COVID-19 even in cases of asymptomatic or mild illness, but notably, the parameter was less robust compared to those who had severe illness [56]. In a prospective, observational study of Ikonomidis et al. assessing 70 COVID-19 patients (34.28% with mild

disease) 12 months post-infection, GLS values in COVID-19 patients showed a borderline improvement compared to values at 4 months, though these remained impaired compared to controls [57]. Our data also supports the observation that GLS is the parameter which shows one of the most significant differences in the post-COVID group. However, these changes are minor (~6% relative change) and are difficult to utilize on a single patient basis since many patients fall into the "normal" range. In another important study, 383 patients were screened for cardiac involvement in the post-acute phase of COVID-19 [58]. Approximately a quarter of the patients (n=102) had some sort of cardiac sequelae, including left ventricular systolic and diastolic dysfunction, increased pulmonary arterial pressure and pericardial disease, however, most had moderate pulmonary involvement initially. The authors found that during follow-up the number of patients with any abnormality steadily decreased and the remaining showed less severe alterations. It is also important to note that this patient population was enrolled in three different waves of the pandemic, and that according to the authors' conclusions differing viral strains showed different patterns.

Our results showed that apart of GLS, myocardial work (MW) parameters were the ones that was most significantly altered in the post-COVID group. Although GLS is still a relatively new, well-validated tool for the evaluation of cardiac alterations, its clinical performance is influenced by its dependency on changes in ventricular load. On the other hand, LV MW is a novel parameter, based on the same speckle tracking-based method which eliminates some of the load dependency of GLS [25] and has been found to be a more sensitive index of segmental and global LV performance compared to EF and GLS. With regard to COVID-19, significantly reduced GWI has been first demonstrated in a COVID-19 positive patient who had normal EF and GLS parameters on admission which showed marked improvement after one month [59]. In the study of Ikonomidis et al., the authors found that, when examined at 4 months after infection, COVID-19 patient showed significantly worse myocardial work efficiency and higher degree of wasted work compared to control group. Furthermore, their findings showed that at 12 months, there was some relevant improvement of these values; however, these markers remained impaired compared to controls [57]. In a retrospective cohort of 136 patients hospitalized for COVID-19, 79% of patients had abnormal GWE despite 81% had normal left ventricular ejection fraction. Higher GWE was associated with lower in-hospital mortality, in addition, increased systemic inflammation measured by interleukin-6 level was associated with reduced GWE [60].

The impact of SARS-COV-2 infection on the right ventricle was among the first cardiac phenomena described. In our study, parameters of right ventricular systolic function and contractility, TAPSE and RV free ventricular strain was impaired in post-COVID patients. The involvement of the right ventricle is thought to be due to the increase in afterload secondary to increases in pulmonary vascular resistance caused by pulmonary inflammation, ARDS or pulmonary embolism/thrombosis. RV dysfunction may also be caused by direct myocardial damage by SARS-Cov-2, endothelitis, due to microvascular and macrovascular dysfunction, overload of vasoactive peptides, and inflammatory injury. As our patient group did not require any or prolonged hospitalization due to respiratory complications the latter mechanisms seem to be prominent in explaining the RV impairment in our patient group. Similarly to our findings, others have reported the value of RV strain in detection of long-term persisting right ventricular involvement, appearing to be one of the strongest predictors. The correlation of RV strain values and inflammatory markers also suggest that the immune response plays a decisive role in cardiac involvement [61].

As for cardiac MRI, both a recent state-of-the-art review, and a large meta-analysis highlight that CMR is a highly sensitive imaging tool for cardiac alterations in convalescent patients [23, 24]. Not only detecting ventricular dysfunction but confirming the presence of fibrosis and oedema as well, that was detectable in 26–60% of patients. However, a number of the reviewed studies contained a large spectrum of disease severity in the acute phase and were not limited to the mildest of cases. Studies with predominantly mild disease severity found significantly less severe cardiac involvement, some interesting results actually showing no significant alterations at 6 months after asymptomatic-mild infections.

9. STUDY LIMITATIONS

A clear limitation of our study on oHCM patients with mavacamten treatment is the small number of patients in the cohort, particularly the low number of patients completing the week 48 visit. However, our study focused more on the short-term effects of mavacamten treatment. As mavacamten has only recently been introduced for the treatment of oHCM, real-world studies typically report a similar number of patients. The variability and reproducibility of LVOT gradients may pose another challenge; however, the magnitude of changes and the level of significance in the statistical analyses were so high that they are unlikely to be altered in larger patient cohorts. Additionally, 45% of the study patients had prior unsuccessful attempts at alcohol septal ablation. While the inclusion of these patients with more severe conditions may limit the generalizability of our results, it also provides evidence that mavacamten treatment is effective in this challenging subgroup.

As for the Covid-study, the study was conducted during the COVID pandemic with restricted medical resources and limited possibilities to perform serial patient visits. As a result of this, adequate control group was possible to be recruited well after the study population was assessed. In addition, serial echocardiographic measurements were not possible to perform in order to follow the time-course of the alterations detected in the patients.

10. SUMMARY AND ORIGINAL FINDINGS

10.1 Mavacamten lead to a **significant decrease even of >100 mmHg LVOT gradients** in patients with oHCM.

10.2 The **significant decrease of the LVOT gradient can be observed even after one week** of mavacamten treatment.

10.3 The decrease in the LVOT gradient is paralleled by a decrease in laboratory biomarker levels, significant improvement in NYHA functional class and 6-minute walk distance, with favourable changes in the degree of mitral regurgitation, diastolic function and left atrial volumes during mavacamten treatment and without significant change of LV diameters, LV volumes, LV ejection fraction or global longitudinal strain.

10.4 Despite of no change in global longitudinal strain, **myocardial work parameters show favourable significant changes** during mavacamten treatment.

10.5 During the post-acute phase of even mild COVID-19 **subtle functional alterations can be detected** by advanced echocardiographic protocols.

10.6 Deformation imaging appears to be able to detect the most pronounced relative difference for both left and right ventricular function after mild COVID-19, with **left ventricular global myocardial work index** and **right ventricular free wall strain being the most robust alteration**.

10.6 Although altered echocardiographic parameters may include traditional echocardiographic parameters after mild COVID-19 (e.g., LV ejection fraction, LV end diastolic diameter, etc.), **their relative change is generally modest**.

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13. SUPPLEMENTARY MATERIAL

Supplementary Table 1. Clinical, demographic and echocardiographic characteristics all the studied patients with hypertrophic cardiomyopathy treated with mavacamten (n=29).

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS	
Age, years	
Mean (SD)	55 (10.8)
Median (IQR)	55 (49-61)
Female, n (%)	12 (41)
BMI, mean (SD), kg/m^2	30.2 (4.1)
Genetic testing	
genetic testing results available, n (%)	20 (69)
carrier of pathogenic/likely pathogenic (P/LP) variant, n (%)	6 (30)
identified P/LP variants	*MYBPC3* p.Phe1159TyrfsTer9, *MYBPC3* p.Tyr1136del, *MYBPC3* p.Ala1056GlyfsTer9, *MYBPC3* p.Ser25fs, *MYH7* p.Arg869Cys/*MYH7* p.Arg1712Gln, *MYH7* p.Pro307Ser
carrier of VUS (variant of unknown significance), n (%)	3 (15)
identified VUS variants	*DSP* p.Arg1537Cys, *MYL3* p.Pro23His, *DSC2* p.Ala452Val
no variant, n (%)	11 (55)
Baseline NYHA class, n (%)	
Class II	10 (34)
Class III	19 (66)
Duration since HCM diagnosis, mean (SD), years	8 (4.6)

ECHOCARDIOGRAPHIC AND CLINICAL CHARACTERISTICS	
Transthoracic echocardiographic parameters, mean (SD)	
LVEF, %	65.0 (5.9)
Maximal LV wall thickness, mm	24.4 (3.8)
Resting LVOT peak gradient, mmHg	110 (42.7)
Valsalva LVOT peak gradient, mmHg	156 (44.9)
Cardiac rhythm, n (%)	
Sinus rhythm	28 (97)
Comorbidities, n (%)	
Hypertension	20 (69)
Paroxysmal atrial fibrillation	6 (20)
Coronary artery disease	3 (10)
Prior attempted septal reduction therapy, n (%)	
Septal myectomy	0 (0)
Alcohol septal ablation	13 (45)
Background HCM medical therapy prior to mavacamten start, n (%)	
BB monotherapy	8 (28)
Non-dihydropyridine CCB monotherapy	0 (0)
BB and non-dihydropyridine CCB	0 (0)
BB and disopyramide	21 (72)
Prior device therapy, n (%)	
ICD	5 (17)

Data are expressed as mean (standard deviation, SD), median (interquartile range, IQR) or number (percentage). BMI: body mass index, *MYBPC3*: cardiac myosin binding protein C gene, *MYH7*: beta myosin heavy chain 7 gene, *MYL3*: myosin light chain 3 gene, *DSC2*: desmocollin 2 gene, *DSP:* desmoplakin gene, VUS: variant of unknown significance, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, BB: beta-blocker, CCB: calcium channel blocker, ICD: implantable cardioverter defibrillator.

Supplementary Table 2. Change in clinical, echocardiographic and biomarker parameters after one week (W01), 4 weeks (W04) and 8 weeks (W08) of mavacamten treatment in the entire oHCM patient cohort (n=29)

	baseline	W01	W04	W08
LVOTG, resting peak (mmHg)	110±8	**79±8*****	**62±8*****	**52±9*****
LVOTG, resting peak, mean difference (mmHg)		**-31 (-49 to -14)*****	**-48 (-70 to -26)*****	**-58 (-83 to –33)*****
LVOTG, Valsalva peak (mmHg)	156±10	**118±10*****	**95±9*****	**74±10*****
LVOTG, Valsalva peak, mean difference (mmHg)		**-38 (-57 to -18)*****	**-61 (-86 to -36)*****	**-82 (-110 to -54)*****
NT-proBNP (pg/ml)	2979±553	**1519±555*****	**1239±555*****	**825±572*****
NT-proBNP, mean difference (pg/ml)e		**-1460 (-2278 to -641)*****	**-1740 (-2835 to -644)*****	**-2154 (-3474 to -833)*****
Troponin T (ng/l)	38±9	38±9	32±9	**26±9****
6-minute walk distance (m)	405±21	421±21	**460±21*****	**457±21****
EF (%)	65±1	65±1	62±1	64±1
GLS (%)	-13.9±0.6	-13.5±0.6	-13.7±0.6	-13.5±0.6
GWI (mmHg%)	2059±92	**1840±93***	**1706±92****	**1628±97****
GCW (mmHg%)	2602±106	**2323±107***	**2169±106****	**2067±113****
GWW (mmHg%)	294±23	289±24	283±23	287±25
GWE (mmHg%)	85±1	85±1	85±1	85±1
LAV (ml)	130±5	123±5	117±5	119±5
LAVI (ml/m2)	65±3	63±3	59±3	61±3
e' lateral (cm/s)	6.8±0.5	7.3±0.5	7.4±0.5	8.0±0.5
E/e'	17±1	17±1	17±1	14±1
mitral insufficiency ≥3, n/n (%)	16/29 (55%)	12/29 (41%)	**5/29 (17%)****	**3/29 (10%)*****
mitral insufficiency ≥2, n/n (%)	22/29 (76%)	18/29 (62%)	**14/29 (48%)***	**7/29 (24%)*****
LV EDD (mm)	46±0.9	45±0.9	46±0.9	46±0.9
LV ESD (mm)	30±0.8	30±0.8	30±0.8	29±0.8
LV EDV (ml)	104±5	98±5	94±5	103±5
LV EDV-index (ml/m^2)	51±2	49±2	48±2	52±2
LV ESV (ml)	36±2	34±2	35±2	38±2
LV ESV-index (ml/m^2)	18±1	17±1	18±1	19±1
IVS (mm)	24±1	24±1	24±1	24±1
PW (mm)	13±1	13±1	13±1	13±1
maximal LV wall thickness (mm)	25±1	25±1	24±1	24±1

Data are expressed as mean±SEM or mean (95% confidence intervals). Values are considered significantly different at $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***). Significant changes are highlighted in bold. SEM: standard error of mean, LVOTG: left ventricular outflow tract gradient, EF: ejection fraction, GLS: global longitudinal strain, GWI: global work index, GCW: global constructive work, GWW: global wasted work, GWE: global work effectiveness, LAV: left atrial volume, LAVI: left atrial volume index, LV: left ventricular, EDD: end-diastolic diameter. EDV: end-diastolic volume, ESD: end-systolic diameter, ESV: end-systolic volume, IVS: interventricular septum, PW: posterior wall.

14. APPENDIX

14.1 Dr. Viktória Nagy's list of 'in extenso' publications

14.2 Co-author certification

14.3 Reprint of publications related to the thesis

14.1 Dr. Viktória Nagy's list of 'in extenso' publications

1. **Nagy V**, Rácz G, Takács H, Boda K, Polestyuk B, Schvartz N, Vidács LD, Pintér JA, Pálinkás A, Kormányos Á, Szűcsborus T, Borbás J, Szili-Török T, Sepp R. Mavacamten effectively reduces > 100 mmHg left ventricular outflow tract gradients as early as one week of treatment in obstructive hypertrophic cardiomyopathy. INTERNATIONAL JOURNAL OF CARDIOLOGY 442 Paper: 133882, 7 p. (2026). Q1, IF: 3.2.

2. **Nagy V**, Takács H, Kormányos Á, Sepp R. Az Európai Kardiológus Társaság 2021-es szívelégtelenség-ajánlásának 2023-as, fókuszált update-je [2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure] CARDIOLOGIA HUNGARICA 54: 286-293 (2024). Q4.

3. Vereckei A, Besenyi Zs, **Nagy V**, Radics B, Vágó H, Jenei Zs, Katona G, Sepp R. Cardiac Sarcoidosis: A Comprehensive Clinical Review. REVIEWS IN CARDIOVASCULAR MEDICINE 25: 2 Paper: 37, 18 p. (2024). Független idéző: 9, Q3, IF: 1.3.

4. Kormányos Á, Takács H, **Nagy V**, Sepp R. Mineralokortikoidreceptor-antagonisták alkalmazása a szívelégtelenség kezelésében : irodalmi áttekintés [The use of mineralocorticoid receptor antagonists in the treatment of heart failure: a literature review]. CARDIOLOGIA HUNGARICA 54: 294-301 (2024). Q4.

5. Vereckei A, Katona G, Szénási G, Vidács LD, Földeák D, Takács H, **Nagy V**, Sepp R. Novel electrocardiographic criteria may render possible the more accurate recognition of cardiac amyloidosis. ESC HEART FAILURE 11: 1030-1038 (2024). Független idéző: 3, Q1, IF: 3,7.

6. Lopes L, Losi MA, Sheikh N, Laroche C, Charron P, Gimeno J, Kaski JP, Maggioni A, Tavazzi L, Arbustini E et al. Association Between Common Cardiovascular Risk Factors and Clinical Phenotype in Patients with Hypertrophic Cardiomyopathy From the European Society of Cardiology (ESC) EurObservational Research Programme (EORP) Cardiomyopathy/Myocarditis Registry. EUROPEAN HEART JOURNAL - QUALITY OF CARE AND CLINICAL OUTCOMES 9: 42-53 (2023). Független idéző: 20.

7. **Nagy V**, Rácz G, Takács H, Radics B, Borbás J, Kormányos Á, Csányi B, Hategan L, Iványi B, Nagy I et al. Fabry-betegséget okoz-e a GLA gén p.Ala143Thr variánsa? [Does the GLA p.Ala143Thr variant cause Fabry disease?]. CARDIOLOGIA HUNGARICA 53: 343-350 (2023).

8. Takács H, **Nagy V**, Rácz G, Kormányos Á, Polestyuk B, Schvartz N, Gyenes N, Dézsi L, Radics B, Iványi B et al. A szívamyloidosis diagnosztikájának és terápiájának aktualitásai – Az ESC Myocardial and Pericardial Diseases Munkacsoportjának 2021-es position statementje alapján [Current diagnostic and therapeutic strategies in cardiac amyloidosis – According to the position statement of the ESC Working Group of Myocardial and Pericardail Diseases in 2021]. CARDIOLOGIA HUNGARICA 52: 130-141 (2022). Független idéző: 2.

9. **Nagy V**, Takács H, Borbás J, Tringer A, Csányi B, Hategan L, Iványi B, Nagy I, Hegedűs Z, Sepp R. Fabry-kór vagy sarcomer-hipertrófiás cardiomyopathia? [Fabry disease or sarcomeric hypertrophic cardiomyopathy?]. CARDIOLOGIA HUNGARICA 52: 45-49 (2022).

10. Borbás J, Vámos M, Hategan L, Hanák L, Farkas N, Szakács Zs, Csupor D, Tél B, Kupó P, Csányi B, **Nagy V**, Komócsi A, Habon T, Hegyi P, Sepp R. Geno- and phenotypic characteristics and clinical outcomes of CACNA1C gene mutation associated Timothy syndrome, "cardiac only" Timothy syndrome and isolated long QT syndrome 8: A systematic review. FRONTIERS IN CARDIOVASCULAR MEDICINE 9 Paper: 1021009, 17 p. (2022). Független idéző: 12, Q1, IF: 3.6.

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12. Rácz G, Takács H, Kormányos Á, Polestyuk B, Borbás J, Gyenes N, Schvartz N, Németh G, Kincses Zs, Sepp R, **Nagy V**. Screening for Myocardial Injury after Mild SARS-CoV-2 Infection with Advanced Transthoracic Echocardiography Modalities. DIAGNOSTICS 12: 8 Paper: 1941, 13 p. (2022). Független idéző: 8, Q2, IF: 3.6.

13. Sepp R, Hategan L, Csányi B, Borbás J, Tringer A, Pálinkás ED, **Nagy V**, Takács H, Latinovics D, Nyolczas N et al. The Genetic Architecture of Hypertrophic Cardiomyopathy in Hungary: Analysis of 242 Patients with a Panel of 98 Genes. DIAGNOSTICS 12 : 5 Paper: 1132 , 12 p. (2022). Független idéző: 11, Q2, IF: 3.6.

14. Hategan L, Csányi B, Borbás J, Pálinkás ED, Takács H, **Nagy V**, Sepp R. Genetic diagnosis in hypertrophic cardiomyopathy: two steps forward, one step back. CARDIOLOGIA HUNGARICA 51: 109-117 (2021). Független idéző: 1.

15. **Nagy V**, Rácz G, Radics B, Hategan L, Takács H, Kormányos Á, Rudas L, Iványi B, Sepp R. Súlyos szívelégtelenség hátterében álló transthyretin-amyloidosis elkésett diagnózisa [Late diagnosis of transthyretin amyloidosis causing severe heart failure]. CARDIOLOGIA HUNGARICA 51: 2 131-139 (2021).

16. Pozsonyi Z, Peskó G, Takács H, Csuka D, **Nagy V**, Szilágyi Á, Hategan L, Muk B, Csányi B, Nyolczas N et al. Variant Transthyretin Amyloidosis (ATTRv) in Hungary: First Data on Epidemiology and Clinical Features. GENES 12: 8 Paper: 1152, 12 p. (2021). Független idéző: 9, Q2, IF: 4.141.

17. **Nagy V**, Pálinkás A, Tóth L, Takács H, Gavallér H, Simor T, Forster T, Sepp R. Balkamra-hipertrófia mértékét jellemző paraméterek összefüggése MRI-vel meghatározott bal kamrai izomtömeggel hipertrófiás cardiomyopathiában. CARDIOLOGIA HUNGARICA 50: 17-23 (2020).

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23. Tringer A, Grosz Z, **Nagy V**, Gál A, Csányi B, Hategan L, Borbás J, Gavallér H, Pálinkás E, Forster T et al. Mitokondriális génmutáció igazolása dominálóan hipertrófiás cardiomyopathia képében megjelenő szisztémás kórképben [Identification of a mitochondrial gene mutation in a systemic disease manifesting primarily as hypertrophic cardiomyopathy]. CARDIOLOGIA HUNGARICA 47: 35-138 (2017).

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28. Toth T, **Nagy V**, Faludi R, Csanady M, Nemes A, Simor T, Forster T, Sepp R. The Gln1233ter mutation of the myosin binding protein C gene: Causative mutation or innocent

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Co-author certification

I, myself as a corresponding author of the following publication declare that the authors have no conflict of interest, and Dr. Viktória Nagy Ph.D. candidate had significant contribution to the jointly published research. The results discussed in her thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

Szeged, 28-Nov-2025

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The publication(s) relevant to the applicant's thesis:

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