Regional Mechanical Changes Assessed by 2D Speckle-Tracking Longitudinal Strain do not Parallel Electrical Post-Pacing Cardiac Memory

Maria-Claudia-Berenice SURAN[a, b], Andrei-Dumitru MARGULESCU[a, b, c], Ramona BRUJA[b], Calin SILISTE[a, b], Dragos VINEREANU[a, b]

[a]University of Medicine and Pharmacy "Carol Davila" Bucharest, Bucharest, Romania

[b]Department of Cardiology, University Emergency Hospital of Bucharest, Bucharest, Romania

[c]Department of Cardiology, Morriston Hospital NHS Trust, Swansea, United Kingdom

─ABSTRACT─

Background. *Cardiac memory (CM) refers to persistent T-wave changes that appear after cessation of a period of abnormal ventricular activation, such as ventricular pacing. Prior animal studies using tagged magnetic resonance imaging have suggested that CM is associated with prolonged action potential duration and increased strain of late-activated myocardial segments.*

Objective. *The aim of the present study is to determine whether CM induced by ventricular pacing in human subjects is accompanied by regional mechanical changes in late-activated myocardial segments, assessed by left ventricular (LV) longitudinal strain (peak LS) and time-to-peak longitudinal strain (TTP-LS), using 2D-speckle tracking echocardiography (2DSE).*

Material and methods. *We included 20 patients (16 women, age 71±11 years), with DDD pacemakers and with normal AV conduction and QRS/T morphology at baseline. CM was induced by DDD pacing with a short AV delay. ECGs and 2DSE were performed before pacing (baseline), at peak CM (immediately after two weeks of pacing), and at CM washout (4 weeks after cessation of pacing). We measured by echocardiography: left ventricular (LV) ejection fraction, LV diastolic function (E, A, E/E'), peak LS and TTP-LS for the earliest (i.e. adjacent to the pacing site) and latest (i.e. latest-activated during ventricular pacing) segments, using an 18-segment LV model.*

Results. *All patients had electrical (ECG) CM changes, which disappeared by CM washout. LV global systolic and diastolic functions, as well as regional LS (peak LS for both the latest and earliest activated*

Address for correspondence:
Calin Siliste, MD, PhD
Department of Cardiology, University Emergency Hospital of Bucharest, Splaiul Independentei 169, sector 5, 050098, Bucharest, Romania
Fax / telephone number: 0040 21 318 05 76
Email: calin_siliste@yahoo.com

segments) were similar between evaluations. TTP for the latest and earliest activated segments, as well as mean TTP-LS, increased from baseline to peak CM, but did not decrease at CM washout. The dispersion of TTP-LS was not changed.

Conclusion. *These results suggest that regional mechanical changes, as can be assessed by 2DSE longitudinal strain, do not overlap electrical CM.*

Keywords: 2-dimensional strain, 2DSE, echocardiography, cardiac memory.

INTRODUCTION

Cardiac memory (CM) refers to changes in T wave polarity and vector that appear after cessation of a period of abnormal ventricular repolarization, such as cardiac pacing. The CM T wave vector approaches the "abnormal" (paced) QRS vector, so that CM T waves become negative in leads where the abnormal QRS was negative and positive in leads where the abnormal QRS was positive (1).

Previous studies performed on animal models evaluated changes in regional left ventricular (LV) contractility in models of post-pacing CM. In one of these studies, changes in regional circumferential strain, assessed by tagged magnetic resonance imaging (MRI) were found to parallel CM, in a group of in vivo dogs (2). Thus, circumferential strain was increased, and time-to-peak strain was prolonged in the myocardial segments that were the farthest away from ("opposite") the pacing lead. Moreover, another elegant study performed on isolated rabbit hearts concluded that post-pacing cardiac memory could actually be the result of altered mechanical activation and stretch (3). Sosunov *et al* found that excitation-contraction uncoupling abolished post-pacing CM, while electrical changes similar to those produced by post-pacing CM could be induced by locally applied ventricular stretch.

Objective. The aim of the present study is to assess regional changes in LV longitudinal strain in human subjects with post-pacing CM. Using 2D-speckle tracking echocardiography (2DSE), we tested the hypothesis that CM induced by ventricular pacing would be associated with increased myocardial longitudinal strain (LS) and time-to-peak longitudinal strain (TTP-LS) in late-activated segments. ❑

MATERIAL AND METHODS

Patients

The study was approved by the local ethics committee, and patients were included in the study after an informed consent was signed.

We initially studied 23 patients with dual-chamber pacemakers implanted in clinical indications (4) (bradycardia-tachycardia syndrome or sinus node dysfunction), over a period of three years, between June 2014 and April 2017. Of these, we included in the present analysis 20 patients, after excluding three patients with poor acoustic windows.

Inclusion criteria for our study were: septal placement of right ventricular lead, atria predominantly in sinus rhythm (ensuring all study electrocardiograms and echocardiograms were performed in sinus rhythm), and with an estimated need for ventricular pacing less than 10% in the first two months after inclusion.

We excluded patients with: atrio-ventricular or intra-ventricular conduction abnormalities on baseline ECG (including bundle branch block and hemiblocks, with the exception of first degree atrio-ventricular block), ST segment or T wave abnormalities (including abnormal T wave inversions of any cause), prior or current myocardial ischemia (prior acute coronary syndrome, symptoms highly suggestive of ischemia, positive pacing echocardiographic stress test, or significant coronary artery stenoses on a prior coronary angiogram – if performed), significant left ventricular dysfunction (left ventricular ejection fraction

<35%), severe valvular dysfunctions, and severe heart failure (NYHA class III or IV).

In all patients, active-fixation right ventricular (RV) pacing leads were used, implanted in septal positions, based on fluoroscopic criteria during the procedure and using established implant techniques (5, 6). At the first study echocardiography, the septal position of the RV lead was confirmed by 3-dimensional echocardiography (7).

We were careful to exclude myocardial ischemia in the study patients, by performing a non-invasive pacing echocardiographic stress test (PASE) before enrolment. The PASE test was performed according to previously published protocols (8), using a GE Vivid-9 echocardiograph (General Electric, Horten, Norway) for image acquisition. The test was considered positive if at either peak stress or during recovery there was evidence of abnormal regional wall motion in at least two myocardial segments, compared to the baseline images. The test was not performed in those patients who had a recent normal coronary angiogram due to a clinical indication.

Each patient was evaluated in three study visits.

At visit 1 (baseline), we collected history, performed clinical examination, electrocardiogram (ECG) and echocardiography. The baseline pacemaker programming at this time was AAI or DDD mode, with a long atrio-ventricular (AV) interval, ensuring ventricular depolarization took place entirely over the normal conduction system. The pacemaker was then reprogrammed in DDD mode with a short AV interval, in order to obtain a paced QRS complex, while we ensured adequate left ventricular filling was maintained, assessed by pulsed-wave Doppler echocardiography.

Visit 2 (peak CM) was performed after two weeks of pacing. We confirmed by interrogating the pacemaker that the patient had been paced in the ventricle for more than 90% of the time since the baseline visit. We first performed ECG and echocardiography with a paced QRS. Then, we reprogrammed the pacemaker in either AAI or DDD mode with a long AV interval (so ventricular depolarization occurred entirely over the normal conduction system) and repeated ECG and echocardiography to assess peak CM changes.

Visit 3 (CM washout) was performed four weeks after visit 2 and consisted of ECG and echocardiography. We ensured that the patient had been paced in the ventricle for less than 10% of the time since the peak CM visit.

Echocardiography

All echocardiograms were performed using a single GE Vivid-9 echocardiograph (General Electric, Horten, Norway), with a 2.5 MHz probe. Patients were examined in the left lateral decubitus position.

For this study, two-dimensional gray-scale loops from the parasternal long axis, parasternal short axis (at mid-papillary muscle level) and apical 4-chamber, 2-chamber and apical long axis views were stored for analysis. As recommended by published guidelines (9), we recorded at least three cardiac cycles, and optimized the images to obtain frame rates between 50-80 frames *per* second.

Off-line analysis was performed at a later date, using the same software (EchoPAC version 113, GE Vingmed Ultrasound AS, Horten, Norway).

Conventional echocardiographic parameters
We measured the following conventional echocardiographic parameters:
- Left ventricular (LV) end-diastolic and end-systolic volumes (from the apical 4-chamber and 2-chamber views);
- LV ejection fraction (using the bi-plane Simpson method);
- LV wall thickness (end-diastolic interventricular septum and posterior wall thickness from the parasternal long-axis view);
- LV diastolic function: peak E and A waves of transmitral flow using pulsed-wave Doppler, E/A ratio, deceleration time of the E wave (TdE), E/E' ratio (using the mean E' of basal interventricular septum and lateral wall);
- Left atrial (LA) volume at the beginning of the P wave;
- Mitral regurgitation degree;
- Systolic pulmonary artery pressure.

2DSE measurements
Longitudinal systolic LV deformation indices were calculated from the three standard apical views, using the recommended methods (9). We measured the following parameters:
- Global longitudinal LV strain (GLS) – as the average systolic strain of all myocardial segments from the apical views;
- Segmental peak longitudinal LV strain (peak LS) – the individual longitudinal strain of each LV myocardial segment, using the 18 segment model (corresponding to six basal, six mid-ventricular and six apical segments: septal anterior,

anterior, lateral, posterior, inferior, septal posterior);

• Time-to-peak longitudinal strain (TTP-LS) for each myocardial segment (measured from onset of the QRS complex to peak strain, see also Figure 1 for peak LS and TTP-LS measurements).

We defined the **earliest segment** as the segment adjacent to the pacing site (by direct visualization of the pacing lead insertion) and the **latest segment** as the latest activated segment (longest TTP-LS) on the visit 2 echocardiogram performed during ventricular pacing.

In addition to individual segmental peak LS and TTP-LS measurements, we calculated the mean TTP-LS for all segments and dispersion of TTP-LS (the coefficient of variation).

Statistical analysis was performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, United States of America), using independent-samples t-test for continuous data and Chi-square test for categorical data. A p-value of <0.05 was considered significant. ANOVA for repeated measures was used to test between the three visits for differences in echocardiographic parameters. ❑

RESULTS

Patient characteristics

General characteristics of the study patient population are summarized in Table 1. All patients developed electrical CM changes at peak CM (Figure 2 shows an example of typical

Parameter		Value (N=20)
Age (years)		71 ± 11
Number of women		16 (80%)
Hypertension		15 (75%)
Diabetes		4 (20%)
Dyslipidemia		11 (55%)
History of stroke		1 (5%)
Medication	Beta-blockers	12 (60%)
	Amiodarone	8 (40%)
	ACEI/ ARBs	10 (50%)
	CCBs	4 (20%)

TABLE 1. General patient characteristics. ACEI=angiotensin converting enzyme inhibitors, ARB=angiotensin receptor blockers, CCB=calcium-channel blockers. Continuous parameters presented as mean ± standard deviation.

post-pacing CM in our study), which were completely reversible by the final visit.

Conventional echocardiogram

There were no significant differences between evaluations with regard to conventional echocardiographic parameters (Table 2).

2DSE parameters and regional contractility analysis

The earliest segments were found to be as follows: in 11 patients (55%) the lead was placed on the basal interventricular septum (corresponding to
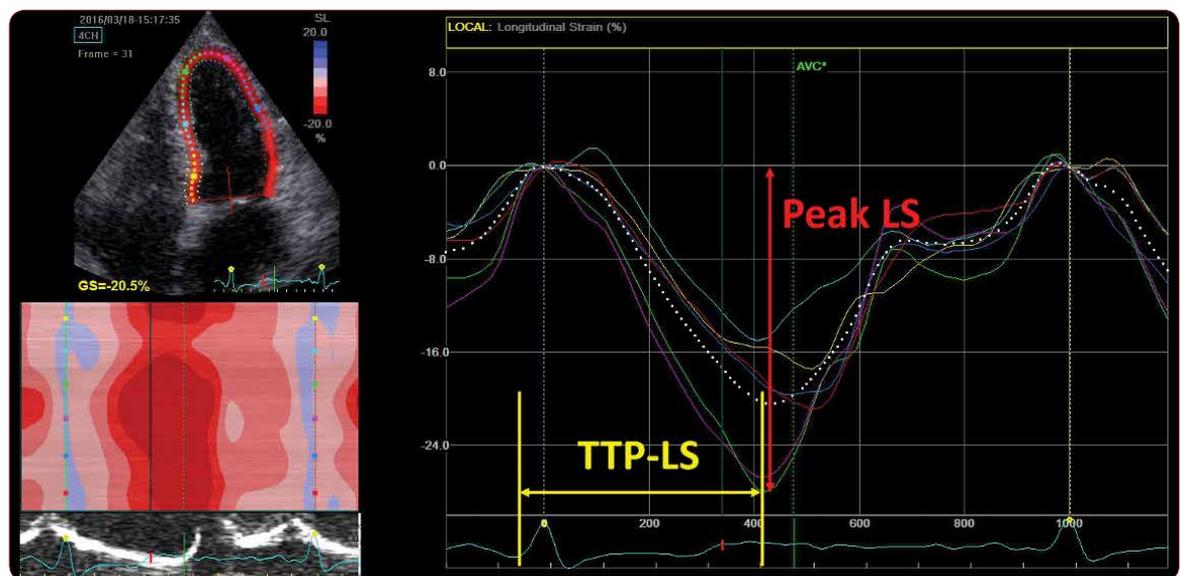

FIGURE 1. Example of measurement of peak longitudinal strain (LS) and time-to-peak longitudinal strain (TTP-LS), by 2D speckle tracking echocardiography.
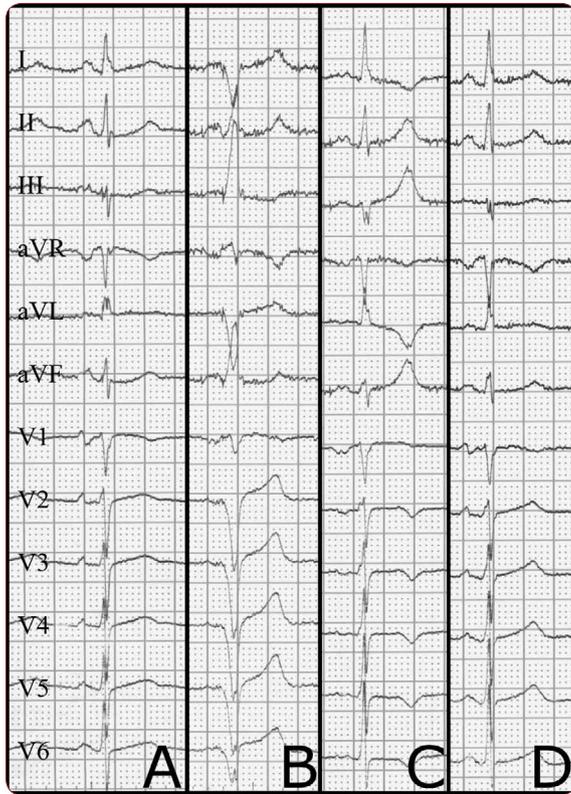
FIGURE 2. ECG example of post-pacing cardiac memory. Panel A: baseline ECG; panel B: ventricular pacing with short atrio-ventricular interval; panel C: post-pacing cardiac memory (negative T waves in the leads where the paced QRS complex was negative); and panel D: ECG performed four weeks after pacing cessation, showing resolution of cardiac memory.

the RV outflow tract or high septal positions) and in the remaining nine patients (45%) in the mid-interventricular septum.

The latest-activated segments were found to be as follows: the basal lateral segment in seven patients (35%), basal anterior wall segment in se-

ven patients (35%), the basal inferolateral wall in five patients (25%), and the mid-lateral segment in one patient (5%).

There were no differences in GLS values between visits. Peak LS did not show any significant differences between study visits (Table 3) for neither the earliest, nor the latest activated segments.

TTP-LS increased significantly from baseline at peak CM for all segments (earliest and latest segments, as well as mean TTP-LS), but remained increased at CM washout. Dispersion of TTP-LS did not change between visits. ❑

DISCUSSION

Our results showed that regional LV contractility parameters, assessed by 2DSE longitudinal strain, did not parallel the apparition and resolution of electrical cardiac memory in neither the earliest, nor the latest-activated myocardial segments.

As a consequence, these results do not reproduce the previously-published findings on regional mechanical contractility changes in CM discovered in animal studies (2, 3).

However, there are a number of differences between our study and the previously-mentioned studies:

- Firstly, the method used by Jeyaraj et al to assess mechanical contractility was circumferential strain, measured by tagged MRI. In contrast, our study used echocardiography, which is less reproducible (10) and suffers from potential interference resulting from variable acoustic windows. We chose to assess longitudinal strain (not circumferential), as this is the most reproducible echocardiographic 2DSE method for evaluation of regional strain (11, 12). We believe this could be an

Parameter	Baseline	Peak CM	CM washout	p value (ANOVA)
Interventricular septum thickness (mm)	11.5 ± 1.7	11.6 ± 1.7	11.6 ± 1.8	0.990
Posterior wall thickness (mm)	10.3 ± 1.4	9.9 ± 1.5	9.9 ± 1.24	0.603
End-diastolic LV volume (mL)	82.3 ± 22.7	83.7 ± 24.0	88.0 ± 23.5	0.730
LV ejection fraction (%)	61.6 ± 7.6	62.3 ± 6.1	63.2 ± 6.2	0.739
E/A ratio	0.92 ± 0.28	1.00 ± 0.32	1.02 ± 0.28	0.478
E/E' ratio	9.73 ± 4.98	10.10 ± 3.58	9.70 ± 2.80	0.950
LA volume (mL)	76.0 ± 19.7	77.2 ± 18.7	73.2 ± 16.6	0.779
Mitral regurgitation (degree)	0.9 ± 0.7	1.0 ± 0.7	1.0 ± 0.7	0.640
Systolic pulmonary artery pressure (mm Hg)	27.3 ± 9.0	30.7 ± 8.1	28.3 ± 9.0	0.452

TABLE 2. Comparison of conventional 2D echocardiography parameters between study visits.
CM=cardiac memory; LA=left atrium; LV=left ventricle.

Parameter	Baseline	Peak CM	CM washout	p value (ANOVA)
Peak LSearliest (%)	-18.4 ± 4.8	-17.9 ± 4.7	-17.8 ± 3.6	0.900
Peak LSlatest (%)	-17.8 ± 5.4	-18.9 ± 4.9	-18.9 ± 4.1	0.690
TTP-LSearliest (ms)	400 ± 38	428 ± 27	421 ± 24	0.014
TTP-LSlatest (ms)	462 ± 54	513 ± 44	496 ± 37	0.003
Mean TTP-LS (ms)	421 ± 39	448 ± 25	451 ± 26	0.007
Dispersion of TTP-LS (coefficient of variation)	0.083 ± 0.029	0.088 ± 0.024	0.084 ± 0.022	0.810
Global LS (%)	-19.5 ± 2.9	-19.9 ± 2.3	-19.1 ± 2.9	0.680

TABLE 2. Comparison of 2D speckle-tracking echocardiography parameters between study visits. CM=cardiac memory; LS=longitudinal strain; TTP-LS=time-to-peak longitudinal strain; earliest=earliest-activated myocardial segment; latest=latest-activated myocardial segment.

important difference, as LV longitudinal strain (as can be currently measured by 2DSE) may be insufficiently accurate to detect small regional changes between post-pacing CM and baseline.

- Secondly, in both the in vivo canine model (2), and the in vitro rabbit heart study (3), placement of the pacing leads was epicardial, on the surface of the left ventricle. Our human subjects all had conventional transvenous endocardial right ventricular leads placed on the interventricular septum. We cannot ascertain at present whether this difference has significant impact on regional mechanical strain, as no studies exist comparing endocardial with epicardial post-pacing CM and mechanical changes.

We note that we included patients on any previous medication, without changing it. Molecular ion channel studies have found links between multiple ion channels and CM, including the finding that electrical cardiac memory could be blunted or suppressed *in vitro* by calcium-channel blockers or angiotensin II receptor blockers (13, 14). However, a study on human subjects, published in 2014, did not reproduce these observations in the clinical setting (losartan or diltiazem administration did not influence electrical T-wave memory compared to placebo) (15). All patients in our study did develop electrical CM, so we chose to maintain their previous medication regime, irrespective of whether this included an-giotensin conversion enzyme inhibitors/ angiotensin receptor blockers or calcium-channel blockers.

Study limitations

We had a relatively low number of patients in this analysis, due to strict inclusion and exclusion criteria and exclusion of patients with poor acoustic windows. However, previous studies on animal models had similar or lower number of subjects.

The echocardiographic method used for quantifying LV regional strain (2DSE) has its own limitations (9, 16, 17), including those regarding image feasibility, inter-vendor variability, and reproducibility of measurements (especially those of regional analysis), while still being the most widely used method for human test subjects. ❑

CONCLUSION

CM was not associated with significant differences in peak LS between myocardial segments. Global (homogeneous) mechanical activation delay was present at peak CM, but did not then parallel the resolution of CM. These results suggest that mechanical changes, as can be assessed by 2DSE longitudinal strain, do not overlap electrical CM. ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. **Rosenbaum MB, Blanco HH, Elizari MV, Lazzari JO, et al.** Electrotonic modulation of the T wave and cardiac memory. *Am J Cardiol* 1982;50:213-222.
2. **Jeyaraj D, Wilson LD, Zhong J, Flask C,** et al. Mechanoelectrical feedback as novel mechanism of cardiac electrical remodeling. *Circulation* 2007;25:3145-3155.
3. **Sosunov EA, Anyukhovsky EP, Rosen MR.** Altered ventricular stretch contributes to initiation of cardiac memory. *Heart Rhythm* 2008;1:106-113.
4. **European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA), Brignole M, Auricchio A,**

Baron-Esquivias G, Bordachar P, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;8:1070-1118.

5. **Mond H.** The road to right ventricular septal pacing: techniques and tools. *Pacing Clin Electrophysiol* 2010;33:888-898.

6. **Osmancik P, Stros P, Herman D, Curila K, et al.** The insufficiency of left anterior oblique and the usefulness of right anterior oblique projection for correct localization of a computed tomography-verified right ventricular lead into the midseptum. *Circ ArrhythmElectrophysiol* 2013;4:719-725.

7. **Margulescu AD, Suran BM, Rimbas RC, Dulgheru RE, et al.** Accuracy of fluoroscopic and electrocardiographic criteria for pacemaker lead implantation by comparison with three-dimensional echocardiography. *J Am Soc Echocardiogr* 2012;7:796-803.

8. **Biagini E, Schinkel AF, Elhendy A, Bax JJ, et al.** Pacemaker stress echocardiography predicts cardiac events in patients with permanent pacemaker.

Am J Med 2005;12:1381-1386.

9. **Lang RM, Badano LP, Mor-Avi V, Afilalo J, et al.** Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;1:1-39.e14.

10. **Amzulescu MS, Langet H, Saloux E, Manrique A, et al.** Head-to-Head Comparison of Global and Regional Two-Dimensional Speckle Tracking Strain Versus Cardiac Magnetic Resonance Tagging in a Multicenter Validation Study. *Circ Cardiovasc Imaging* 2017;11.pii:e006530.

11. **Armstrong AC, Ricketts EP, Cox C, Adler P, et al.** Quality Control and Reproducibility in M-Mode, Two-Dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year 25 Examination Experience. *Echocardiography* 2015;8:1233-1240.

12. **Sjøli B, Ørn S, Grenne B, Ihlen H, et al.** Diagnostic capability and reproducibility of strain by Doppler and by speckle tracking in patients with acute myocardial infarction. *JACC Cardiovasc Imaging* 2009;1:24-33.

13. **Patberg KW, Plotnikov AN, Quamina A, Gainullin RZ, et al.** Cardiac memory is associated with decreased levels of the transcriptional factor CREB modulated by angiotensin II and calcium. *Circ Res* 2003;5:472-478.

14. **Patberg KW, Shvilkin A, Plotnikov AN, Chandra P, et al.** Cardiac memory: mechanisms and clinical implications. *Heart Rhythm* 2005;12:1376-1382.

15. **Chiale PA, Etcheverry D, Pastori JD, Garro HA, et al.** Clinical evaluation of losartan and diltiazem on the development of T-wave memory by right apical ventricular pacing. *J Am Coll Cardiol* 2014;18:1929-1931.

16. **Barbier P, Mirea O, Cefalù C, Maltagliati A, et al.** Reliability and feasibility of longitudinal AFI global and segmental strain compared with 2D left ventricular volumes and ejection fraction: intra- and inter-operator, test-retest, and inter-cycle reproducibility. *Eur Heart J Cardiovasc Imaging* 2015;6:642-652.

17. **Collier P, Phelan D, Klein A.** A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. *J Am Coll Cardiol* 2017;8:1043-1056.