SPECT and PET in Sympathetic Innervation

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CHAPTER 6

Identification of the role of sympathetic innervation in heart failure patients treated with cardiac resynchronization therapy. A pilot study.

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ABSTRACT

Objectives: Cardiac resynchronization therapy (CRT) by biventricular pacing has become an established therapeutic strategy in patients with severe heart failure with electrical and or mechanical delay. In addition, CRT restores autonomic balance. The aim of this pilot study was to evaluate whether changes in cardiac sympathetic innervation can be visualised by carbon-11 labelled meta-hydroxyephedrine ([^{11}C]-mHED), in heart failure patients who are responders to CRT

Methods: Patients eligible for CRT underwent [^{11}C]-mHED and rest nitrogen-13 labelled ammonia positron emission tomography scans for cardiac sympathetic innervation and myocardial perfusion, respectively, transthoracic echocardiography, and Multiple gated equilibrium radionuclide angiography (MUGA), before (baseline) and six months after (follow up) implantation.

Results: Seven patients with non-ischemic heart failure (three male; median age 61 (range 56-71) years) were included. Response to CRT was high: median change in left ventricular end-systolic volume was 38 (range 29-72)%. Median LVEF increased from 26 (range 14-37)% at baseline to 33 (range 19-54)% (p = 0.028) at follow up. Median global [^{11}C]-mHED retention and global myocardial perfusion were not different between baseline and follow up: median 48 (range 40-58) $x10^{-3}$ min^{-1} vs 52 (range 41-60) $x10^{-3}$ min^{-1}, and median 64 (range 59-85) mL/min/100g vs 57 (range 50-96) mL/min/100g, respectively.

Conclusion: Response to CRT is in all patients accompanied by improvement in global [^{11}C]-mHED retention. However, improvement in innervation of individual patients was accompanied by an increase in LVEF. Future prospective studies should focus on the role of sympathetic innervation imaging for individual patients who will be treated with CRT.

INTRODUCTION

Heart failure is the fastest growing cardiovascular diagnosis; the lifetime risk is estimated at nearly 20%. Cardiac resynchronization therapy (CRT) by biventricular pacing has become an established therapeutic strategy in patients with severe heart failure with electrical and or mechanical delay. It reduces symptoms and improves objective measures of left ventricular (LV) function in selected patients (1-3). Still, 20 to 30% of these selected patients do not respond to CRT. Success of CRT is defined as a reduction in left ventricular end-systolic volume (LVESV) ≥ 10% (4).

Cardiac resynchronization on top of optimal pharmacological therapy has been shown to improve symptoms of heart failure, reduce hospital admission, improve LV function and mortality (5,6). Several mechanisms underlying the benefit of CRT have been identified: reduction of interventricular dyssynchrony, reversion of intraventricular conduction delay, and optimization of the AV delay.

Sympathetic activity is increased in patients with congestive heart failure. This is evidenced by elevated levels of circulating norepinephrine levels and increases in adrenergic nerve outflow, as measured with microneurography (7-10). Although the increase in sympathetic activity may play a compensatory role early during the disease process, chronic adrenergic activation is recognized as a contributor to the vicious cycle that promotes progression of the disease through multiple effects, including increased afterload, exertion of a direct toxic effect on the failing myocardium, increased myocardial oxygen demand, and ventricular arrhythmias. CRT results in a decrease in serum norepinephrine levels and in less sympathetic dominance in patients with severe symptoms of heart failure, and eventually restores autonomic balance in patients with severe heart failure (11-13. The precise mechanism of autonomic restoration is as of yet unknown.

Carbon-11 labelled meta-hydroxyephedrine ([^{11}C]-mHED) is a well established positron emission tomography (PET) tracer for the visualisation of cardiac sympathetic innervation (14,15). However, imaging of changes in cardiac sympathetic innervation induced by CRT' using [^{11}C]-mHED has not yet been reported. The aim of the present study was to evaluate whether changes in cardiac sympathetic innervation can be visualised by [^{11}C]-mHED, in heart failure patients who are responders to the treatment with CRT.

PATIENTS AND METHODS

Seven patients with non-ischemic chronic heart failure (CHF) who had an indication for CRT, were included to take part in the study. Inclusion criteria were: indication for CRT (New York Health Association (NYHA) class II+ or III despite optimal pharmacological treatment, had an left ventricular ejection fraction (LVEF) < 30%, left ventricular end-diastolic diameter (LVEDD) > 55mm, QRS duration ≥ 150 ms or QRS > 120 ms with evident dyssynchrony on cardiac ultrasound), on stable beta-blockade, Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blocker and other heart failure medication during the last 3 months prior to inclusion, stable NYHA class during the last 3 months, and ability to lie flat for 2 hours. Excluded were those patients with previous implanted biventricular pacemaker, acute or chronic infection, untreated clinical hypo- or hyperthyroidism or <3 months euthyroidism, uncontrolled hypertension (defined as systolic blood pressure >160 mm Hg and/or diastolic pressure >95 mmHg, and concurrent medical condition (i.e. alcohol or drug abuse, or severe progressive cardiac disease or Parkinson's disease).

Prior to implantation all patients were treated for at least 3 months with a β-adrenoceptor inhibitor and an Angiotensin Converting Enzyme-inhibitor (ACE-i) or Angiotensin Receptor Blocker (ARB), and diuretics. No changes in the dose of previous mentioned medication occurred in the 3 months prior to inclusion. During the 6 months of follow up no changes in β-adrenoceptor inhibitor and ACE-i or ARB occurred to prevent bias due to medication changes unless the patient's situation warrants dose adjustment(s).

Previous medical history was retrieved from the electronic patient chart. Electrocardiograms (ECG) were performed at inclusion. ECGs were re-evaluated regarding rhythm, heart rate, QRS axis, PQ interval, QRS duration, presence of bundle branch block, QTc interval and STT segments. Transthoracic echocardiography (TTE) findings at the same time point were performed and stored in the local digital archive of the Department of Cardiology of our hospital. Patients were followed until six months after CRT implantation. This study was approved by the Institutional Ethics Review Board.

PET scanning

PET scans for myocardial perfusion and cardiac sympathetic innervation were performed using a 1-day protocol, at two weeks prior to (baseline) and six months after CRT implantation (follow up). All scans were performed on ECAT EXACT HR+ PET camera system (Siemens Medical System, Knoxville, Tennessee, U.S.A.). Before dynamic scanning, a transmission scan for attenuation correction according to standard procedures was performed, using a rotating rod source filled with [Ga^{68}]/[Ge^{68}], which is incorporated in the PET camera.

Myocardial perfusion: to assess myocardial perfusion, following the transmission scan 400 MBq of nitrogen-13 labelled ammonia ([^{13}N]-NH_3) was administered. Dynamic data of [^{13}N]-NH_3 were acquired over 15 minutes, followed

by gated mode acquisition. This allowed quantification of perfusion at rest. After reorientation, short-axis images of [^{13}N]-NH_3 were obtained with a plane thickness of about 7 mm at an in-plane resolution of approximately 7 mm. Myocardial tissue activity was corrected for spill over of activity from the LV cavity. A fully automatic non-operator dependent program (MATLAB) quantified the mean blood flow (MBF) of the segments of the left ventricle (mL/min/100g).

Sympathetic innervation: after injection of approximately 350 MBq (range 200-400 MBq) of [^{11}C]-mHED, dynamic imaging was performed for 60 minutes and heart rate and blood pressure were monitored continuously. The [^{11}C]-mHED emission data were corrected for attenuation and residual activity of the earlier [^{13}N]-NH_3 scan. For quantification, a retention index was calculated by dividing the mean myocardial radioactivity concentration in the last 20 minutes of the PET scan by the integral of the time-activity curve in arterial blood (derived from a region of interest in the right ventricular chamber). Images were reoriented to the long and short axes of the left ventricle using a special workstation. Gating files were processed in QGS software.

Image analysis: perfusion and innervation data from baseline and follow up were compared. Mean [^{11}C]-mHED retention (min-1) was determined for those areas with both normal perfusion (>80% of the maximum myocardial blood flow) and innervation (>75% of the segment with maximum [^{11}C]-mHED retention), areas with a mismatch pattern: normal perfusion and decreased cardiac sympathetic innervation (<75% of the segment with maximum [^{11}C]-mHED retention), and both abnormal perfusion (<80% of the maximum myocardial blood flow) and innervation.

CRT implantation

Within 2 weeks after the PET scans a CRT system was implanted. The right atrial lead was placed in the high right atrium or right atrial appendage. The right ventricular lead was placed in the right ventricular apex. In case of difficulties placing the lead in the preferred position or unacceptable electrical measurements (e.g. low R-wave measurement, high pacing threshold), placement in the right septal position was accepted. Pacing of the left ventricle was done from a place preferably on the (postero)-lateral wall. If this is not achievable epicardial lead placement was considered. The device programming was done according to protocol of our hospital. Pacemaker interrogation occurred according to the standardised protocol for patients with CRT. This was 2 months after implantation and after six months, unless more frequent interrogations were necessary. Special attention was paid to atrial and ventricular rhythm disorders and heart rate variability

Transthoracic echocardiography

The following variables were measured according to standard recommendations in the M-mode transthoracic echocardiographic examination: left ventricular internal end-diastolic and end-systolic dimensions, inter-ventricular wall thickness and left ventricular posterior wall thickness at end-diastole. An eyeballing left ventricular ejection fraction (LVEF) > 55% was considered to be normal, between 55% and 40% mildly disturbed, between 30% and 40% moderately disturbed, and < 30% was considered to represent a severely impaired systolic function.

Multiple gated equilibrium radionuclide angiography (MUGA)

MUGAs were standardized and performed in the left anterior oblique projection after the in vivo labelling of red blood cells with 750 MBq of technetium-99m ([^{99m}Tc]) labelled pertechnetate to determine LVEF. Images were collected in a 64×64 matrix in 20 frames/cycle during a 10 minute acquisition. A Symbia S gamma camera (Siemens Medical System, Knoxville, Tennessee, U.S.A.) with a low energy, all purpose collimator was used. The camera head was positioned in the best septal left anterior oblique projection, typically with a caudal tilt of 5 to 10°. R-wave triggering was performed in a 20% beat acceptance window with 2/3 forward and 1/3 backward framing per cardiac cycle, for 20 frames per R-R interval for a total of six minutes. Data were acquired using 64×64 matrices in a 15% energy window centred on the 140 keV photopeak. Processing was performed on dedicated available computers (Syngo MI, Siemens Medical Systems, Knoxville, Tennessee, U.S.A.). For each of the 20 frames a region of interest (ROI) was automatically drawn around the left ventricle using a validated, fully automated, operator independent, contour detection algorithm. Frames were automatically corrected for background activity. Background activity ROIs were generated automatically. All LVEF values were generated without decimals and are highly reproducible (16).

Statistical analysis

For this pilot study no formal sample size calculations were performed. For descriptive statistics the mean ± standard deviation (SD) or median (range) for continuous variables will be used, and counts with percentages for categorical variables. Student t-test in case of normally distributed variables and a Mann-Whitney U-test in case of skewed variables. Paired t test will be used for comparison of measurements at different time point. Analyses will be performed using the statistical package SPSS 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. Median age was 61 (range 56-78) years, and there was a slight female predominance (57%). Six of the seven included had a dilating cardiomyopathy, one patient suffered from another type of non-ischemic cardiomyopathy. All patients had stable heart failure, and were in NYHA class III. The majority of the patients used β-adrenoceptor inhibitor, ACE-i and diuretics. Median NT-pro-BNP was 877 (range 195 - 2875) ng/L. All patients were in sinus rhythm. Left bundle branch block was present in six patients, with median QRS duration 178 (range 110-206) ms. Median MUGA-based LVEF was 26 (range 14-37) %.

PET results

All baseline PET scans were performed within 2 days before the implantation of the CRT. Median time between CRT implantation and the follow up PET scans was 6 (range 5-8) months. Table 2 shows the results of the [^{11}C]-mHED and [^{13}N]-NH_3 scans. On group level, both global perfusion and innervation were not different from baseline to follow up. There was also no difference in the presence of matched normal perfusion and innervation segments, perfusion and innervation mismatch segments, or matched abnormal perfusion and innervation segments. However, three patients showed an improvement in [^{11}C]-mHED retention (Figure 1). In two of these three patients, MUGA based LVEF increased from baseline to follow up. Both of these two patients showed an improvement in perfusion-innervation pattern: one patient showed both an increase in matched normal segments (from four to seven) and a decrease in matched abnormal segments (from 11 to six), and one patient showed a decrease in mismatch segments (from six to one).

Table 1
Baseline characteristics of all patients

	Frequency (*n*), median (range)
Age (years)	61 (56-78)
Male	3 (43%)
Medical history	
Dilating cardiomyopathy	6 (86%)
Other non-ischemic cardiomyopathy	1 (14%)
NYHA class	
III or higher	7 (100%)
Medication	
β-adrenoceptor inhibitor	7 (100%)
ACE-i	6 (86%)
Statin	4 (57%)
Diuretics	6 (86%)
ARB	2 (28%)
Laboratory results	
N-terminus pro-brain natriuretic peptide (ng/L)	877 (195-2875)
Electrocardiogram	7 (100%)
Sinus rhythm	7 (100%)
Heart rate (beats per minute)	72 (63-90)
Axis	
Left	6 (86%)
Intermediate	1 (14%)
PQ interval (ms)	182 (158-252)
QRS duration (ms)	178 (110-206)
QRS shape	
Normal	1 (14%)
Left bundle branch block	6 (86%)
STT segments	
Normal	7 (100%)
QTc duration (ms)	497 (403-550)
MUGA	
Left Ventricular Ejection Fraction (%)	26 (14-37)

NYHA New York heart association, ACE-i Angiotensin converting enzyme inhibitor, ARB Angiotensin Receptor Blocker, NT-pro-BNP N-terminus pro-brain natriuretic peptide, MUGA Multiple gated equilibrium radionuclide angiography

Table 2
Results of the [^{11}C]-mHED and [^{13}N]-NH_3 scans

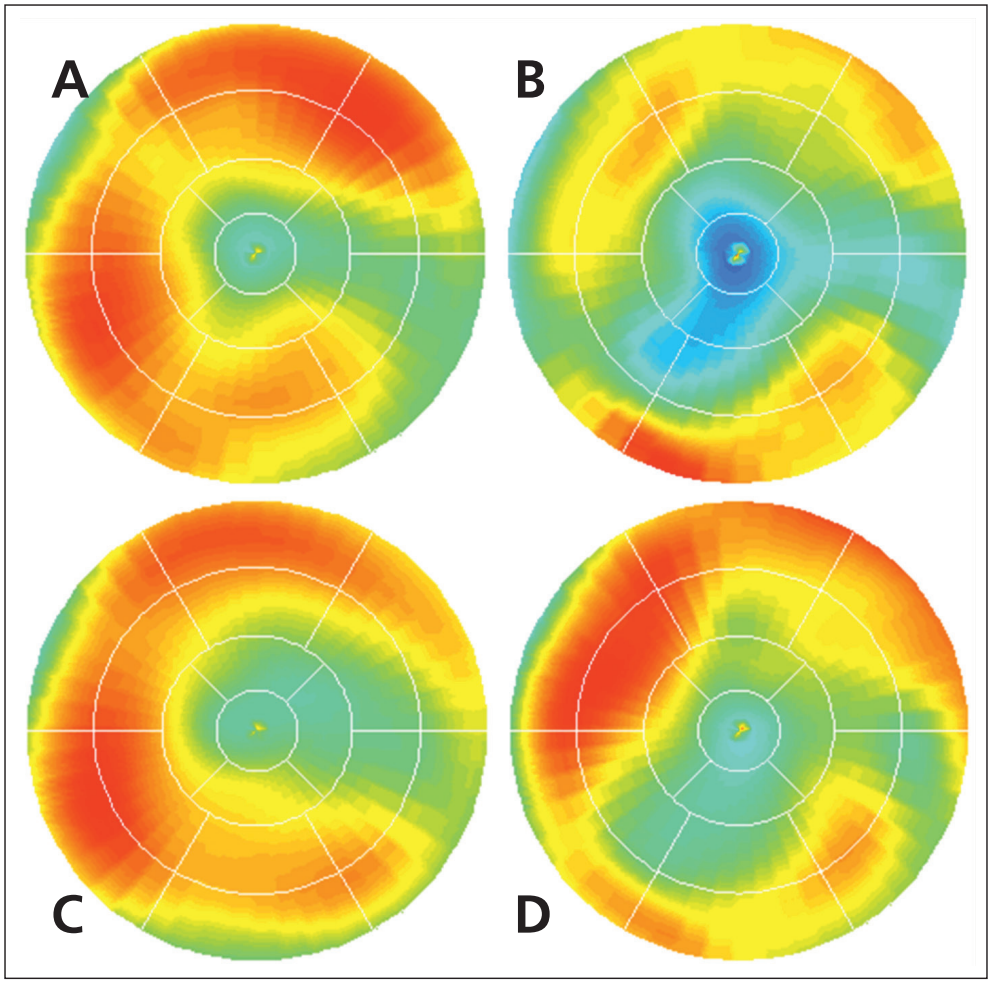
	Frequency (*n*), median (range)		
	Baseline	**Follow up**	***p*-value**
Median [^{13}N]-NH_3 uptake (mL/min/100g)	64 (59-85)	57 (50-96)	ns
Median [^{11}C]-mHED retention ($x10^{-3}$ min^{-1})	48 (40-58)	52 (41-60)	ns
Normal segments	6 (4-9)	7 (4-12)	ns
Mismatch segments	1 (0-7)	1 (1-3)	ns
Abnormal segments	3 (1-11)	5 (2-6)	ns

Table 3
Echocardiography results

	Frequency (*n*), median (range)		
	Baseline	**Follow up**	***p*-value**
Transthoracic echocardiography	7 (100%)	7 (100%)	
Heart rate (beats per minute)	74 (62-85)	70 (55-78)	ns
IVS (mm)	9.0 (7.0-11)	11 (9.1-12)	0.028
LVPW (mm)	9.3 (7.7-10)	9.4 (6.8-11)	ns
LVEDV (mL)	180 (170-282)	130 (78-349)	ns
LVESV (mL)	121 (103-245)	87 (34-177)	0.028
LVdID (mm)	61 (60-66)	59 (42-80)	ns
LVsID (mm)	51 (47-59)	49 (27-60)	ns
LVEF (%)	30 (13-43)	33 (24-57)	ns

IVS Inter-ventricular septum thickness, LVPW Left ventricle posterior wall thickness, LVEDV Left ventricle end diastolic volume, LVESV Left ventricle end systolic volume, LVdID Left ventricle diastolic internal diameter, LVsID Left ventricle systolic internal diameter, LVEF Left ventricular ejection fraction

Figure 1
Bulls-eye plots of [^{13}N]-NH_3 and [^{11}C]-mHED PET scans, at baseline and follow up, of the patient with decrease in perfusion-innervation mismatch segments. (**A**) Global rest [^{13}N]-NH_3 distribution at baseline, showing a perfusion defect in the lateral wall; (**B**) global [^{11}C]-mHED distribution at baseline, with overall low retention; (**C**) global rest [^{13}N]-NH_3 distribution at follow up, showing no significant alteration compared to (**A**); (**D**) global [^{11}C]-mHED distribution at follow up, showing an increase in [^{11}C]-mHED retention especially in the anteroseptal segments.



Echocardiography

Table 3 summarizes the echocardiographic examination results. There was a significant decrease in LVESV: median baseline LVESV 121 (range 103-245) mL vs follow up 87 (range 34-177) mL, p = 0.028. Six of the patients were responders to CRT. Median change in LVESV in these patients was 38 (range 29-72)%. In one patient, baseline LVESV was not determined. Therefore, in this patient response to

CRT could not be determined. Decrease in LVESV was not related to changes in [^{11}C]-mHED retention.

At baseline, median interventricular septum and posterior wall thickness was within normal ranges: 9.0 (range 7.0-11) and 9.3 (range 7.7-10) mm, respectively. At follow up, interventricular septum thickness was significantly increased: median 11 (range 9.1-12) mm, *p* 0.028. All other parameters were not different at follow up compared to baseline.

Follow up

Table 4 shows all other results at follow up. There was a significant decrease in both PQ and QRS duration. In addition, MUGA based LVEF showed a significant increase: median baseline LVEF 26 (range 14-37)% vs follow up 33 (range 19-54)%, $p = 0.028$. At six months follow up after CRT implantation, in none of the patients ventricular tachycardias were registered.

Table 4
Follow up results

	Frequency (*n*), median (range)		
	Baseline	**Follow up**	***p*-value**
NT-pro-BNP (ng/L)	877 (195-2875)	1019 (106-3652)	ns
Electrocardiogram	7 (100%)	7 (100%)	ns
Rhythm			
Sinus rhythm	7 (100%)	1 (13%)	
Pacemaker rhythm	0	6 (87%)	
Heart rate (beats per minute)	72 (63-90)	73 (57-90)	ns
Axis			
Left axis	6 (87%)	1 (13%)	
Intermediate axis	1 (13%)	2 (26%)	
Right axis	0	1 (13%)	
Extreme axis	0	3 (39%)	
PQ interval (ms)	182 (158-252)	112 (88-154)	0.018
QRS duration (ms)	178 (110-206)	154 (118-182)	0.043
QRS shape			
Normal	1 (13%)	0	ns
Left bundle branch block	6 (87%)	7 (100%)	ns
QTc duration (ms)	497 (403-550)	489 (446-557)	ns
MUGA			
LVEF(%)	26 (14-37)	33 (19-54)	0.028

NT-pro-BNP N-terminus pro-brain natriuretic peptide, MUGA Multiple gated equilibrium radionuclide angiography, LVEF Left ventricular ejection fraction

DISCUSSION

The purpose of this study was to visualize differences in [^{11}C]-mHED retention in CRT-responders during six months of follow-up. In this study six patients were responders to CRT (based on > 10% decrease in baseline LVEDV) and showed a significant increase in MUGA based LVEF. Six months after CRT implantation global [^{11}C]-mHED retention of all patients was not different from baseline. However, two patients who showed an improvement in innervation (increase in matched normal perfusion-innervation segments and decrease in perfusion-innervation mismatch segments) also showed an increase in LVEF.

Cardiac resynchronization reduces the risk of cardiac events in both high (NYHA class III or IV) and low symptomatic (NYAH class I or II) heart failure patients, with either ischemic or non-ischemic cardiomyopathy (17,18). Within the first two years after CRT implantation, there appears to be no difference in survival in patients with ICM or DCM (18,19). However, during long-term follow-up, patients with DCM show lower mortality than those with ICM. This may be explained by both better hemodynamic and clinical improvement in DCM patients on one side, and the inherent poor prognosis of ICM on the other side (20). It is unclear if restoration of autonomic innervation after CRT implantation plays an additional role in this improvement in DCM patients.

In non-ischemic cardiomyopathy, especially DCM, [^{11}C]-mHED retention is significantly lower than in healthy controls subjects, especially in apical and inferoapical segments, and is inversely related to severity of heart failure symptoms (14,21). Furthermore, [^{11}C]-mHED retention seems to be independently determined by LVEF (14). In the few available small studies there appears to be no difference in global or regional [^{11}C]-mHED retention between patients with ischemic or non-ischemic causes of chronic heart failure (22,23). However, low [^{11}C]-mHED retention is associated with poor prognosis (23). The same is true for cardiac sympathetic innervation imaging using iodine-123 labelled meta-iodobenzylguanide ([^{123}I]-MIBG), another analogue of norepinephrine. Low heart-to-mediastinum ratio's (HMR) determined with planar [^{123}I]-MIBG imaging in patients with non-ischemic cardiomyopathy are associated with higher risk of arrhythmic events and cardiac death. (24,25)

The effect of CRT on cardiac sympathetic innervation has not yet been visualized using [^{11}C]-mHED. Several small studies, however, investigated the value of [^{123}I]-MIBG in determination of those patients who will responds to CRT (26-29 HFR). Responders to CRT were defined differently in of these studies: improvement in functional class in one study, improvement in LVEF in one study and ≥ 15% decrease in LVESV in two studies. Nonetheless, responders to CRT had higher baseline HMR and lower was out, than non-responders. Furthermore, response to CRT was accompanied by an improvement in cardiac sympathetic innervation, based on increase in HMR and decrease in [^{123}I]-MIBG wash out (26-28). According to these studies, responders may already be identified using cardiac sympathetic innervation imaging prior to CRT implantation.

The main limitation of this study is the low number of patients included. In spite of this low sample size, global myocardial [^{11}C]-mHED retention may increase as a result of a response to CRT. Large prospective studies should provide additional information on improvement of cardiac sympathetic innervation and its role in further identification of responders to CRT.

CONCLUSION

In spite of the good response rate to CRT and increase in LVEF, global [^{11}C]-mHED retention of all patients at follow up was not different from baseline. However, improvement in innervation of individual patients was accompanied by an increase in LVEF. Future prospective studies should focus on the role of sympathetic innervation imaging for individual patients who will be treated with CRT.

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