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Omecamtiv mecarbil in precision-cut living heart failure slices: A story of a double-edged sword

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ABSTRACT

Heart failure (HF) is a rapidly growing pandemic while medical treatment options remain limited. Omecamtiv mecarbil (OM) is a novel HF drug that directly targets the myosin heads of the cardiac muscle. This study used living myocardial slices (LMS) from patients with HF to evaluate the direct biomechanical effects of OM as compared to dobutamine. LMS were produced from patients with end-stage HF undergoing cardiac transplantation or left ventricular assist device implantation and cultured under electromechanical stimulation (diastolic preload: ca. 1 mN, stimulation frequency: 0.5 Hz). Dobutamine and omecamtiv mecarbil (OM) were administered on consecutive days and biomechanical effects were continuously recorded with dedicated force transducers. OM and dobutamine significantly increased contractile force to a similar maximum force, but OM also increased median time-to-peak with 48 % ($p = 0.046$) and time-to-relaxation with 68 % ($p = 0.045$). OM administration led to impaired relaxation of HF LMS with increasing stimulation frequencies, which was not observed with dobutamine. Furthermore, the functional refractory period was significantly shorter after administration of OM compared to dobutamine (235 ms (200–265) vs. 270 ms (259–283), $p = 0.035$). In conclusion, OM increased contractile force and systolic duration of HF LMS, indicating an improvement in cardiac function and normalization of systolic time intervals in patients with HF. Conversely, OM slowed relaxation, which could lead to diastolic filling abnormalities. As such, OM showed benefits on systolic function on one hand but potential hindrances of diastolic function on the other hand.

1. Introduction

Heart failure (HF) is a rapidly growing pandemic with an estimated prevalence of >64.3 million individuals globally [1]. Morbidity and mortality remain high in this population, despite advances in optimized medical therapy [2]. The reasons for reduced myocardial contractility are complex and include extracellular matrix changes, reduced availability of high energy substrates, impaired calcium recycling and myofilament abnormalities [3–5]. The latter plays a crucial role in the generation of a strong power stroke for cardiac contraction where myosin forms cross-bridges with actin.

Traditionally, the medical treatment of HF targets second messenger pathways that increase cardiac contractility by increasing cardiomyocyte intracellular calcium concentrations using phosphodiesterase inhibitors or beta-adrenergic receptor agonists [6,7]. However, these drugs also significantly increase heart rate and myocardial oxygen consumption [8,9]. In addition, elevations in intracellular calcium concentrations and calcium transients contribute to increased arrhythmogenicity and these drugs also possess vasodilatory effects resulting in significant hypotension [9].

Omecamtiv mecarbil (OM), a cardiac myosin activator, has been presented as novel therapeutic option for patients with HF [10]. OM is a small molecule that directly targets the kinetics of cardiac myosin by increasing the rate of myosin cross-bridge formation [11,12]. This results in increased duration and amount of cardiomyocyte contractions in pre-clinical studies, without altering intracellular calcium

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concentrations and thus potentially improving cardiac energetics [11,13]. Nevertheless, these pre-clinical studies were predominantly performed in cellular and animal models [11,13–18], being less representative of the human in-vivo setting of patients with HF and complicating data extrapolation. To date, only few studies with OM were performed on more complex in-vitro cardiac disease models [19–21].

In this study, we used living myocardial slices (LMS) from patients with end-stage HF to evaluate the biomechanical and arrhythmogenic properties of OM as compared to dobutamine. LMS are ultrathin sections of intact myocardium cultured under conditions of electromechanical stimulation and present a novel platform for high-throughput and disease-specific drug safety screening [22,23]. Human HF LMS are directly produced from explanted tissue of patients with end-stage HF undergoing cardiac transplantation or left ventricular assist device implantation. As such, the three-dimensional structure and HF phenotype of the tissue remain intact, with different cardiac cell types, extracellular matrix proteins and connections between these components. The purpose of this study was to evaluate the acute biomechanical response of OM on HF-specific tissue in a near-physiological state.

2. Materials and methods

2.1. Tissue acquisition

Cardiac tissue was obtained from patients with end-stage HF undergoing cardiac transplantation or left ventricular assist device implantation surgery, as approved on 7 January 2021 by the medical ethics committee of the Erasmus MC, Rotterdam, the Netherlands (MEC 2020–0988). Patients were informed about use of their surgical residual material for scientific research (opt-out method of consent), in accordance with local regulations and guidelines. Ventricular specimens were immediately submerged in 4 °C Tyrode slicing buffer (NaCl 136 mM, KCl 5.4 mM, $MgCl_2{\cdot}6H_2O$ 1 mM, $NaH_2PO_4{\cdot}H_2O$ 0.33 mM, Glucose 10 mM, $CaCl_2{\cdot}2H_2O$ 0.9 mM, 2,3-butanedione monoxime 30 mM, HEPES 5 mM, pH 7.4) and transported on ice to the laboratory.

2.2. LMS production

The technique to produce LMS has been previously described in detail [24]. In short, ventricular tissue was submerged in 37 °C 4 % low-melting agarose (Agarose II, VWR Chemicals LLC, Solon, OH, USA) and cooled until the gel solidified. A high-precision cutting vibratome (VT1200S, Leica BioSystems, Nussloch, Germany) cut slices of the embedded tissue with the blade moving parallel to the myocardial fibre orientation (settings: slice thickness 300 μm, vibration amplitude 1.3 mm, blade advance speed 0.07 mm/s). The surrounding agarose was subsequently removed from the slices and miniature plastic triangles were glued to both ends of the slices, with longitudinally aligned fibre orientation in between. Slices were mounted in custom-made biomimetic cultivation chambers (BMCCs) (InVitroSys GmbH, Munich, Germany) [24] and a preload of ca. 1 mN was applied by providing mechanical stretch to the tissue. BMCCs were filled with 2.4 mL of 37 °C culture medium (Gibco Medium-199 (Grand Island, NY, USA) supplemented with 5 % penicillin-streptomycin, 5 % Insulin-Transferrin-Selenium-X and 50 μM 2-Mercaptoethanol) and 1.6 mL medium was refreshed after 1 h and 24 h respectively. Preload was readjusted to 1 mN at these first two medium exchanges. BMCCs were placed in a standard 37 °C 5 % CO_2 incubator and placed on a rocking plate (30 rpm) for continuous agitation. Electrical field stimulation (frequency 0.5 Hz, output 50 mA, pulse duration 7.0 ms) resulted in strong isotonic contractions of the LMS. Contraction force was continuously measured by a magnetic force transducer in the BMCC [24].

2.3. Dose-response curve

OM (10 mM, MedChemExpress, NJ, USA) was diluted in culture medium and 4 μL were added to the BMCCs with incremental dosages (from 0.30 to 10.0 μM) and 30 min in between dosages. Contractility was analyzed before and 10 min after addition of OM by averaging 30 s of data. Curves were constructed using logarithmic value scales on the x-axis and percentage responses relative to the maximum effect on the y-axis.

2.4. OM versus dobutamine

The biomechanical profile of OM was compared to that of beta-adrenergic agonist dobutamine (Centrafarm B.V., Breda, the Netherlands) (Fig. 1). Drugs were diluted in culture medium and 4 μL were added to the BMCCs resulting in a final concentration of 3.0 μM. Dobutamine was added 1 h after 1.6 mL medium refreshment on day 1 of LMS culture. Dobutamine was washed out after 90 min of incubation by refreshing all medium in the BMCC. The next day, OM was added 1 h after 1.6 mL medium refreshment, equivalent to the administration of dobutamine.

2.5. Force-frequency relationship

The effect of higher heart rates after drug administration was assessed by increasing the electrical stimulation frequency from 30 to 300 beats per minute (bpm) with increments of 30 bpm and 1 min between intervals. Contraction force was measured the last 30 s of the interval, and only if LMS captured all electrical stimuli.

2.6. Functional refractory period

The functional refractory period (FRP) before and after OM or dobutamine administration was determined by decremental pacing with a fixed S1-rate of 1000 ms and decreasing the extra S2-stimuli delay from 450 to 130 ms, with decrements of 5 ms. The first interval that did not show contractile capture on the S2-stimulus was defined as the FRP.

2.7. Model of tachycardia

After drug administration, LMS were stimulated for 30 min at a frequency of 180 bpm as a test of exercise capacity and as a model for tachycardia.

2.8. Data acquisition

For each contraction, force amplitude (F_{max}), peak area (AUC), contraction duration (CD), peak width at 50 % of the maximum amplitude (CD_{50}), peak width at 90 % of the maximum amplitude (CD_{90}), time to peak (TTP), time to relaxation (TTR), steepest positive slope (+dF/dt), and steepest negative slope (−dF/dt) were extracted from the system recordings with the peak analysis module of LabChart 8 software (ADInstruments, v8.1.19, Oxford, UK). Parameters were defined as previously described [25] and start and end of the peak were chosen at 10 % away from the baseline to compensate for baseline noise [26] (Fig. 1).

2.9. Statistics

An average F_{max}, AUC, CD, CD_{50}, CD_{90}, TTP, TTR, dF/dt, and −dF/dt was calculated for each LMS over a stable period of 30 s before and at peak F_{max} after drug administration as a summary measure per slice. Medians and interquartile ranges (IQR) were calculated for all biomechanical parameters. To take into account clustering of LMS that were produced from the same patient, clustered Wilcoxon signed-rank tests were performed. All other data was tested for normality and paired parametric or non-parametric testing was applied as appropriate. A p-value of $\leq$0.05 was considered statistically significant. Statistical analyses were executed in R (version 4.2.2; R foundation for statistical

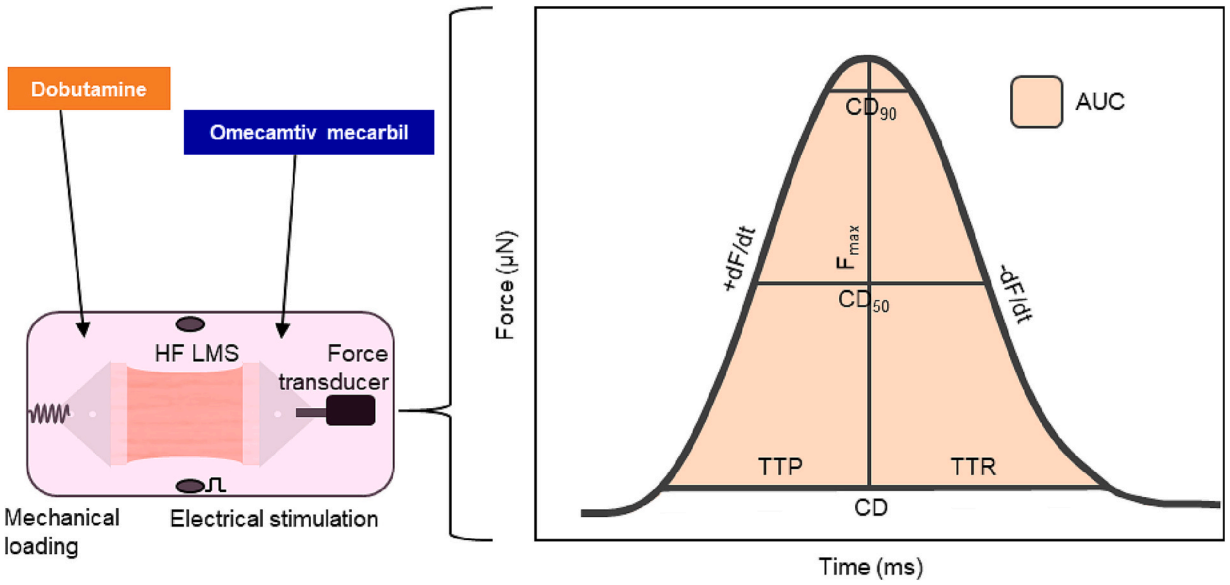

Fig. 1. Dobutamine and OM were subsequently administered to living myocardial slices (LMS) from heart failure (HF) patients and cultured with electromechanical stimulation. Contractility was measured with force transducers to assess contraction, relaxation and other biomechanical parameters after drug administration. *AUC* = area under the curve. *CD* = total contraction duration; CD_{50} = contraction duration at 50 % of the maximum amplitude. CD_{90} = contraction duration at 90 % of the maximum amplitude. F_{max} = maximum contraction force. *TTP* = time to peak. *TTR* = time to relaxation. + *dF/dt* = steepest positive slope. − *dF/dt* = steepest negative slope.

Computing, Vienna, Austria). Radar plots of biomechanical profiles, dose-response curves and force-frequency relation curves were created in R.

3. Results

Dose-response curves of OM were created in 31 LMS from 4 HF patients, showing the steepest increase in F_{max} up till 3.0 µM (Supplementary Fig. 1). In addition, TTP and TTR were prolonged at this concentration (Supplementary Figs. 2 and 3), resulting in the selected concentration of 3.0 µM of OM for evaluation of the biomechanical effect. This evaluation was performed in 28 additional LMS from 5 ensuing patients with end-stage HF (age: 52 ± 12 years, 80 % male), of which baseline characteristics are presented in Table 1.

3.1. Biomechanical response

The biomechanical effects of OM or dobutamine administration were presented in Tables 2 and 3. OM as well as dobutamine significantly increased contractile force and resulted in a similar median maximum contractile force (F_{max}: 5189 µN (2820–6938) vs. 4626 µN (1740–11,175), $p = 0.305$). Yet, the effect on the CD was significantly different between both drugs as demonstrated by the biomechanical profile plots in Fig. 2 and Supplementary Table 1. OM increased contraction durations (CD: +64 %, $p = 0.046$), including TTP, TTR, CD_{50}, and CD_{90} (Table 2), whereas dobutamine decreased CD with 19 % ($p = 0.049$) and TTR (Table 3). Also, maximum positive and negative dF/dt slopes appeared higher after dobutamine administration compared to OM (+dF/dt: 37645 µN/s (11470–82,605) vs. 21,590 µN/s (11975–27,448), $p = 0.119$; −dF/dt: −33,350 µN/s (−67,425 to −10,269) vs. −12,005 µN/s (−17,383 to −6914), $p = 0.075$). Consequently, the AUC also appeared bigger with OM, although those results also did not reach statistical significance (2682 µN.s (1349–3494) vs. 1009 µN.s (423–2285) $p = 0.079$) (Supplementary Table 1).

3.2. Force-frequency relationship

Increasing stimulation frequencies resulted in a cumulatively decreasing F_{max} after administration of OM (Fig. 3). LMS relaxation aggravated at each increase with OM, but not with dobutamine, as indicated by the upward shift in point of relaxation (Fig. 3C).

No difference was observed in the absolute FFR after administration

Table 1
Characteristics of patients with HF from whom tissue was obtained to produce living myocardial slices (LMS) for experimentation with OM and dobutamine.

Patient characteristics	*N* = 5
Age, years	52 ± 12
Male, n	4
BMI, kg/m^2	26.6 ± 3.7
Etiology of heart failure	
	2
- Ischemic cardiomyopathy, n	2
- Dilated cardiomyopathy, n	1
- Congenital heart disease, n	
Surgery	
	1
- LVAD implantation, n	4
- Heart transplant, n	
LVAD pre-operatively	2
Medication pre-operatively	
	0
- Omecamtiv mecarbil	0
- Dobutamine	2
- ARNI/ACE-I	3
- Beta-blocker	3
- MRA	1
- SGLT2i	

LMS characteristics	*N* = 28
Ventricle	
	23
- Left, n	5
- Right, n	

ACE-I = angiotensin-converting enzyme inhibitor. *ARNI* = angiotensin receptor/neprilysin inhibitor. *LVAD* = left ventricular assist device. *MRA* = mineralcorticoid receptor antagonist. *SGLT2i* = sodium-glucose cotransporter-2 inhibitor.

Table 2
Comparison between biomechanical parameters before and after administration of OM ($n = 28$). Significant p-values are expressed bold.

OM	0 μM	3.0 μM	Δ (%)	P-value
F_{max} (μN)	943 (528–1713)	5189 (2820–6938)	+363 %	**0.043**
CD (ms)	568 (538–612)	975 (923–1043)	+64 %	**0.046**
CD_{50} (ms)	290 (263–297)	508 (475–544)	+81 %	**0.038**
CD_{90} (ms)	97 (91–110)	189 (174–200)	+80 %	**0.034**
−dF/dt (μN/s)	−4488 (−9348 to −2583)	−12,005 (−17,383 to −6914)	+104 %	**0.043**
+dF/dt (μN/s)	5608 (3309–9305)	21,590 – (11975–27,448)	+235 %	**0.043**
AUC (μN.s)	281 (171–514)	2682 (1349–3494)	+714 %	**0.041**
TTP (ms)	222 (205–237)	337 (312–362)	+48 %	**0.046**
TTR (ms)	349 (330.8–390.6)	639 (587–687)	+68 %	**0.045**

Table 3
Comparison between biomechanical parameters before and after administration of dobutamine ($n = 28$). Significant p-values are expressed bold.

Dobutamine	0 μM	3.0 μM	Δ (%)	P-value
F_{max} (μN)	480 (210–728)	4626 (1740–11,175)	+956 %	**0.042**
CD (ms)	523 (478–597)	410 (377–433)	−19 %	**0.049**
CD_{50} (ms)	248 (233–262)	239 (219–252)	−4 %	0.589
CD_{90} (ms)	75 (46–91)	93 (88–100)	+23 %	**0.046**
−dF/dt (μN/s)	−2594 (−4198 to −1264)	−33,350 (−67,425 to −10,269)	+971 %	**0.041**
+dF/dt (μN/s)	3551 (1673–5058)	37,645 (11470–82,605)	+1035 %	**0.043**
AUC (μN.s)	138 (74–215)	1009 (423–2285)	836 %	**0.042**
TTP (ms)	200 (182–210)	187 (175–199)	−6 %	0.780
TTR (ms)	323 (285–395)	225 (194–243)	−27 %	**0.043**

of both OM and dobutamine (Fig. 3A). However, the variation on relative F_{max} (Fig. 3B) was larger after dobutamine administration as compared to OM.

The TTP declined with increasing stimulation frequencies after administration of both drugs (Supplementary Fig. 4), but was higher for all stimulation frequencies with OM as compared to dobutamine. The prolonged TTR with OM declined with increasing stimulation frequencies and was similar to dobutamine at a stimulation frequency of 180 bpm and more (Supplementary Fig. 4).

3.3. Model of tachycardia

LMS were stimulated at 180 bpm for 30 min after administration of OM and dobutamine as a test of exercise capacity and model of tachycardia (Fig. 4). Start of tachypacing immediately resulted in impaired relaxation of LMS with OM in all HF LMS, contrary to the minimal effects on relaxation seen after dobutamine administration. Moreover, beat-to-beat variation in the endpoints of contraction and relaxation of the contractile peaks was observed after OM administration (Fig. 4).

3.4. Functional refractory period

The effect of dobutamine or OM on refractoriness was assessed by evaluation of the shortest time interval that showed contractile capture (Table 4). A decrease in FRP was observed after administration of OM, although this did not reach statistical significance (260 ms (239–303) vs. 235 ms (200–265), $p = 0.126$). Yet, the FRP was significantly different after administration of OM or dobutamine (OM: 235 ms (200–265) vs. dobutamine: 270 ms (259–283), $p = 0.035$), while there was no difference at baseline ($p = 0.675$) (Table 4).

4. Discussion

OM as well as dobutamine increased F_{max} of HF LMS, whilst only OM prolonged TTP. If these results are translated to the intact in-vivo heart, OM thus increased systolic duration which could normalize systolic ejection time (SET) intervals of patients with HF. In addition, it would result in less peak loading on the ventricular wall as compared to dobutamine, also indicated by differences in dF/dt kinetics. However, these favorable force kinetics come at the cost of slower diastolic relaxation as shown by the prolonged TTR and smaller −dF/dt. Slowed relaxation could lead to diastolic filling abnormalities. Our study showed that this negative effect of OM on LMS relaxation became more prominent with increasing stimulation frequencies as indicated by the FFR and tachypacing data. As such, OM therapy poses as a double-edged sword with benefits on systolic function but hindrances of diastolic function.

4.1. Biomechanical response of HF LMS to OM and dobutamine

OM and dobutamine showed a similar increase to maximum contractile force, but with an increased systolic duration for OM as expressed by prolongation of the TTP. These effects are in line with previous in-vitro studies, animal studies and clinical trials with HF patients where a prolongation of SET intervals was observed after OM administration [11,15,20,21,27–29]. Shortened SET intervals were shown to be associated with increased risks of cardiovascular morbidity and mortality in patients with HF [30–32] and OM's "pharmacological signature" is normalization of these SET intervals [27–29].

In addition, OM administration also resulted in a smaller, although non-significant, maximum positive and negative dF/dt compared to dobutamine, indicating less peak loading on HF LMS. This supports the hypothesis from Teerlink et al. that direct augmentation of cardiac function with OM could reduce myocardial wall stress and possibly promotes favorable ventricular remodeling in patients with HF [27]. Moreover, the smaller +dF/dt could implicate improved handling of myocardial energetics as the maximal velocity of muscle shortening tightly correlates with the rate of energy conversion from ATP by the myofibril [33]. Previous studies corroborate this improved myocardial energetic profile showing that OM does not increases total myocardial oxygen consumption despite substantial improvements in cardiac function [13], contrary to the well-known increase in myocardial oxygen consumption caused by dobutamine [8].

Conversely, the positive effects of OM on F_{max}, TTP and +dF/dt come at the expense of slower relaxation, indicated by prolonged TTR and smaller insignificant −dF/dt as compared to dobutamine. In-vivo, this would result in a shortened diastolic duration possibly leading to filling abnormalities and/or malperfusion of the coronary arteries during

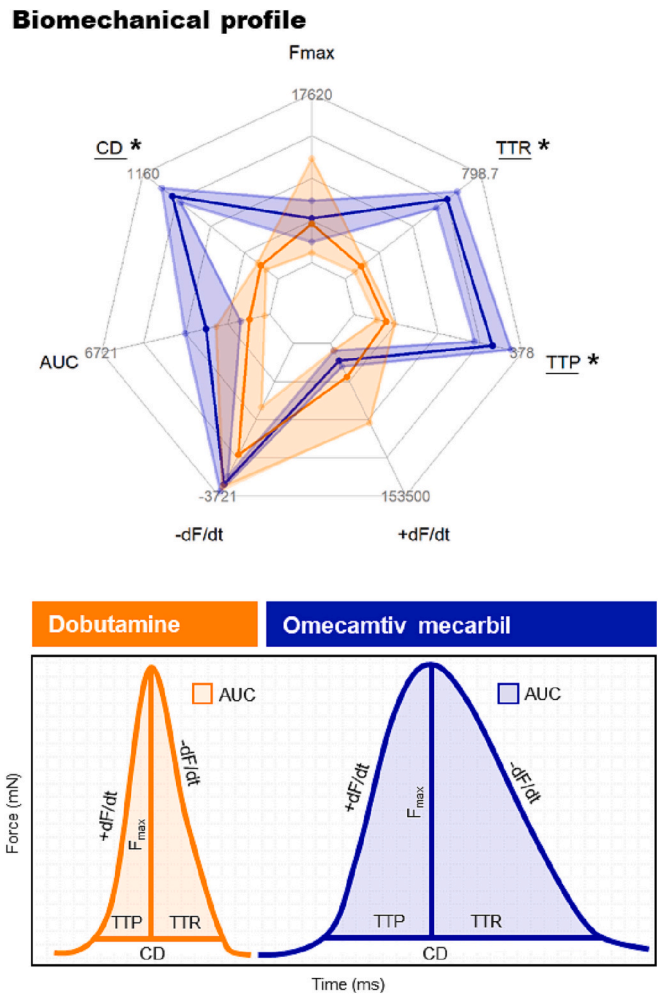

Fig. 2. Biomechanical profile plots after administration of OM (blue) and dobutamine (orange), expressed as median with IQR (n = 28). *Underscored parameters indicate a significant difference between both drugs.
AUC = area under the curve. *CD* = total contraction duration; F_{max} = maximum contraction force. *TTP* = time to peak. *TTR* = time to relaxation. + *dF/dt* = steepest positive slope. − *dF/dt* = steepest negative slope. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diastole. Slowed relaxation after OM treatment was previously described in isolated cardiomyocytes, skinned myocardial preparations and engineered heart tissues [16,17,20,21], and diastolic filling impairments due to this mechanical disruption were confirmed in a rat model [15]. However, OM was reported to induce species-dependent effects on relaxation [21] and the current study is the first to demonstrate prolongation of TTR in intact LMS from individuals with HF. Unfortunately, clinical data with respect to diastolic function after OM administration is scarce as detailed diastolic function assessments were not performed in the available clinical trials [10,27,29,34]. Of note, prolongation of TTR was smaller at lower dosages (Supplementary Fig. 3) suggesting that the described diastolic "side-effects" might be less pronounced at lower plasma concentrations of OM (clinical therapeutic range 0.5–2.0 μM [27,28]). This highlights the importance of appropriate dosing of OM.

4.2. Contractile effect of tachycardia and OM

Increasing stimulation frequencies resulted in a reduction of F_{max} and upward baseline shift of point of relaxation after administration of OM, aggravating relaxation of HF LMS with faster heart rates (Fig. 3). This was also observed when tachypacing was applied to the HF LMS, with an immediate increase in baseline at onset of stimulation with 180 bpm, and immediate shift back after termination of tachypacing (Fig. 4). This is probably due to a prolongation of the CD with OM, leading to initiation of the next contraction before the LMS reached full relaxation. Deterioration of LMS relaxation with increasing stimulation frequencies was not observed after dobutamine administration. Furthermore, beat-to-beat variation was observed in F_{max} and point of relaxation during tachypacing after administration of OM, which was previously described by Fülöp et al. in rats with normal systoles followed by diminished cardiac contractions [15]. Furthermore, this beat-to-beat variability in contraction force was accompanied by oscillations in T-wave amplitude as measured with surface electrocardiograms in their study. Electrical activity was not measured in our study, but it has been suggested that T-wave alternans might be responsible for the initiation of tachyarrhythmias [35] which are known to be poorly tolerated by patients with HF. The potential occurrence of cardiac alternans was not described in the clinical studies [10,27–29,34], but could occur at elevated plasma ranges of OM as indicated by our study and Fülöp et al. [35] and therefore requires further clinical investigation.

4.3. Effect on refractory period of LMS

The difference in FRP before and after drug administration was not significant for both individual drugs (Table 4). However, a significant difference was found when comparing the FRP after drug administration between OM and dobutamine. Yet, OM directly acts on the β-myosin heavy chain and is thought to have no direct effects on intracellular ion concentrations and thus refractoriness. However, previous studies showed OM to have direct effects on cardiac ion currents at a dosage of 10 μM with a depression of the action potential plateau, a reduction of early repolarization and a shortening of the action potential [18,36,37]. This probably explains the change in FRP observed in the current study, but it remains unknown whether this is a direct effect of OM on the cardiac ion channels, or a consequence of the modified myosin-actin interaction. On the other hand, the effects on the cardiac action potential were not observed at lower OM plasma concentrations that are closer to the clinical plasma range [18,37]. This highlights the importance of appropriate dosing of OM treatment as overdosing could lead to electrophysiological alterations triggering cardiac arrhythmias.

4.4. Limitations

The comparison between OM and dobutamine was performed with a clustered analysis in a small sample size of 5 patients, even though the group consisted of 28 LMS, which could result in potential type II error. Contractile performance varied between individual LMS, as is inherent to the LMS model and use of biological tissues, yet the net effect of the drugs was comparable between groups. Since each LMS served as its own control, the effects of OM and dobutamine were not compared to a control with administration of only culture medium as vehicle. Hence, effects of components in the culture medium could not be excluded, although drug effects were large and only small volumes of culture medium were added. In addition, no parallel control arm was included to compare effects of OM and dobutamine in healthy LMS due to the limited availability of healthy cardiac tissue. For this reason, differences in biomechanical response to OM and dobutamine between healthy and diseased tissue could not be tested. Also, no molecular analyses were performed to assess which pathways led to the observed effects, as we only focussed on the biomechanical effects of OM and further molecular analyses were beyond the scope of this study.

The study did not account for differences in etiology of heart failure nor drugs that patients received prior to surgery, which could have influenced the results. Yet, most HF drugs have a relatively short half-life and LMS underwent various wash-out steps with Tyrode buffer and culture medium before experimentation.

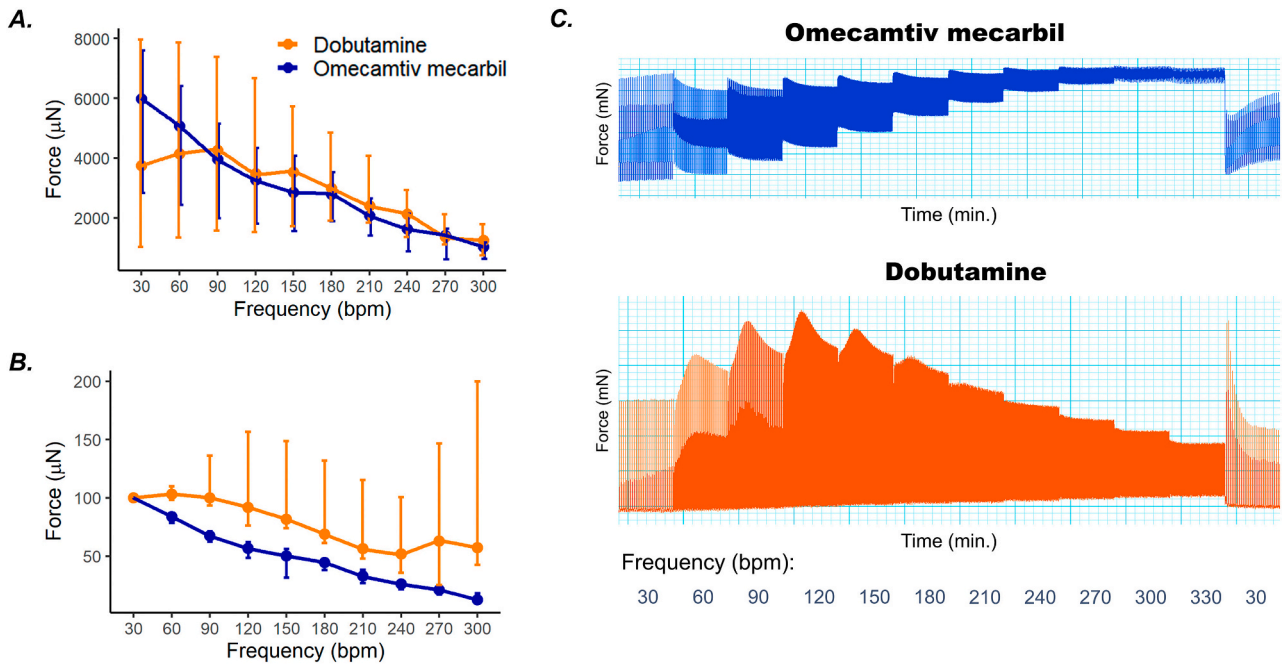

Fig. 3. Absolute and relative force-frequency relationship (FFR) curves after administration of OM and dobutamine ($n = 28$), together with exemplary contractile traces of the FFR. *A*. No difference was observed in the absolute FFR curves. *B*. Relative FFR curves. *C*. Increasing stimulation frequencies resulted in an upward baseline shift of point of LMS relaxation after OM (blue), but not after dobutamine administration (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

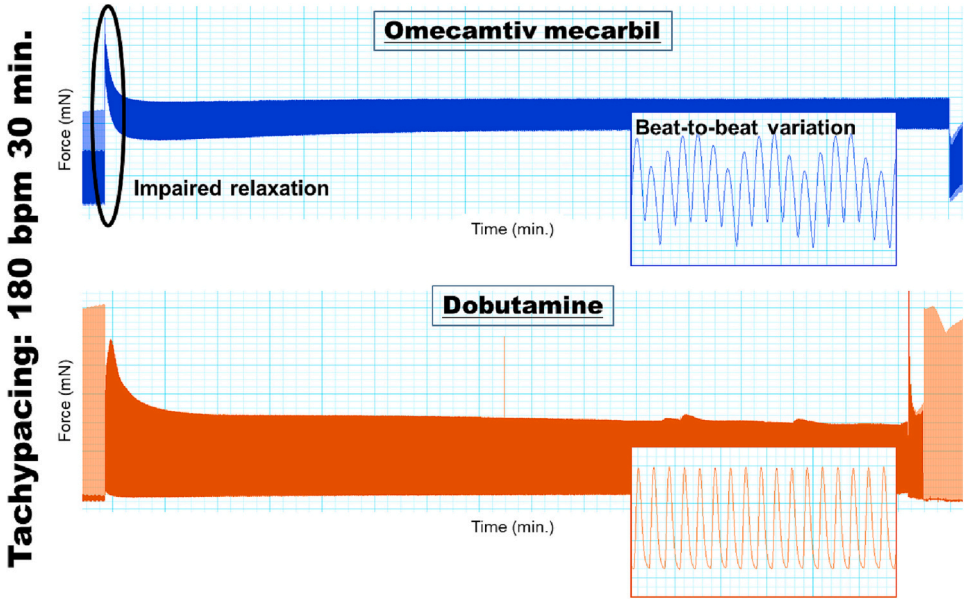

Fig. 4. The effect of tachypacing at 180 bpm for 30 min, after administration of OM and dobutamine. Tachypacing resulted in impaired relaxation of the LMS and beat-to-beat variation in contraction and relaxation after administration of OM.

Table 4
Functional refractory period of OM or dobutamine before and after drug administration ($n = 28$). Significant *p*-values are expressed bold.

	0 µM (ms)	3.0 µM (ms)	P-value
OM	260 (239–303)	235 (200–265)	0.126
Dobutamine	268 (241–288)	270 (259–283)	0.498
P-value	0.675	**0.035**	

5. Conclusion

This is the first study to examine the acute biomechanical effects of OM on LMS from individuals with HF. OM increased contractile force and systolic duration of HF LMS, indicating an improvement in cardiac function and normalization of SET intervals in patients with HF. However, OM also slowed relaxation which was aggravated by faster stimulation frequencies, possibly leading to diastolic filling abnormalities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmccpl.2023.100040.

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