Reduced myocardial carbon-11 hydroxyephedrine retention is associated with poor prognosis in chronic heart failure

Mikko Pietilä[1, 5], Kimmo Malminiemi[3], Heikki Ukkonen[1, 5], Markku Saraste[4], Kjell Någren[5], Pertti Lehikoinen[5], Liisa-Maria Voipio-Pulkki[1, 2]

[1] Department of Medicine, Turku University Central Hospital, PL 52, 20521 Turku, Finland
[2] Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland
[3] Department of Clinical Chemistry, Tampere University Hospital, Tampere, Finland
[4] Department of Clinical Physiology, Turku University Central Hospital, Turku, Finland
[5] Turku PET Centre, Turku, Finland

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Abstract. Abnormalities of the autonomic nervous system are known to be of prognostic significance in chronic heart failure (CHF). The prognostic value of positron emission tomography (PET) imaging of cardiac autonomic innervation in CHF has not been explored previously. We retrospectively studied the survival data of 46 NYHA class II–III CHF patients (mean LVEF 35%±8%) who had undergone carbon-11 hydroxyephedrine (^{11}C-HED) studies at the Turku PET Centre between August 1992 and March 1996. The origin of CHF was dilated cardiomyopathy in 13 of the 46 patients and coronary artery disease with at least one prior myocardial infarction in the remaining 33. Data on causes of death and heart transplantation were collected, and the statistically significant predictors of prognosis were analysed using Cox's proportional hazards regression. During the mean follow-up period of 55±19 months, 11 deaths occurred and two patients underwent heart transplantation successfully. Eleven end-points were classified as cardiac (nine sudden cardiac deaths and two deaths due to progressive heart failure) and two as non-cardiac. When divided into two groups based on the median of ^{11}C-HED retention (mean 0.184±0.061, median 0.183), eight end-points (death or cardiac transplantation) were reached in the group with ^{11}C-HED retention below the median and three in the group with ^{11}C-HED retention above the median (P<0.02). In proportional hazards regression analysis, only peak oxygen uptake (peak VO_2), left ventricular end-diastolic volume and HED retention were found to be statistically significant. It is concluded that ^{11}C-HED PET provides independent prognostic information in patients with CHF.

Mikko Pietilä (✉)
Department of Medicine, Turku University Central Hospital,
PL 52, 20521 Turku, Finland
e-mail: mikko.pietila@tyks.fi
Tel.: +358-2-2611611, Fax: +358-2-2612030

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Introduction

The severity of abnormal autonomic nervous function, such as elevated plasma noradrenaline concentration [1] or decreased heart rate variability [2], is of prognostic significance in patients with chronic heart failure (CHF). Abnormalities in cardiac sympathetic innervation are present in CHF, and can be demonstrated by nuclear imaging using both single-photon emission tomography (SPET) with iodine-123 metaiodobenzylguanidine (MIBG) imaging [3] and positron emission tomography (PET) with carbon-11 hydroxyephedrine (^{11}C-HED) [4, 5, 6]. A recent report by Merlet et al. [7] has confirmed the prognostic significance of these abnormalities as assessed by MIBG imaging in patients with severe idiopathic dilated cardiomyopathy. Since ^{11}C-HED PET may quantitate the abnormalities of cardiac presynaptic sympathetic innervation more accurately than MIBG SPET, we studied the prognostic value of ^{11}C-HED PET imaging in a patient population with less severe, multiple-aetiology CHF who were on adequate drug treatment for a follow-up period of 55±19 months (mean±SD).

Materials and methods

Forty-six out-patients (41 men, 5 women, mean age 55.9±8.8 years) with CHF due to either idiopathic dilated cardiomyopathy (n=13) or coronary artery disease and at least one prior myocardial

infarction (n=33) underwent ^{11}C-HED PET between September 1992 and March 1996. All subjects had given their informed consent to participation in the studies, which were approved by the Joint Ethical Committee of Turku University and Turku University Central Hospital. All subjects had had at least one well-documented episode of decompensated heart failure, an ejection fraction before the PET study of less than 45% and congestive heart failure symptoms of New York Heart Association class II–III for at least 3 months. All patients with dilated cardiomyopathy had undergone coronary angiography, which had revealed no significant (greater than 50%) narrowing of any coronary artery. The patients' medication during the time of the PET study consisted of ACE inhibitors (32/46 patients), β-adrenergic receptor antagonists (29/46), diuretics (29/46) and digoxin (16/46). Eight healthy controls (age 49±5.6 years) were used to determine the ^{11}C-HED retention values in normal subjects.

Data for survival at 29 February 2000 were collected from medical records and through the Finnish Bureau of Official Statistics (Statistics Finland). The causes of death were determined using data from death certificates and medical records. They were first divided into cardiac and non-cardiac and then, within the cardiac category, into sudden death (death without preceding symptoms while awake or during sleep or within 1 h of onset of any new symptoms) and progressive heart failure. The combined endpoint of cardiac death or cardiac transplantation was used.

All patients underwent ^{11}C-HED PET in the morning after an overnight fast and had abstained from taking medication other than diuretics for at least 10 h. The PET study was performed at rest using a 15-slice ECAT 931/08-12 tomograph (Siemens /CTI Inc., Knoxville, Tenn., USA). The production of the radiotracer, the imaging procedure and the methods of analysis have been previously described in more detail [6, 8]. In brief, the subjects were positioned supine in an eight-ring ECAT 931/08-12 tomograph (Siemens/CTI Corp., Knoxville, Tenn., USA). After transmission imaging, 15.3±6.0 MBq of ^{11}C-HED was injected intravenously over a 60-s period and ^{11}C-HED imaging was continued for 40 min. All data were corrected for dead-time, decay and photon attenuation and transaxial images were reconstructed in a 128× 128 matrix. After image processing [6], large horseshoe-shaped regions of interest were used on six to ten transaxial planes, avoiding myocardial borders. The ^{11}C-HED retention index was calculated as the mean tracer counts within the myocardial regions of interest between 30 and 40 min divided by the integral of the time-activity curve in plasma from 0 to 40 min from the time of injection. The mean^{11}C-HED retention index of all planes was taken as the measure of the ^{11}C-HED retention in each study.

Echocardiography studies were carried out on the same day as the PET studies, in accordance with standard recommendations. The left ventricular ejection fraction and left ventricular end-diastolic diameter (LVEDD) were both measured using M-mode images. In 34 patients, the peak oxygen uptake (peak VO_2) was determined using a spiroergometry stress test with 15 W per minute increments.

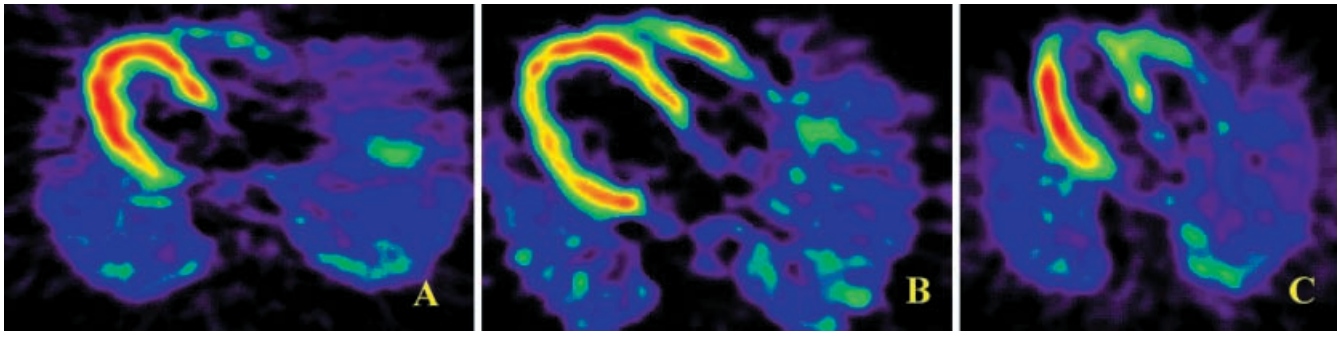
Survival data consisted of discretely censored survival times with a range from 6 to 89 months. Patients were retrospectively divided into four groups according to quartiles of the ^{11}C-HED retention index. Kaplan-Meier product limit estimates of the survivor function in each group were calculated using the BMDP Solo Survival Analysis program set (BMDP Solo Statistical Software Inc., Los Angeles, Calif., USA). Data fitted best to log-normal distribution. Survival distributions of the four groups were compared using the non-parametric log-rank test. Cox-Mantel test was used in two-group comparisons. The relationships among the different variables were studied using linear correlation analysis, and their influence on survival time was evaluated using Cox's proportional hazards regression analysis. Means and standard error of mean are presented, if not otherwise stated.

Results

As reported previously [6], patients with CHF had significantly lower ^{11}C-HED retention than healthy subjects (0.184±0.061 vs 0.283±0.044, P<0.0001). Patients with NYHA class III CHF symptoms had lower ^{11}C-HED retention values than patients with NYHA class II CHF: 0.143±0.014 vs 0.193±0.009 (P=0.015). Representative examples of the pattern of ^{11}C-HED retention in healthy subjects and patients with different origins of heart failure are shown in Fig. 1.

Eleven deaths occurred during the follow-up. In addition, two subjects underwent successful heart transplantation. All deaths except two were cardiac. Of the nine cardiac deaths, seven were classified as sudden and two as due to progressive heart failure. Using the median of the ^{11}C-HED retention index in the study group as the cut-off point, eight cardiac end-points were reached in the group with a mean ^{11}C-HED retention index value equal to or less than the median, while only three end-points occurred in the group with an ^{11}C-HED retention index greater than the median (P<0.02). No cardiac end-points

Fig. 1A–C. Typical patterns of myocardial ^{11}C-HED uptake in a healthy subject and two patients with different origins of heart failure. **A** Healthy subject; **B** patient with dilated cardiomyopathy; **C** patient with previous anteroseptal myocardial infarct



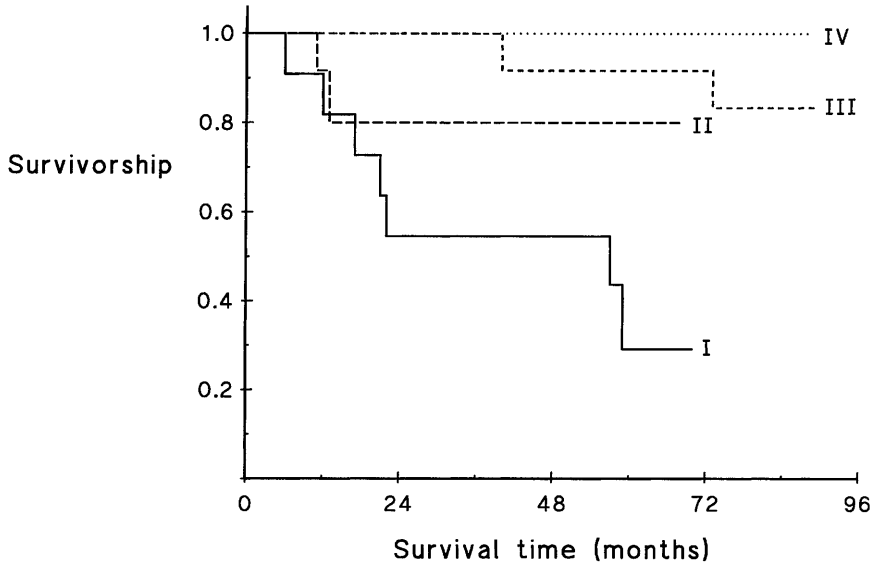


Fig. 2. Product-limit survivorship for the cardiac end-points in patient groups divided into quartiles based on myocardial ^{11}C-HED retention. The survival (freedom from cardiac death or transplantation) was poorest in the group with the lowest ^{11}C-HED retention values ($P<0.05$ between the two quartiles with lowest ^{11}C-HED retention). The Roman numerals refer to quartiles of ^{11}C-HED retention (I = quartile with the lowest ^{11}C-HED retention, IV = quartile with the highest ^{11}C-HED retention)

Table 1. Age-adjusted odds ratios of cardiovascular mortality between the lowest and highest quartiles of the variable[a]

Variable	Odds ratio	95% confidence interval
HED	19.3	2.6–142
LVEDD	18.1	2.2–145
Peak VO_2	12.4	1.85–78
LVEF	8.0	1.05–61

[a] In the case of LVEDD, the odds ratio was calculated conversely, i.e. high vs small LVEDD

occurred in CHF patients with an ^{11}C-HED retention index higher than 0.195 (the lower 95% confidence limit of the ^{11}C-HED retention index in healthy subjects) or in the quartile of CHF patients with highest ^{11}C-HED retention (Fig. 2). In addition to age, three variables proved to be significant independent predictors of cardiac mortality or transplantation in Cox's proportional hazards regression analysis with nine predictive factors: ^{11}C-HED retention (P=0.014), peak VO_2 (P=0.011) and LVEDD (P=0.037). Ejection fraction as measured by echocardiography, duration of heart failure, diabetes and aetiology of heart failure all failed to reach statistical significance in the hazards regression model. Odds ratios of cardiac mortality between the lowest and highest quartiles of the variables are presented in Table 1. NYHA class was shown not to be statistically significantly independent when the model contained peak VO_2 and LVEDD.

The frequency of use of β-receptor antagonists and ACE inhibitors was similar in the non-survivors and in survivors (53.8% vs 66.7% and 76.9% vs 66.7%, respectively; P=NS), while the use of diuretics and digoxin was more frequent in non-survivors than in survivors (92.3% vs 47.1%, $P<0.05$ and 76.9% vs 17.6%, $P<0.005$, respectively).

Discussion

The work of Merlet et al. [7] has demonstrated the usefulness of ^{123}I-MIBG SPET imaging as a prognostic tool in heart failure patients considered for heart transplantation. ^{123}I-MIBG and ^{11}C-HED share the same uptake and storage mechanisms as noradrenaline [9, 10]. ^{11}C-HED PET enables more accurate quantification of possible abnormalities of cardiac presynaptic sympathetic innervation and also allows more detailed regional analyses, but its availability is more limited. ^{11}C-HED uptake has been shown to correlate with tissue noradrenaline content and the density of uptake-1 sites in the cardiomyopathic human heart, probably due to loss of cardiac noradrenergic nerve terminals [5]. In addition to reduced uptake of ^{11}C-HED in patients with heart failure, marked regional variation in uptake-1 sites has been observed, which correlated with local differences in ^{11}C-HED retention [4, 5]. This in turn could form the electrophysiological substrate for some forms of life-threatening arrhythmias, leading to sudden cardiac death. It is of note that in our study population with moderate heart failure, seven of nine cardiac deaths were classified as sudden deaths. On the other hand, it seems that patients with relatively normal ^{11}C-HED retention are at particularly low risk of cardiac death.

In the 46 subjects included in this study, only 11 major cardiac events (cardiac death or transplantation) occurred. Therefore, the results of multivariate analysis must be interpreted with caution. Also, the low total number of events prevented separate subgroup analysis in patients with different origins of heart failure.

Effects of medication on the results of this study cannot be fully excluded since the effects of different medications on ^{11}C-HED retention have not been comprehensively studied. Despite its limitations, our study shows that reduced uptake of ^{11}C-HED, a marker of abnormal

Table 2. Characteristics of patients grouped according to outcome (non-cardiac deaths not included)

	Age (years)	CHF duration (months)	LVEDD (mm)	LVEF (%)	Peak VO_2 (ml min^{-1} kg^{-1})	NYHA class (II/III)	^{11}C-HED retention
No end-points (n=33)	56.3±8.3	28±38	66±8	37±8	19.6±4.1	31/2	0.198±0.062
Death or transplantation (n=11)	54.2±10.8	28±21	76±8**	27±7*	12.8±4.0***	6/5**	0.137±0.041**

CHF, Chronic heart failure; LVEDD, left ventricular end-diastolic diameter; peak VO_2, maximal uptake of oxygen
Independent t-test: *P<0.05, **P<0.005 and ***P<0.0005 between the groups

cardiac presynaptic sympathetic innervation, characterizes CHF of either ischaemic or cardiomyopathic aetiology and that the reduction in uptake is of greater magnitude in patients with more advanced disease.

In spite of the limited sample size, other clinically important predictors of prognosis in CHF reached statistical significance in our study (Table 2). It is possible that measurement of ^{11}C-HED uptake represents an additional tool for the evaluation of prognosis in this patient group.

In conclusion, the data reported in this study suggest that PET with ^{11}C-HED, a false noradrenaline analogue, provides independent prognostic information in patients with moderate CHF. They also emphasise the importance of abnormalities in cardiac sympathetic innervation as a factor contributing to cardiac mortality in such patients.

References

1. Cohn JN, Levine BT, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl Med* 1984; 311:819–823.
2. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banasiak W, Wrabec K, Coats AJS. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79:1645–1650.
3. Merlet P, Valette H, Dubois-Rande J-L, Moyse D, Duboc D, Dove P, Bourguignon M, Benvenuti C, Duval A, Agostini D, Loisance D, Castaigne A, Syrota A. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992; 33:471–477.
4. Hartmann F, Ziegler S, Nekolla S, Hadamitzy M, Seyfarth M, Richardt G, Schwaiger M. Regional patterns of myocardial sympathetic denervation in dilated cardiomyopathy: an analysis using carbon-11 hydroxyephedrine and positron emission tomography. *Heart* 1999; 81:262–270.
5. Ungerer M, Hartmann F, Karoglan M, Chistalla A, Ziegler S, Richardt G, Overbeck M, Meisner H, Schömig A, Schwaiger M. Regional in vivo and in vitro characterization of autonomic innervation in cardiomyopathic human heart. *Circulation* 1998; 97:174–180.
6. Vesalainen R, Pietilä M, Tahvanainen K, Jartti T, Teräs M, Någren K, Lehikoinen P, Huupponen R, Ukkonen H, Saraste M, Knuuti J, Voipio-Pulkki L-M. Cardiac PET imaging with [^{11}C]hydroxyephedrine, a specific tracer for sympathetic nerve endings, and its functional correlates in congestive heart failure. *Am J Cardiol* 1999; 84:568–574.
7. Merlet P, Benvenuti C, Moyse D, Pouillart F, Dubois-Rande J-L, Duval A, Loisance D, Castaigne A, Syrota A. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. *J Nucl Med* 1999; 40:917–923.
8. Någren K, Muller L, Halldin C, Swahn C-G, Lehikoinen P. Improved synthesis of some commonly used PET radioligands by the use of methyl triflate. *Nucl Med Biol* 1995; 22:235–239.
9. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthorne NH, Otto CA, Swanson DP, Beierwaltes WH. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981; 22:22–31.
10. Wieland DM, Hutchins GD, Rosenspire K, et al. ^{11}C-Hydroxyephedrine (HED): a high specific activity alternative to F-18 fluorometaraminol (FMR) for heart neuronal imaging. *J Nucl Med* 1989; 30:767.