University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medicine

USE OF ADVANCED TRANSTHORACIC ECHOCARDIOGRAPHY IN SPECIAL CARDIAC CONDITIONS

PhD Thesis

Dr. Viktória Nagy

Supervisor: Prof. Dr. Róbert Sepp, MD, PhD, DSc

Szeged
2026

1. LIST OF PUBLICATIONS RELATED TO THE THESIS

1.1 List of 'in-extenso' publications related to the thesis

1.1.1 **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). https://doi.org/10.1016/j.ijcard.2025.133882. Available online 6 September 2025. Q1, IF: 3.2.

1.1.2 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.

1.2 List of citable abstracts related to the thesis

1.2.1 **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).

1.2.2 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).

1.2.3 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).

1.2.4 **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).

2. 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. 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. Among them, 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. 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.

2.1 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. In HCM sarcomeric gene mutations lead to profound alterations in myocardial contraction and relaxation (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. The selective and reversible cardiac myosin inhibitor mavacamten was developed for the treatment of HCM. 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. Based on landmark trials, mavacamten was approved for clinical use as a second-line therapy for obstructive HCM (oHCM), in addition to a beta-blocker or non-dihydropyridine calcium channel blockers to improve symptoms in adult patients with resting or provoked left ventricular outflow tract (LVOT) obstruction.

2.2 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). The involvement of the cardiovascular system has been proven in all stages of the illness. 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. 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.

3. AIMS

3.1 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: i) effectiveness of mavacamten in oHCM patients with extreme (>100 mmHg) LVOT gradients; ii) the short-term effects of the drug after one week of treatment; iii) the effect of mavacamten on advanced transthoracic echocardiography parameters, including that of global longitudinal strain and myocardial work.

3.2. Echocardiographic alterations indicating myocardial involvement of the heart are frequent and widely reported in patients hospitalized for acute COVID-19 infection, 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**, to address 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.

4. PATIENTS AND METHODS

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

4.1.1 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.

4.1.2 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. 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. 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.

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

4.2.1 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. 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.

4.2.2 Methods

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

5. RESULTS

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

5.1.1 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 ($p<0.001$). 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 ($p<0.001$).

5.1.2 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); $p<0.001$]. 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; $p=0.021$). In the 7 patients completing W48 visit the mean troponin T levels decreased to 12 ng/l ($p=0.021$).

5.1.3 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 ($p=0.0008$). 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), $p<0.001$]. Further improvement was observed in patients completing W48 visits [median difference 92 m (95% CI: 2-182), $p=0.043$].

5.1.4 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. No further significant decrease was seen in the 7 patients completing W48 visits.

5.1.5 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, $p=0.984$).

As values for normal ranges are available for all MW parameters, 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 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).

5.1.6 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).

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), 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), the changes were significant in the 7 patients completing W48 visits regarding E/e' (mean difference: -7, p=0.035).

5.1.7 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.

5.1.8 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.

5.2 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).

5.2.1 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. 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.

5.2.2 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. 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%. The decreased GLS values correlated with many parameters of LV dimension and function in univariate correlation analysis 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.

5.2.3 Myocardial work parameters

With regard to myocardial work parameters, global myocardial work index (GWI) values (1975 vs. 1829 mmHg%; p=0.007) 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 LV global wasted work (99 vs. 107 mmHg%; p=0.088) also showed marked differences, close to significancy. The decreased GWI and GWE values correlated with many parameters of LV dimension and function in univariate correlation analysis but correlated with none of the parameters in the multivariate regression analysis (apart of GLS and systolic RR which they are derived from).

5.2.4 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) 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%.

5.2.5 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.

6. DISCUSSION

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

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 and VALOR-HCM trials, and studies reporting real-world data in HCM patient cohorts also assessed gradient reduction only after 4 weeks. As mavacamten is readily absorbed with a median t_{max} of 1 hour after oral administration with an estimated oral bioavailability of approximately 85%, 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; while in the VALOR-HCM study the resting and the Valsalva gradient was 51 mmHg and 75 mmHg, respectively. 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. 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, 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. 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). 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 and GWE are less correlated with the LVOT gradient. 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.
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 and VALOR-HCM 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.

6.2 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, 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 and 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. 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. 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. 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. 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%. Janus et al. also demonstrated that a reduction in GLS is a powerful predictor of mortality in COVID-19 patients.

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. 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. 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. 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. 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. 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 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. 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. 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.

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.

7. SUMMARY AND ORIGINAL FINDINGS

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

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

7.3 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.

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

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

7.6 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**.

7.7 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**.

8. ACKNOWLEDGEMENTS

The completion of any significant research, especially a PhD dissertation, is invariably a collaborative effort. I am deeply grateful to the numerous individuals in my professional and personal life who contributed to this work and provided the essential support that made this thesis possible.

Firstly, I extend my most sincere and profound gratitude to my supervisor, Prof. Dr. Róbert Sepp, for his continuous mentorship, unwavering support throughout my PhD studies, and for guiding the related research. His patience, insightful direction, intellectual rigor, and immense knowledge were invaluable at every stage of research and the writing of this thesis.

I owe a debt of sincere thanks to Professor Miklós Csanády and Professor Tamás Forster for providing me with the initial opportunity to join the institute as a resident physician. Them, and Professor Albert Varga were instrumental in introducing me to the fascinating and essential world of echocardiography and the field of heart failure, the foundation of this research. Their early and precious support was indispensable. I am also grateful to Prof. Dr. Szili-Török Tamás, the current Head of the Cardiology Center, for his ongoing leadership and continuous institutional support.

I wish to recognize the dedication of the entire clinical staff. From the outset, the colleagues, residents, research assistants, and nurses at the former 2nd Department of Internal Medicine and the Cardiology Center provided a supportive environment that allowed my research to be conducted effectively and undisturbed. I extend my special gratitude to the cardiology residents, assistants, and nurses for their indispensable, high-quality contribution to the day-to-day management of clinical work, which was vital for data collection.

Furthermore, I thank my colleagues within the Working Group of Heart Failure and Heart Muscle Diseases at the Cardiology Center. Specifically, Dr. Hedvig Takács, Dr. Gergely Rácz, Dr. Árpád Kormányos, Dr. János Borbás, Dr. Noémi Schvartz, and Dr. Bianka Polestyuk were a constant source of intellectual inspiration, professional motivation, and camaraderie throughout this research endeavour. The friendship and professional support provided by Dr. Attila Pálinkás is also gratefully acknowledged.

Last, but most certainly not least, I extend my deepest appreciation to my family. To my parents, my husband, and my children, thank you for your unwavering emotional support, patience, and sacrifice, which sustained me throughout the demanding process of writing this thesis and my life in general. This accomplishment is as much yours as it is mine.