

Alcohol septal ablation markedly reduces energy loss in hypertrophic cardiomyopathy with left ventricular outflow tract obstruction: A four-dimensional flow cardiac magnetic resonance study

Zehao Dai^{a,b,1,*}, Nobuo Iguchi^{a,c,1}, Itaru Takamisawa^{a,1}, Morimasa Takayama^{a,1}, Mamoru Nanasato^{a,1}, Mitsuru Kanisawa^{c,1}, Naokazu Mizuno^{c,1}, Shohei Miyazaki^{d,1}, Mitsuaki Isobe^{e,1}

^a Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu, Tokyo 183-0003, Japan

^b Department of Cardiovascular Medicine, The University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

^c Department of Radiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu, Tokyo 183-0003, Japan

^d Cardio Flow Design Inc., 22-3 Ichibancho, Chiyoda-ku, Tokyo 102-0082, Japan

^e Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu, Tokyo 183-0003, Japan

ARTICLE INFO

Keywords:

4D flow MRI
Energy loss
Alcohol septal ablation
Hypertrophic cardiomyopathy
Left ventricular outflow tract obstruction

ABSTRACT

Background: Functional follow-up modalities of hypertrophic cardiomyopathy (HCM) with left ventricular (LV) outflow tract obstruction (LVOTO) subjected to alcohol septal ablation (ASA) are limited.

Methods: This retrospective cohort study included patients of HCM with LVOTO who underwent ASA and four-dimensional (4D) flow cardiac magnetic resonance imaging (MRI) both before and after ASA. We analyzed energy loss in one cardiac cycle within the three-chamber plane of the LV and aortic root, and compared between pre- and post-ASA measurements.

Results: Of the 26 included patients, 10 (39%) were male, and median age was 71 (interquartile range 58–78) years. ASA significantly reduced not only LVOT pressure gradient (70 [19–50] to 9 [3–16], $P < 0.001$), but also energy loss during one cardiac cycle within the three-chamber plane of the LV and aortic root (80 [65–99] to 56 [45–70], $P < 0.001$). A linear association was observed between the reductions of energy loss and pressure gradient ($R^2 = 0.58$, $P < 0.001$).

Conclusions: ASA significantly reduced energy loss within the LV and aortic root as quantified by 4D flow MRI, reflecting the decreased cardiac workload. This approach is a promising candidate for serial functional follow-up in patients undergoing ASA.

1. Introduction

Septal myectomy is indicated for relieving symptoms and improving exercise capacity in hypertrophic cardiomyopathy (HCM) patients who have left ventricular outflow tract (LVOT) obstruction (LVOTO), a resting or provoked LVOT pressure gradient ≥ 50 mmHg, and moderate to severe symptoms (usually New York Heart Association [NYHA] functional class III–IV) that are drug-refractory [1,2]. Alcohol septal

ablation (ASA), a transcatheter procedure, is an alternative to septal myectomy, that is indicated in patients with high surgery risk due to serious comorbidities or advanced age [2].

Functional follow-up modalities for HCM with LVOTO subjected to ASA are mainly limited to echocardiography, which visualizes the morphology and measures the peak velocity at LVOT, and catheterization, which directly assesses the LVOT pressure gradient. Recently, four-dimensional (4D) flow magnetic resonance imaging (MRI) has been

Abbreviations: ASA, alcohol septal ablation; HCM, hypertrophic cardiomyopathy; LV, left ventricle/left ventricular; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; ROI, region of interest; TTE, transthoracic echocardiography; 4D, four-dimensional.

* Corresponding author at: Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu, Tokyo 183-0003, Japan.

E-mail address: daizh@luke.ac.jp (Z. Dai).

¹ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

<https://doi.org/10.1016/j.ijcha.2021.100886>

Received 9 June 2021; Received in revised form 23 September 2021; Accepted 26 September 2021

2352-9067/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Patient characteristics and parameters before and after alcohol septal ablation.

Number = 26	pre-ASA		post-ASA		P-value
Male	10	(39)			
Age (yr)	71	(58–78)			
Height (cm)	155	(151–165)			
Weight (kg)	57	(50–71)			
Body mass index (kg/m ²)	25	(21–27)			
Family history of HCM	3	(12)			
Smoker	8	(31)			
History of syncope/pre-syncope	2	(8)			
Comorbidities					
Hypertension	6	(23)			
Diabetes	2	(8)			
Dyslipidemia	12	(46)			
Coronary artery diseases	1	(4)			
Atrial fibrillation	4	(15)			
Stroke	1	(4)			
eGFR (ml/min/1.73 m ²)	57	(53–76)			
Hemoglobin (g/dL)	14	(13–15)			
Use of beta-blockers	24	(92)			
Use of cibenzoline/disopyramide	25	(96)			
Catheterization					
PG between the LV apex and aortic root at rest (mmHg)	70	(19–50)	9	(3–16)	< 0.001
Cardiac index (L/min/m ²)	3.0	(2.7–3.3)	3.2	(2.8–3.5)	0.090
Transthoracic echocardiography					
LVEF (%)	66	(62–68)	64	(61–67)	0.200
Peak velocity at LVOT (m/s)	4.6	(2.9–5.6)	2.4	(1.9–3.1)	< 0.001
Left atrial diameter (mm)	42	(37–45)	40	(37–43)	0.138
Systolic anterior motion of the mitral valve	26	(100)	17	(65)	0.008*
Mitral regurgitation, mild or more	18	(69)	9	(35)	0.016*
MRI					
Heart rate (beats/min)	66	(62–77)	69	(65–79)	0.218
Left ventricular mass (g)	118	(105–138)	123	(107–139)	0.893
Energy loss within 3-chamber plane (mJ/m)	80	(65–99)	56	(45–70)	< 0.001
ECG					
Left/right bundle branch block	0	(0)	17	(65)	< 0.001*
Atrioventricular block	0	(0)	0	(0)	–
NYHA functional class 3 or more	8	(31)	0	(0)	0.013*
NT-proBNP (ng/mL)	1123	(402–4583)	715	(342–1835)	< 0.001

Data are presented as number (percentage) or median (interquartile range).

*McNemar test, otherwise Wilcoxon signed rank test.

ASA = alcohol septal ablation; eGFR = estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PG = pressure gradient.

increasingly applied in the cardiovascular field, given its advantages of providing information from the perspective of fluid dynamics by non-invasively visualizing blood flow and calculating quantitative parameters such as wall shear stress and energy loss within the cardiac chambers or blood vessels [3–5]. Several reports have demonstrated elevated intra-cardiac energy loss in various cardiac diseases, as well as its reduction along with the improvement of cardiac function achieved by optimal treatment [6,7]. This study aimed to investigate the influence of ASA on energy loss in the left ventricle (LV) and aortic root as measured by 4D flow MRI in HCM patients with LVOTO.

2. Methods

2.1. Study design and study population

This single-center retrospective cohort study was approved by the institutional research board of Sakakibara Heart Institute (NO. 19–120). All patients provided informed consent under an opt-out policy.

We screened consecutive patients who underwent ASA for drug-refractory symptomatic HCM with LVOTO at Sakakibara Heart Institute, a referral center in Tokyo, Japan, from April 2019 to December 2020. The study included patients who underwent 4D flow cardiac MRI before and after ASA (within 6 months from the procedure). The diagnosis of HCM with LVOTO was made based on current guidelines [1,2].

2.2. Indication and procedure for ASA

For each symptomatic HCM patient with LVOTO, both a beta-blocker and a class Ia antiarrhythmic agent (cibenzoline or disopyramide) were started and up-titrated according to residual symptoms unless intolerable. Patients presenting with NYHA functional class II–IV symptoms despite maximum tolerated medications were evaluated by catheterization including right heart catheterization, left ventriculography, coronary angiography, and recording of the LVOT pressure gradient. An LVOT peak-to-peak pressure gradient ≥ 50 mmHg at rest or upon provocation by the Valsalva maneuver, premature ventricular beat, or intravenous nitroglycerin (up to 100 μ g) warrants septal reduction therapy, based on current guidelines [1,2]. The decision to perform ASA was made based on high surgery risk, suitable coronary anatomy, absence of the need for concomitant cardiac surgery, and informed patient consent, via a focus group discussion consisting of multidisciplinary HCM experts (including but not limited to ASA operators, septal myectomy operators, and cardiac imaging experts).

The ASA procedure was performed as previously described [8,9]. Briefly, after confirmatory coronary angiography and identifying the perfusion bed of the target septal branch with echocardiographic contrast injected through the over-the-wire balloon catheter, desiccated ethanol was infused through the balloon catheter, with continuous transthoracic echocardiography (TTE) monitoring to help determine the infusion endpoint. Pressure gradient recording and right heart

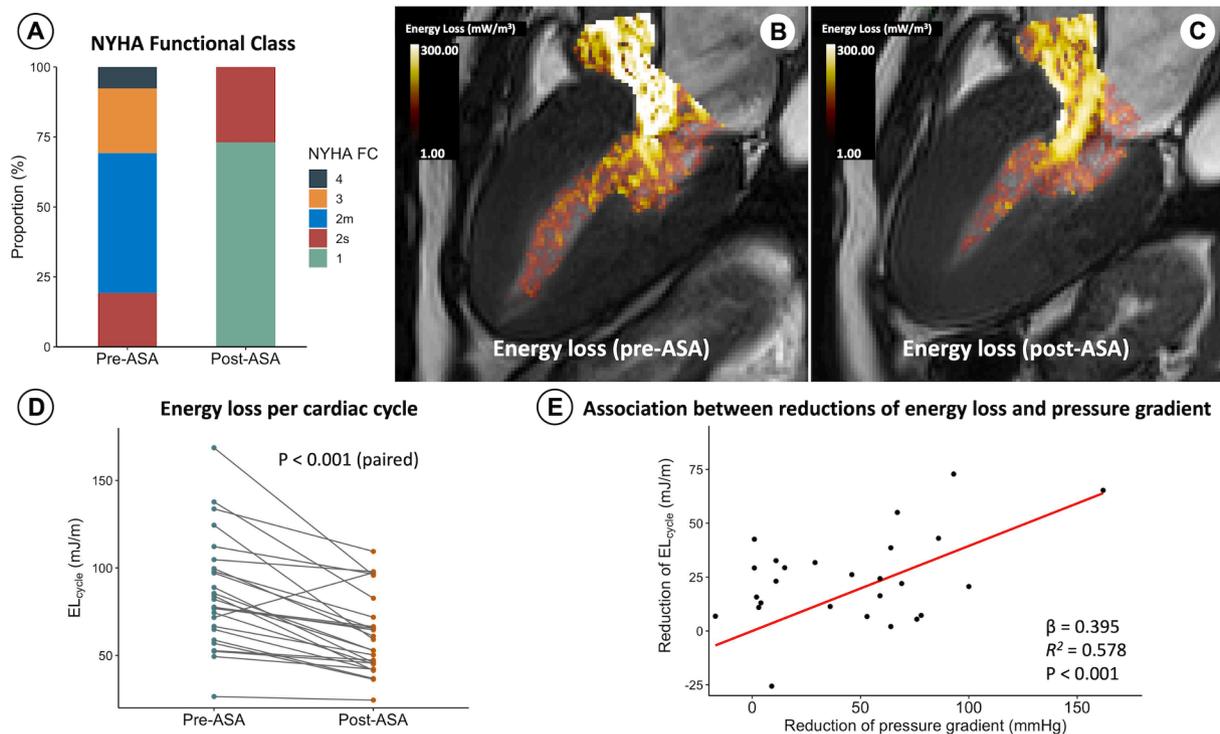


Fig. 1. Alcohol septal ablation (ASA) improved New York Heart Association (NYHA) functional class (FC) (A). B and C demonstrates representative images of energy loss within the left ventricle and aortic root, before (B) and after (C) ASA in a same patient. Energy loss per cardiac cycle (EL_{cycle}) decreased significantly after ASA (D), which was linearly associated with the reduction of pressure gradient directly measured by catheterization (E).

catheterization were performed immediately before and after the ASA procedure.

2.3. Acquisition of MRI

All patients included in the present study underwent standard-of-care cardiac MRI within 6 months before and after ASA, along with 4D flow MRI, on a 1.5 T MRI system (MAGNETOM Sola, Siemens, Germany), with a maximum gradient strength of 45 mT/m and a maximum slew rate of 200 T/m/s, using a commercially available 18-channel phased array body coil. Standard-of-care cardiac MRI included electrocardiogram-gated steady-state free precession cine cardiac MRI and late gadolinium enhancement if renal function was preserved. The imaging protocol for HCM with LVOTO in our institute specifies that three-chamber plane images should be included in each imaging series [10]. For the assessment of fluid dynamics, all 4D flow MRI acquisitions were performed during the waiting period after gadolinium injection. Time-resolved two-dimensional phase-contrast MRI of the three-chamber plane with three-directional velocity encoding (i.e. 4D flow) was implemented during breath-holding with prospective electrocardiogram-gating. The pulse sequence parameters were as follows: spatial resolution $1.8 \times 1.8 \times 6 \text{ mm}^3$; field of view $340 \times 340 \text{ mm}^2$; velocity sensitivity 150 cm/s; echo time 2.4 ms; repetition time 33.2–49.8 ms; flip angle 12° ; and view per cardiac phase 15–17. All 4D flow MRI scans were acquired with parallel imaging (GRAPPA) with an acceleration factor of $R = 2$ and 34 reference lines.

2.4. Post-processing and quantitative analysis of 4D flow MRI

Quantitative analysis of the 4D flow MRI was performed by a commercially available post-processing software (iTFlow version 1.9; Cardio Flow Design, Japan) [11]. We described the region of interest (ROI) as the area surrounded by the LV endocardium, sinotubular junction, and mitral annulus within the three-chamber plane. The ROI was traced manually by an experienced observer (ZD) in each single

phase of the cine MRI, allowing the software to automatically calculate the in-plane energy loss (mW/m^2) within the region in each phase based on a previously established formula as follows [11,12]:

$$\int (\mu) \sum_{ij} \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right)^2 dS$$

where μ is the viscosity of the blood ($\mu = 0.004 \text{ Pa}\cdot\text{s}$), i and j correspond to the principal velocity directions, u is the velocity field measured by 4D flow MRI, and S corresponds to pixels in the ROI. Energy loss generated within the ROI in each single phase was then integrated upon one cardiac cycle, yielding in-plane energy loss per cardiac cycle (EL_{cycle} [mJ/m]).

2.5. Statistical analysis

Continuous variables are presented as the median (interquartile range). Categorical variables are presented as number (percentage). Both continuous and categorical variables were compared between pre- and post-ASA using paired tests (Wilcoxon signed rank and McNemar tests). All statistical analyses were performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

3. Results

We screened 69 patients who underwent ASA for HCM with LVOTO during the study period, among whom 26 had standard-of-care as well as 4D flow cardiac MRI within 6 months before and after ASA, thus were included in this study. The included patients had a median age of 71 (58–78) years, and 10 (39%) were male (Table 1). A median of 1 (1–2) septal branch was treated, with a total ethanol volume of 3.5 (2.3–4.4) mL. The postprocedural peak creatine kinase was 1201 (953–1557) IU/L. ASA significantly improved the LVOT pressure gradient and cardiac index measured by catheterization and LVOT peak velocity measured by

TTE, and resulted in a better NYHA functional class (Table 1, Fig. 1A).

Pre- and post-ASA MRI was taken with comparable heart rates (Table 1). A typical presentation of pre- and post-ASA energy loss within the ROI in a single phase is illustrated in Fig. 1B–C. EL_{cycle} decreased significantly with ASA, from 80 (65–99) to 56 (45–70) mJ/m ($P < 0.001$; Table 1, Fig. 1D). The reduction of EL_{cycle} was significantly associated with a decrease in pressure gradient ($R^2 = 0.58$, $P < 0.001$; Fig. 1E).

4. Discussion

This study demonstrated that ASA reduced energy loss within the LV and aortic root, which was detected by serial 4D flow cardiac MRI. To our knowledge, this study is the first attempt to evaluate changes in fluid dynamics driven by ASA, with the exception of several single-case reports.

It has been shown that elevated energy loss arises from the altered blood flow due to the obstruction in aortic stenosis and HCM with LVOTO, which increases cardiac workload [13,14]. Case reports have also demonstrated that in HCM with LVOTO, ASA successfully optimized blood flow in the LVOT, and reduced turbulent kinetic energy. Although it is still debatable whether estimating energy deprivation via turbulent kinetic energy based on turbulent flow or via energy loss based on laminar flow, as in this study, is the best parameter, such quantifications are thought to be a promising approach to evaluate cardiac workload, and to follow-up patients serially [13,15]. Energy loss is an indirect calculation from velocity in every in-plane pixel in 4D flow MRI, reflecting the deprivation in energy corresponding to the alteration of total pressure, including both static and kinetic pressure. Conversely, pressure gradient in catheterization only measures that of static pressure. This might theoretically explain the discrepancy between the improvement of EL_{cycle} and that of pressure gradient which was observed in few patients in this study.

Besides invasive procedures, mavacamten, a recently developed selective allosteric inhibitor of cardiac myosin ATPase, has also been proven to significantly relieve LVOT obstruction, and to improve exercise capacity and NYHA functional class in HCM with LVOTO [16]. Given the mechanism of mavacamten, which reduces cardiac workload during contraction, improves relaxation and promotes efficient energy use [17], the hemodynamic improvement is also expected to be reflected by 4D flow MRI parameters.

Taken together, 4D flow cardiac MRI is an appropriate candidate modality for serial assessment in HCM with LVOTO. It is more objective and reproducible when compared with TTE, and less invasive when compared with catheterization, though is not currently available in all institutions, nor valid in patients with arrhythmia such as atrial fibrillation.

4.1. Limitations

This was a single-center retrospective study with a small sample size. In this study, we evaluated EL_{cycle} within the three-chamber plane, but not within the three-dimensional whole heart. The latter approach requires a longer time for MRI acquisition, precluding the use of breath-holding. Thus, it would be less feasible in clinical practice, especially in symptomatic patients. Our approach is less time-consuming and could be performed within the waiting period after gadolinium injection, adding no excessive burden to the patients.

4.2. Conclusions

ASA in HCM patients with LVOTO significantly reduced energy loss within the LV and aortic root as quantified by 4D flow MRI, indicating a substantial decrease in the cardiac workload. This approach is a promising candidate for serial functional follow-up in patients who undergo

ASA.

Funding

This study is supported by Japan Research Promotion Society for Cardiovascular Diseases (to ZD).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SM is an employee of Cardio Flow Design Inc., Tokyo, Japan, the producer of iTFlow, a 4D flow MRI processing software. Other authors report no relationships that could be construed as a conflict of interest.

References

- [1] P.M. Elliott, A. Anastakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, et al., ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC), *Eur. Heart J.* 35 (2014) 2733–2779.
- [2] B.J. Gersh, B.J. Maron, R.O. Bonow, J.A. Dearani, M.A. Fifer, M.S. Link, et al., ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *Circulation*. 124 (2011) e783–e831.
- [3] S. Crandon, M.S.M. Elbaz, J.J.M. Westenberg, R.J. van der Geest, S. Plein, P. Garg, Clinical applications of intra-cardiac four-dimensional flow cardiovascular magnetic resonance: A systematic review, *Int. J. Cardiol.* 249 (2017) 486–493.
- [4] H. Ota, K. Sugimura, M. Miura, H. Shimokawa, Four-dimensional flow magnetic resonance imaging visualizes drastic change in vortex flow in the main pulmonary artery after percutaneous transluminal pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension, *Eur. Heart J.* 36 (2015) 1630.
- [5] S. Schnell, C. Wu, S.A. Ansari, Four-dimensional MRI flow examinations in cerebral and extracerebral vessels - ready for clinical routine? *Curr. Opin. Neurol.* 29 (2016) 419–428.
- [6] V.P. Kamphuis, M.S.M. Elbaz, P.J. van den Boogaard, L.J.M. Kroft, R.J. van der Geest, A. de Roos, et al., Disproportionate intraventricular viscous energy loss in Fontan patients: analysis by 4D flow MRI, *Eur. Heart J. Cardiovasc. Imaging*. 20 (2019) 323–333.
- [7] T. Nabeta, K. Itatani, K. Miyaji, J. Ako, Vortex flow energy loss reflects therapeutic effect in dilated cardiomyopathy, *Eur. Heart J.* 36 (2015) 637.
- [8] Y. Imori, H. Takano, M. Kitamura, R. Aoyama, H. Sengen, O. Kenta, et al., Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy through non-left anterior descending septal perforators, *Heart Vessels* 35 (2020) 647–654.
- [9] P. Sorajja, S.R. Ommen, D.R. Holmes Jr., J.A. Dearani, C.S. Rihal, B.J. Gersh, et al., Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy, *Circulation* 126 (2012) 2374–2380.
- [10] C.M. Kramer, J. Barkhausen, C. Bucciarelli-Ducci, S.D. Flamm, R.J. Kim, E. Nagel, Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update, *J. Cardiovasc. Magn. Reson.* 22 (2020) 17.
- [11] S. Miyazaki, K. Itatani, T. Furusawa, T. Nishino, M. Sugiyama, Y. Takehara, et al., Validation of numerical simulation methods in aortic arch using 4D Flow MRI, *Heart Vessels* 32 (2017) 1032–1044.
- [12] K. Itatani, T. Okada, T. Uejima, T. Tanaka, M. Ono, K. Miyaji, et al., Intraventricular flow velocity vector visualization based on the continuity equation and measurements of vorticity and wall shear stress, *Jpn. J. Appl. Phys.* 52 (2013) 07HF16.1–07HF16.6.
- [13] J. Garcia, A.J. Barker, M. Markl, The role of imaging of flow patterns by 4D flow MRI in aortic stenosis, *JACC Cardiovasc. Imaging*. 12 (2019) 252–266.
- [14] K. Iwata, J. Matsuda, Y. Imori, T. Sekine, H. Takano, Four-dimensional flow magnetic resonance imaging reveals the reduction in turbulent kinetic energy after percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy, *Eur. Heart J.* 41 (2020) 1454.
- [15] A.J. Barker, P. van Ooij, K. Bandi, J. Garcia, M. Albaghdadi, P. McCarthy, et al., Viscous energy loss in the presence of abnormal aortic flow, *Magn. Reson. Med.* 72 (2014) 620–628.
- [16] I. Olivetto, A. Oreziak, R. Barriales-Villa, T.P. Abraham, A. Masri, P. Garcia-Pavia, et al., Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet*. 396 (2020) 759–769.
- [17] R.L. Anderson, D.V. Trivedi, S.S. Sarkar, M. Henze, W. Ma, H. Gong, et al., Deciphering the super relaxed state of human beta-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers, *Proc. Natl. Acad. Sci. USA* 115 (2018) E8143–E8152.