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# Speckle tracking echocardiography in early detection of myocardial injury in a rat model with stress cardiomyopathy

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**Abstract**

**Aim:** Studies on the usefulness of speckle tracking echocardiography (STE) in the evaluation of the left ventricle in rats with stress cardiomyopathy (SCM) are limited. Our aim was to investigate whether strain values by STE and cardiac troponin I (cTnI) could predict early myocardial injury in rats with SCM. **Material and methods:** SCM was induced in Sprague-Dawley female rats using immobilization (IMO) stress. Biomarkers and echocardiographic parameters were evaluated and compared among groups (group 1 - 30 minutes after IMO stress, group 2 - 24 hours after IMO stress, and control group). We defined myocardial injury as a left ventricular ejection fraction <50%. Possible predictors of early myocardial injury were determined by univariate logistic regression, and independent predictors of early myocardial injury were investigated with multivariable logistic regression. **Results:** A total of 44 rats with a mean weight of 426±33 g were evaluated. Group 1 had the highest plasma epinephrine and norepinephrine levels ($p<0.001$) and the highest heart rate ($p<0.001$). In univariate logistic regression, cTnI (OR=2.61 [1.02–10.25], p=0.043) and global longitudinal strain (GLS) (OR=2.13 [1.12–6.26], p=0.022) were predictive of early myocardial injury. When GLS and cTnI were included in a multivariate analysis, only GLS remained an independent predictor of early myocardial injury (OR=2.67 [1.14–14.76], p=0.027). **Conclusions:** STE is useful for the quantitative detection of subtle myocardial abnormalities in rats with SCM. GLS may provide a reliable and non-invasive method to predict early myocardial injury.

**Keywords:** early myocardial injury; speckle tracking echocardiography; stress cardiomyopathy

## Introduction

Stress cardiomyopathy (SCM), also known as Takotsubo cardiomyopathy, is an acute syndrome characterized by transient left ventricular systolic dysfunction and triggered by emotional or physical stress [1,2]. It was initially thought to be a relatively benign disease; however, current data have shown that it may be associated with considerable inpatient morbidity and a small risk of mortality [3]. Studies in immobilization (IMO) using animal models for SCM have added substantially to the understanding of molecular mechanism and associated propensity toward emotional stress in the acute phase of the disorder. However, the findings of these investigations do not address the pathophysiology and echocardiographic characteristics of rats in response to immobilization stress and to the causal relation between stress and this syndrome [4,5].

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To better elucidate its pathophysiology and develop effective therapeutic strategies, experiments using appropriate animal models are required. Previous studies observed that cardiac biomarkers such as cardiac troponin I (cTnI) and B-type natriuretic peptide (BNP) may play a role in the early clinical recognition of SCM. However, to the best of our knowledge, data is limited regarding the pattern in which cardiac biomarkers are released in patients with SCM [6,7]. In addition, the changes in myocardial function during IMO stress and the optimal measurement time point are still unknown, even though this is of clinical importance [3].

To date, assessment of the effects of strain values by speckle tracking echocardiography (STE) has been mainly focused on the clinical setting and retrospective studies [8]. A recent study reported that echocardiographic indices by STE may be more precise and distinctive than traditional echocardiography for early detection of subtle abnormalities [9]. However, studies on the usefulness of STE in the evaluation of the left ventricle (LV) in rat models with SCM are scarce.

The aim of this study was to compare the pathophysiology and echocardiographic characteristics of rats with SCM to controls, and to investigate whether the strain values by STE combined with cTnI could predict early myocardial injury.

## Material and methods

### *Experimental animals*

All experimental protocols were approved by the Institutional Animal Care and Animal Ethics Committee of Capital Medical University. It is known that the female rat model tends to have high results variability in metabolic (hormones) related diseases and SCM is a unique cardiomyopathy in that it usually occurs in postmenopausal women [1]. Healthy female Sprague-Dawley rats aged 30 weeks were initially selected and housed in an air-conditioned room at 20-25 $^{o}$C with an automatic 12-hour light-dark cycle and free access to water and food [10]. All animal work was performed in accordance with the NIH guidelines for the use of animals in experiments.

### *Immobilization stress procedure*

In the IMO stress protocol, rats are restrained by the wrapping of their upper and lower limbs with adhesive tape for 120 minutes [11]. This procedure causes LV apical akinesia (apical ballooning) and characteristic hypercontractility of the basal LV segments which is similar to what happens in humans. SCM was confirmed by observation of changes in color and motion of the LV wall on echocardiography. The rats were randomly assigned to 3 groups: group 1 (30 minutes after IMO stress), group 2 (24 hours after IMO stress) and a control group. The rats in the control group had no history of IMO stress and were completely normal.

### *Measurement of biomarkers*

Serum samples of epinephrine (EPI) and norepinephrine (NE) obtained from the three groups were stored at -80 $^{o}$C until being analyzed. The concentrations of plasma EPI and NE were measured by ELISA kits according to the manufacturer's protocol. Plasma samples for the analysis of cTnI were obtained from the three groups and then on the following day from group 2 (48 hours after IMO stress). They were measured using a chemiluminescent microparticle immunoassay on an Architect i2000 analyzer, according to the manufacturer's instructions. All samples were assayed in triplicate and the average values were used for analysis.

### *Conventional echocardiography*

Echocardiography was performed by an experienced operator using a Vivid 7 Dimension ultrasound scanner (GE Healthcare, Horten, Norway). Two-dimensional (2D) echocardiography data were collected using 12MHz sector transducer and stored digitally on an EchoPac 8.1 workstation (GE Medical Systems) for further analysis. The heart rate was obtained by an electrocardiogram (ECG). The LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and stroke volume (SV) were calculated by the biplane Simpson's method [12]. The minimal frame rate was 250 per second. Echocardiography was evaluated in accordance with the guidelines of the American Society of Echocardiography [13]. Data were measured over 5 heart beats and averaged by echocardiographic experts who were blinded to the animal groups.

### *Cardiac magnetic resonance imaging*

A 7-T horizontal-bore animal magnetic resonance scanner (Bruker BioSpin GmbH, Ettlingen, Germany) with an 86-mm radio-frequency volume coil (Bruker BioSpin GmbH) and Paravision 5.1 software was used. After axial, sagittal, and coronal localizer sequences were obtained, the coil was tuned and matched. Then, bright-blood cine images of two-chamber, three-chamber, and four-chamber views of the left ventricle were obtained using a retrospectively self-gated protocol (IntraGate; Bruker BioSpin GmbH). Acquisition parameters were as follow: echo time, 2.96 msec; repetition time, 9.8 msec; field of view, 50x50 mm$^2$; matrix size, 256x256; number of repetitions, 200; cardiac frames reconstructed, 20; slice thickness, 1 mm; and scan time, approximately 3 min. Analysis of global LV function was calculated using Segment version 1.9 (Medviso, Stockholm, Sweden). Myocardium segmentation was performed among at least

seven LV short-axis slices outlining both endocardial and epicardial borders in all cardiac frames. LVEDV, LVESV and LVEF were calculated from the largest and smallest areas, respectively, of the LV cavity in each slice. Myocardial injury was defined as LVEF<50%. Because of the potential shortage of geometric assumption in volumetric calculation in the biplane Simpson's method by echocardiography, we used cardiac magnetic resonance imaging (CMRI) to determine LVEF changes [14].

***Speckle tracking echocardiography***

Echo Pac version 8.1 (Echo Pac, GE Healthcare) was used for strain analyses. The automatic tracking analysis was performed by blinded investigators in the apical four-chamber and two-chamber view for longitudinal strain (LS) and in the parasternal short-axis view at the basal and mid-papillary level for circumferential and radial strain according to the vendor's instructions. The endocardial border was manually traced at end-diastole. Peak circumferential strain (CS) and radial strain (RS) measurements were obtained from the basal, mid-segments of the anteroseptal, anterior, anterolateral, inferior, inferolateral and inferoseptal walls in a total of 12 segments. Regional strain values were averaged to determine global circumferential and radial strain (GCS and GRS) [10]. Global longitudinal strain (GLS) was calculated as the average LV longitudinal strain across the segments obtained using apical two-chamber and apical four-chamber views [15].

***Statistical analysis***

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables as numbers and percentages. Differences between groups were determined using one-way analysis of variance (ANOVA) for continuous variables and the Kruskal–Wallis test for categorical variables. Inter-group differences were analyzed using the paired t test. Myocardial injury was defined as LVEF<50%. Possible predictors of early myocardial injury were determined by univariate logistic regression, and variables that were statistically significant ($p<0.05$) were selected for evaluation by a multivariate logistic regression model. Receiver operating characteristic curves were obtained for the echocardiographic parameters and biomarkers that were predictive. Areas under the curves (AUC) were compared. Inter-observer and intra-observer reproducibility of LVEF, GLS, GCS, and GRS were assessed using intra-class correlation coefficients (ICCs) and Bland–Altman analysis. Data were analyzed by SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), and two-tailed $p<0.05$ was considered significant.

## Results

Nine rats were excluded from the analysis: 4 because of poor image quality and 5 because of experimental failure. Therefore, 31 rats served as SCM models and 13 rats as controls (success rate was 86.1%). Apical SCM was identified in (15/16) 93.8% of rats, whereas the midventricular form was found in (1/16) 6.7%.

General and echocardiographic characteristics, including CMRI characteristics of the three groups and early myocardial injury of the three groups are summarized in Table I. Group 1 had the highest heart rate, highest level of plasma EPI and plasma NE (all $p<0.001$) compared to group 2 and controls. However, group 2 had

Table I. General, echocardiographic and cardiac magnetic resonance imaging variables in rats between groups

| | Controls (n=13) | Group1 (n=15) | Group2 (n=16) | p value |
|---|---|---|---|---|
| Body weight (g) | 427±24 | 423±21 | 429±22 | >0.05 |
| Heart rate (bpm) | 328±11 | 398±15 | 341±17 | **<0.001** |
| LVEDV (ul) | 357±13 | 351±15 | 362±16 | >0.05 |
| LVESV (ul) | 114±10 | 137±11 | 204±17 | **<0.001** |
| LVEF (%) | 68±5.6 | 62±5.3 | 46±6.7 | **<0.001** |
| Stroke volume (ul) | 243±23 | 214±21 | 159±15 | **<0.001** |
| CMRI-LVEDV (ul) | 371±17 | 366±16 | 376±15 | >0.05 |
| CMRI-LVEF (%) | 67±5.3 | 61±4.8 | 44±5.6 | **<0.001** |
| Early myocardial injury (%) | 0/13 (0) | 1/15 (6.7) | 12/16 (75) | **<0.001** |
| Incidence of ballooning (%) | 0/13 (0) | 1/15 (6.7) | 15/16 (93.8) | **<0.001** |
| Epinephrine (pg /ml) | 16.78±2.16 | 209.7±24.3 | 27.84±3.57 | **<0.001** |
| Norepinephrine (ng/ml) | 12.41±1.56 | 56.43±4.23 | 17.96±1.14 | **<0.001** |
| Peak cTnI (ng/ml) | 0.117±0.029 | 0.184±0.076 | 2.92±0.121 | **<0.001** |

Data are expressed as mean**±standard deviation or** number (%). cTnI=cardiac troponin I; CMRI=cardiac magnetic resonance imaging; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; LVEF=left ventricular ejection fraction.

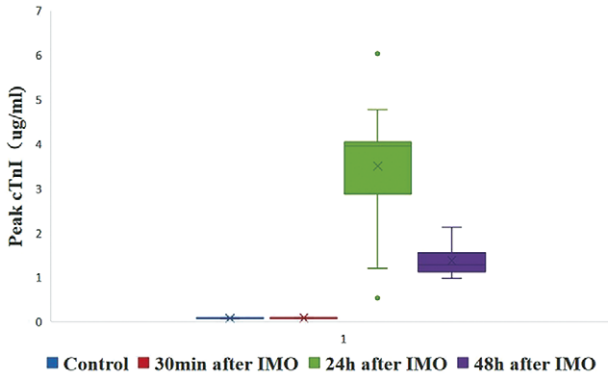


**Fig 1.** Levels of peak cTnI in controls, 30min after IMO, 24h after IMO and 48h after IMO. IMO, immobilization.

the highest peak cTnI compared to group 1 and controls ($p<0.001$) and the level of peak cTnI declined the following day (fig 1).In addition, group 2 had the lowest LVEF, stroke volume, much more prevalent LV apical ballooning and the lowest CMRI-LVEF(all $p<0.001$) compared to group 1 and controls (fig 2). As early myocardial injury was defined as LVEF<50%, 12 (75%) rats developed early myocardial injury in group 2.

Global and regional strain values of segments in SCM groups versus controls are summarized in Table II. Group 2 had the lowest GLS ($p<0.001$), GRS ($p<0.05$), GCS ($p<0.05$), and Apex-LS ($p<0.001$). However, there were no significant differences in Base-CS, Mid-CS, Base-RS, Mid-RS, Base-LS and Mid-LS between the three groups.

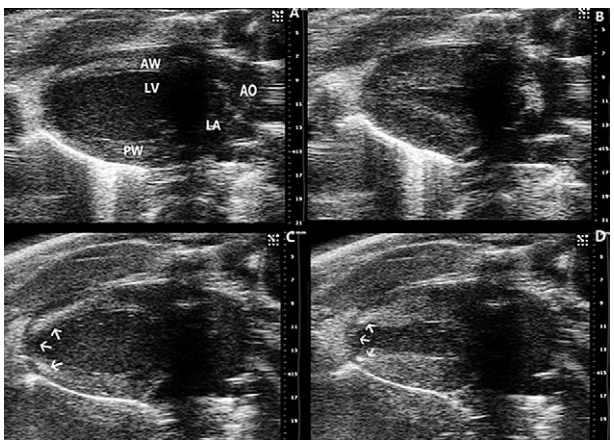


**Fig 2.** End-diastolic (A) and end-systolic (B) echocardiographic images in one control rat and in one rat that developed left ventricular apical ballooning after the immobilization stress in group 2 (C and D). Ao, aorta; AW, anterior wall; LV, left ventricle; LA, left atrium; PW, posterior wall.

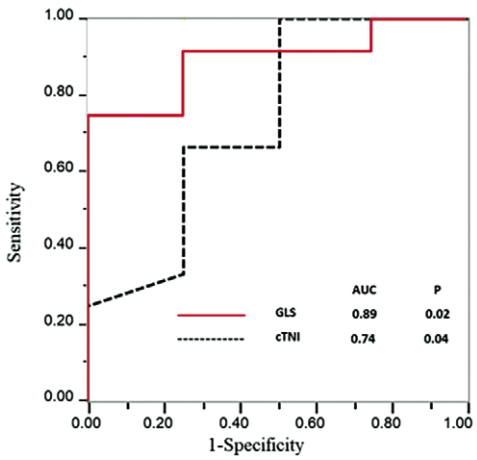


**Fig 3.** Receiver operating characteristics curve for GLS and cTnI in the prediction of early myocardial injury. AUC, areas under the curves; GLS, global longitudinal strain; cTnI, cardiac troponin.

Table II. Global and regional strain values in rats between groups

| | Controls (n=13) | Group 1 (n=15) | Group 2 (n=16) | p value |
|---|---|---|---|---|
| GLS | -15.6±2.7 | -16.0±3.1 | -10.5±2.2 | **<0.001** |
| GRS | 31.2±5.6 | 32.3±5.3 | 29.2±4.8 | **<0.05** |
| GCS | -18.4±3.3 | -19.4±3.8 | -16.7±2.9 | **<0.05** |
| Average longitudinal strain | | | | |
| Base-LS (%) | -17.8±3.7 | -18.9±2.9 | -19.1±3.3 | >0.05 |
| Mid-LS (%) | -16.3±2.4 | -15.6±3.1 | -14.7±2.4 | >0.05 |
| Apex-LS (%) | -14.2±2.7 | -13.7±2.8 | -8.9±1.9 | **<0.001** |
| Average radial strain | | | | |
| Base-RS (%) | 32.4±6.3 | 31.8±5.6 | 30.6±4.5 | >0.05 |
| Mid- RS (%) | 29.5±5.4 | 32.5±4.5 | 30.8±3.5 | >0.05 |
| Average circumferential strain | | | | |
| Base-CS (%) | -18.3±3.7 | -18.9±3.2 | -17.6±4.2 | >0.05 |
| Mid- CS (%) | -16.6±2.8 | -17.4±2.6 | -16.4±4.3 | >0.05 |

The results are expressed as mean±standard deviation. CS = circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; GCS = global circumferential strain; LS = longitudinal strain; Mid-middle; RS = radial strain.

***Predictors of early myocardial injury***

In univariate logistic regression, cTnI (OR=2.61 [1.02–10.25], p=0.043) and GLS (OR=2.13 [1.12–6.26], p=0.022) were predictive of early myocardial injury. In ROC curve analysis for prediction of early myocardial injury, cTnI showed an AUC of 0.74 (p=0.043) at a cutoff of ≥2.12 ng/ml with a sensitivity of 96.4% and specificity of 50.7%. GLS provided a higher AUC of 0.89 (p=0.022) at a cutoff of -13.6% with a sensitivity of 78.5% and specificity of 98% (fig 3). When GLS and cTnI were both included in a multivariate analysis, only GLS remained an independent predictor of early myocardial injury (OR=2.67[1.14–14.76], p=0.027).

Inter-observer measurement showed an ICC=0.91 for GLS, 0.89 for GCS, 0.92 for GRS, and 0.94 for LVEF. Similarly, intra-observer measurement showed an ICC=0.86 for GLS, 0.91 for GCS, 0.93 for GRS, and 0.91 for LVEF, respectively. This indicates reproducibility of the LVEF and strain values.

## Discussions

The principal findings of this study were: 1) rats evaluated 30 minutes after IMO had the highest plasma catecholamine concentrations; 2) rats evaluated 24 hours after IMO had the highest cTnI level (followed by a daily decline) and had more prevalent echocardiographic abnormalities; 3) GLS and cTnI may serve as predictors of early LV myocardial injury in rats with SCM, but only GLS is an independent predictor of early myocardial injury.

Catecholamine cardiotoxicity, metabolic disturbances and coronary microvascular dysfunction have been proposed as possible explanations behind stress cardiomyopathy [16]. However, the precise mechanisms are yet to be determined. Therefore, findings resulting from animal models would be extremely valuable for studying the exact underlying mechanisms behind this syndrome. We found that the concentrations of EPI and NE were higher at 30 minutes after IMO than at 24 hours after IMO. Wittstein et al reported that plasma levels of both EPI and NE in patients with SCM were two to three times higher than those in patients with myocardial infarction [17]. They also suggested that direct catecholamine-associated myocardial toxicity might explain this transient abnormality of LV wall motion [17]. Therefore, abnormal catecholamine dynamics related to emotional distress seems to play a major role in the pathogenesis of SCM [18]. Moreover, the surges in catecholamine levels may be an evolutionary response to sudden shock or danger and therefore stunning occurs as a result of the epinephrine-mediated effects on cardiac myocytes [19].

It is reported that cardiac biomarkers such as cTnI may be useful to differentiate patients with SCM from acute coronary syndrome [20]. However, until now, no single biomarker has been established [21,22]. In our study, cTnI was highest in rats with SCM, and this was followed by a daily decline in cTnI levels. This suggests that myocardial injury occurs early in the course of the disease, likely in part due to catecholamine cardiotoxicity [17]. Yang et al found that only 21% of SCM patients had a higher cTnI level on the day of admission [20]. This may be the reason why most SCM patients have a modest rise in cTnI concentrations followed by a rapid decline in cTnI levels because of the short half-life of cTnI in SCM patients [23,24]. Therefore, measuring cTnI early after admission is recommended as it is the preferred biomarker for assessing early myocardial injury and for early detection of SCM.

SCM is also known as left ventricular apical ballooning syndrome because in the majority of cases wall motion abnormalities typically involve the apical and midventricular segments, which appear akinetic or dyskinetic in contrast to the basal segments which are often hyperkinetic [16,25]. Our data revealed that the prevalence of apical ballooning (93.8%) was consistent with other studies [17,26] but higher than the rate reported by Templin et al (81.7%) [16]. This higher rate can be explained by the fact that the rats in this experiment are all postmenopausal female, and these almost identical features suggest that myocardial stunning resulting from emotional stress may share a common mechanism, which is believed to be mediated by catecholamines [17]. Recent studies [27,28] suggest that the pathophysiology of SCM may lie in changes in β-adrenergic receptor (AR) signaling. Additionally, biased agonism of epinephrine for β2AR-Gs at low concentrations and for Gi at high concentrations consolidates the acute apical cardiodepressive reaction observed in SCM, with an apical-basal gradient in β2ARs explaining the differential regional responses.

Delbertet al [29] successfully identified SCM in patients with subarachnoid hemorrhage using cTnI. The reported sensitivity and specificity of cTnI were 100% and 80-90%, respectively. We found that increased levels of cTnI are associated with a decrease of LVEF in rats with SCM; however, the specificity was only 50.6%. This difference in specificity may reflect that cTnI alone is probably not enough for detection of early myocardial injury. Kang et al [15] reported that the combination of cTnI and myocardial strain measurement increased the sensitivity from 86% to 93%; however, the results of our study were not as expected. This may be due to the smaller sample size or due to the lower rate of detection with the stand-

ard assay, thus reducing the specificity of cTnI in detecting myocardial injury in the present study.

LVEF calculated by conventional two-dimensional echocardiography, which was probably affected by geometric assumptions or by the presence of myocardial stunning, was significantly less sensitive for the detection of a decrease in LVEF in comparison with the gold standard of CMRI. For a more precise method to define early myocardial injury, LVEF was calculated by CMRI in the current experiment. However, echocardiographic indices by STE may be more convenient, inexpensive and distinctive than the variables by CMRI for early detection of subtle abnormalities [14]. In clinical practice, previous studies have reported that STE could provide useful indexes for quantitative evaluation of LV function and suggested that it had higher sensitivity in detecting subtle abnormalities compared to more traditional parameters such as LVEF and wall motion score index [12,30]. Liu et al evaluated the protective effects of ischemic postconditioning on myocardial function using STE and concluded that STE could detect myocardial function improvement in a rabbit model [31].

We showed that, although rats with SCM presented significant decrease in peak systolic longitudinal and circumferential strains, only GLS remained an independent predictor of early myocardial injury. This might be explained by the fact that longitudinal myocardial fibers have a larger radius of curvature and are located in the subendocardium; therefore, they are exposed to more wall stress than the circumferential fibers of the midwall that have a shorter radius [32]. Another explanation might be that the subendocardial longitudinal myofiber is more sensitive and susceptible to myocardial hypoperfusion and thus is prone to earlier damage leading to impaired longitudinal function. However, short-axis function evaluated by circumferential shortening, in contrast, is determined predominantly from circumferential fiber contraction and helps maintain global ventricular function in subclinical LV abnormality or when longitudinal function is severely impaired [33]. Hung et al observed an association between LV sphericity and circumferential function and concluded that graded increase in ESV in the early stage was associated with progressive longitudinal functional deterioration with relatively preserved circumferential function [34]. Furthermore, a previous study on an animal model using tagged magnetic resonance imaging found that longitudinal strain was affected first as perfusion decreased, followed by circumferential and finally radial strain [35]. These data further support the concept that longitudinal function is more sensitive to early myocardial damage. However, circumferential function-which might remain preserved when the LV begins to deteriorate-serves as a short-axis restraint to prevent further LV geometric expansion.

The present study has several limitations. Echocardiography data were collected using 12 MHz transducer. However, new machines with 15 MHz and higher, for animal models may accommodate high frame rates while preserving spatial as well as resolution. We determined only the early changes of myocardial function. Serial evaluations of the changes in LV function were not performed; therefore, further studies regarding changes in LV function over time and the prognostic significance of strain parameters by STE are necessary. The groups were quite small and the relevance of STE and its clinical applications needs to be further confirmed in large clinical samples in the future. Based on these reports, GLS would be the most useful strain variable in LV evaluation and this could help in the development of effective therapeutic strategies.

In conclusion, abnormal catecholamine dynamics related to emotional stress seems to play a major role in the pathogenesis of SCM. STE is useful for quantitative detection of subtle myocardial abnormalities induced by IMO stress in rats with SCM. GLS is an appropriate parameter to detect early myocardial injury. This study provides the experimental foundation for future clinical trials in SCM.

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**Conflict of interest:** none

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