Relation between N-terminal pro-brain natriuretic peptide levels and response to enhanced external counterpulsation in chronic angina pectoris

Anders Sahlén, Eline Wu, Andreas Rück, Inger Hagerman, Gunilla Förstedt, Christer Sylvén, Margareta Berglund and Tomas Jernberg

Objective **Although enhanced external counterpulsation (EECP) provides symptom reduction in many patients with severe angina pectoris, one-quarter of patients fail to respond. Earlier reports have not clearly established whether and how EECP responders may be identified pre-hoc. We hypothesized that clinical and biochemical data may be used to predict EECP response.**

Methods **We explored a database of $n=53$ patients who had undergone clinically indicated EECP during 35 1-h sessions in our unit (65±7 years; 49 male), and sought to clarify which factors are predictive of response. Efficiency of counterpulsation was measured as the diastolic augmentation (DA) ratio, and was recorded both at beginning and end of the EECP treatment course. An increase in 6-min walk (6MW) distance of 5% was indicative of clinical response.**

Results **Response occurred in 28 patients (53%; nonresponse in $n=25$, 47%). Responders had shorter baseline 6MW distance (377±81 vs. 445±62 m; $P<0.01$), lower left ventricular ejection fraction (48±9 vs. 54±8%; $P<0.05$), frequently had an increase in DA ratio during the EECP treatment course (23/28 vs. 5/28 with unchanged or decreased DA ratio; $P<0.05$), and higher levels of N-terminal pro-brain natriuretic peptide [NT-proBNP; 256 (123–547) vs. 62 (26–444) ng/l, $P<0.01$]. In multivariate logistic regression, response was independently predicted by baseline 6MW distance and baseline NT-proBNP levels ($P<0.05$ for both; model sensitivity: 82%, specificity: 72%, accuracy: 79%).**

Conclusion **There is larger clinical benefit of EECP in patients with greater functional impairment and higher levels of NT-proBNP.** *Coron Artery Dis* **00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Department of Cardiology M52, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Correspondence to Anders Sahlén, MD, PhD, MRCP, FESC, Department of Cardiology M52, Karolinska Institutet, Karolinska University Hospital, 141 86 Stockholm, Sweden
Tel: +46 858 585 015; fax: +46 858 586 710;
e-mail: anders.sahlen@ki.se

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Introduction

Enhanced external counterpulsation (EECP) is widely used for treatment of angina pectoris as it has been shown to give subjective [1] and objective reduction of ischemia [2], and leads to better symptom control than with spinal cord stimulation [3]. This was reflected in recently published treatment guidelines where EECP was upgraded on the basis of class IIa evidence (ESC [4]; ACC/AHA: IIb [5]). During treatment, pneumatic cuffs are applied to the lower extremities of a patient and inflated sequentially during cardiac diastole. Benefit is believed to be related to diastolic pressure augmentation [6]: enhanced aortic and coronary blood flow and increased cardiac output are directly related to the effectiveness of augmentation during EECP, and optimal results have been reported to occur at a diastolic: systolic pressure ratio of 1.5 : 2.0 [7]. Associated increased arterial sheer stress [8] is believed to lead to improvements in endothelial function and arterial collateralization [9–11].

While articles in this field have described a reduction in symptoms in most patients undergoing EECP, as many as 22–28% of patients do not respond [12–14]. EECP is typically well tolerated, but does carry a risk of adverse effects. Barotrauma produced by cuffs can produce discomfort or even injury during the relatively protracted course of EECP treatment, which typically takes place during a total of 35 1-h sessions. Accordingly, as the clinical response to EECP is obviously heterogeneous, it may be argued that an individualized approach should be taken where EECP is preferentially offered to patients with a high likelihood of response. However, as published data on the predictors of EECP response are scarce, this approach is presently not feasible.

As part of ongoing clinical data acquisition, our local EECP patient database contains clinical information including routine testing of treatment response by 6-min walk (6MW) distance, as well as serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP). The latter is a marker of adverse cardiovascular remodeling and risk [15]. We wished to analyze whether a combination of clinical and biochemical data may be used

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to predict response to EECP, an issue not addressed in previous research.

Methods

Patients

The present report was based on our local clinical database of patients with chronic stable angina pectoris treated with EECP from April 2005 until April 2013. Only patients treated for the first time with a full course of 35 h of EECP were included.

Enhanced external counterpulsation

EECP was performed during 35 1-h sessions, by inflating pneumatic cuffs wrapped around calves, thighs, and buttocks to 260 mmHg in cardiac diastole. Efficiency of counterpulsation was measured as the diastolic augmentation (DA) ratio of (peak diastolic – end-diastolic pressure) to (peak systolic – end-diastolic pressure), as recorded at each treatment session. At the beginning and end of the EECP treatment course, the DA ratio was recorded, along with arterial systolic blood pressure and diastolic blood pressure.

Outcome assessment

Before and after EECP, maximum exercise capacity was assessed by a standardized 6MW test, performed as recommended by the American Thoracic Society [16]. In brief, patients walked continuously for 6 min on a hard, flat, and unobstructed surface in a hospital corridor, were encouraged to continue until reaching maximal exertion, and were monitored for any developing chest pain. Perceived exertion was rated by the patient according to the Borg scale, and chest pain was recorded using the visual analog scale. A cutoff value of 5% or higher versus less than 5% improvement in 6MW distance was chosen pre-hoc as evidence of clinically meaningful improvement with EECP, corresponding to the minimal clinically important difference (MCID) for 6MW testing (see below) [17]. Importantly, improvement in function was based on objectively measured 6MW distance and not by self-rated angina pectoris class. This approach was taken in view of the large proportion of our patients who are nonnative speakers of Swedish, as it enables functional capacity to be assessed with higher internal validity.

Other analyses

Sphygmomanometric blood pressure and body weight were recorded at the beginning and end of the EECP treatment course. Biochemical analyses were performed before commencing EECP, including: hemoglobin, serum creatinine, random plasma glucose, total cholesterol, and LDL-cholesterol. At baseline and again post EECP, levels of NT-proBNP were analyzed.

Statistical analyses

Normality was assessed using Kolmogorov–Smirnov analysis, using log transformation as appropriate (e.g. in the case of NT-proBNP). Differences between subgroups were analyzed using the Mann–Whitney *U*-test or unpaired *t*-tests as appropriate, or in the case of dichotomous variables by χ^2-analysis or Fisher's exact test as appropriate. Paired data were compared using the Wilcoxon test or paired *t*-test. Multivariate analysis was performed by backward logistic regression, using an *F*-test to exclude variables. Variables were considered for inclusion if *P*-values in univariate testing were less than 0.1. Modeling was performed using categorical variables for 6MW distance (decrements of 50 m), NT-proBNP (increments of 100 ng/l), and serum creatinine (increments of 20 μmol/l). Change in DA ratio was entered as a dichotomous variable that assumed a value of 1 if an increase occurred in DA ratio during EECP and a value of 0 if the DA ratio was unchanged or decreased. Depressed left ventricular ejection fraction (LVEF) was modeled as a dichotomous variable by assigning a value of 1 for LVEF up to 45%, that is below the preserved range (50–55%). Multicollinearity between independent variables was analyzed by variance inflation factors and condition indices. All statistical analyses were performed using IBM SPSS Statistics 20.0.0 (IBM Corporation, Armonk, New York, USA). Logistic regression coefficients were entered into a computer model using the numerical analysis package MATLAB (MathWorks Corporation; Natick, Massachusetts, USA) and the probability of response in individual patients was expressed as a function of NT-proBNP and 6MW distance by the equation:

$$p(\text{response}) = e^{[c + a\,\text{NTproBNP} + b\,6\text{MW distance}]} / (1 + e^{[c + a\,\text{NTproBNP} + b\,6\text{MW distance}]}),$$

where e is the exponential function, c the regression constant, and a and b the respective regression coefficients for each term. All data are represented as mean ± SD or median (interquartile range) as appropriate, or in the case of categorical variables as n (%).

Results

The study population comprised a total of 53 patients [48 males (92%)] with complete data including NT-proBNP and 6MW distance (Fig. 1). Dosages of ongoing drug treatments were adjusted during the course of EECP in a minority of patients: antihypertensive doses were reduced in four patients and increased in three patients. No changes were made to antianginal therapies. As shown in Table 1, coronary artery by-pass grafting had been performed 18 ± 6 years earlier in 30 patients (58%) and redo coronary artery by-pass graft had been performed 6 ± 6 years before EECP in six patients (11%). Diabetes mellitus was present in one-third of patients ($n = 17$, 32%). The 6MW distance in the population as a whole ranged from 245 to 561 m and was centered around a mean of 409 m. Before EECP, NT-proBNP levels ranged from 15 to 3190 ng/l. Post-EECP levels of NT-proBNP were similar to baseline levels.

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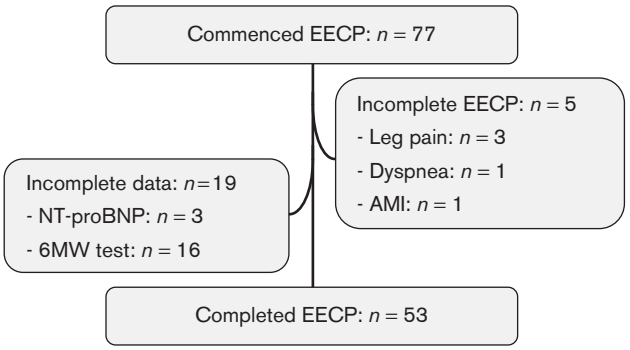
Fig. 1



Flow chart of patients who commenced clinically indicated EECP. AMI, acute myocardial infarction; EECP, enhanced external counterpulsation; 6MW, 6-min walk; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 1 Basic characteristics of study population

Variables	Total (*n*=53; 100%)	Response (*n*=28; 53%)	Nonresponse (*n*=25; 47%)	*P* value
Age (years)	65±7.4	66±5.9	63.9±8.9	NS
Male [*n* (%)]	49 (92.4)	25 (89.3)	24 (96.0)	NS
Smoker [*n* (%)]	1 (1.9)	0 (0)	1 (4.0)	NS
CCS class	2.6±0.43[a]	2.7±0.4[a]	2.5±0.4[a]	0.09[a]
Decrease of ≥ 1 CCS class [*n* (%)]	21/39 (54)[a]	15/19 (79)[a]	6/20 (30)[a]	<0.01[a]
Coronary artery by-pass grafting ([*n* (%)]	31 (58.5)	18 (64.3)	13 (52.0)	NS
Repeat coronary artery by-pass grafting [*n* (%)]	6 (11.3)	4 (14.3)	2 (8.0)	NS
Previous myocardial infarction [*n* (%)]	34 (64.2)	19 (67.9)	15 (60.0)	NS
Pacemaker [*n* (%)]	4 (7.5)	4 (14.3)	0 (0.0)	NS
Diabetes mellitus [*n* (%)]	16 (30.2)	7 (25.0)	9 (36.0)	NS
Hypertension [*n* (%)]	35 (66.0)	20 (71.4)	15 (60.0)	NS
Atrial fibrillation [*n* (%)]	6 (11.3)	4 (14.3)	2 (8.0)	NS
Laboratory analyses				
Creatinine (μmol/l)	93±24	98±21	88±25	<0.05
Estimated glomerular filtration rate (ml/min)	92±20	92±22	93±19	NS
C-reactive protein (mg/l)	1.0 (0.0–5.0)	1 (0–5)	1 (0–3)	NS
Cholesterol (mmol/l)	4.2±1.1	4.2±0.9	4.2±1.3	NS
LDL-cholesterol (mmol/l)	2.4±1	2.4±0.9	2.4±1.1	NS
Hemoglobin (g/l)	142±12.1	143.6±10	140.2±14	NS
Random plasma glucose (mmol/l)	6.7±2.3	5.9±1.1	7.4±2.7	0.05
NT-proBNP (ng/l)	244 (96–509)	256 (123–547)	62 (26–444)	<0.01
Echocardiographic analysis				
Left ventricular ejection fraction (%)	51.1±9.1	47.9±9.4	54.2±7.9	<0.05
Drug treatment				
Antithrombotic agent [*n* (%)]	49 (92.5)	26 (92.9)	23 (92.0)	NS
Long-acting nitrate [*n* (%)]	33 (62.3)	16 (57.1)	17 (68.0)	NS
β-Blocker [*n* (%)]	44 (83.0)	24 (85.7)	20 (80.0)	NS
Calcium blocker [*n* (%)]	24 (45.3)	14 (50.0)	10 (40.0)	NS
Angiotensin receptor blocker [*n* (%)]	15 (28.3)	10 (35.7)	5 (20.0)	NS
Angiotensin converting enzyme inhibitor [*n* (%)]	20 (37.7)	11 (39.3)	9 (36.0)	NS
Diuretic [*n* (%)]	16 (30.2)	11 (39.3)	5 (20.0)	NS

Data are shown as mean±SD or median (interquartile range), or in the case of categorical variables as *n* (%).
CCS, Canadian Cardiovascular Society; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a]Data for CCS class were available for a subgroup of 39 patients.

The impact of EECP on outcome variables is shown in Table 2. EECP was associated with reductions in systolic blood pressure of −5±9% and in diastolic blood pressure of −4±10%, as well as with a significant decrease in body weight of −0.9±1.5 kg (all $P < 0.01$). During the EECP treatment course, the DA ratio increased in 35 patients, was unchanged in three patients, and decreased in 15 patients. There was an improvement in 6MW distance post EECP in 44 patients (83%; +47±39 m) whereas nine patients (17%) had a shorter 6MW distance post EECP (−21±16 m).

There were eight patients (15%) with LVEF less than 45%. This subgroup had more frequently suffered an acute myocardial infarction (8/8 vs. 20/45 patients; $P = 0.039$), more commonly carried a permanent pacemaker (3/8 vs. 1/45; $P = 0.02$), and were more frequently taking

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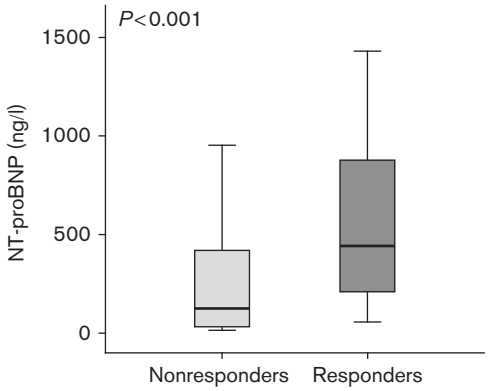
Table 2 Impact of enhanced external counterpulsation treatment on levels of N-terminal pro-brain natriuretic peptide and estimates of clinical function

Variables	Pre EECP	Post EECP	Change	*P* value
Systolic blood pressure (mmHg)	131.2±13.7	124.6±17.4	−6.6±11.2	<0.01
Diastolic blood pressure (mmHg)	78.7±12.3	74.4±6.9	−4.2±10.7	<0.01
Body weight (kg)	83.9 (74.8–96.0)	83.0 (74.4–94.0)	−0.6 (−1.6 to 0.0)	<0.01
Diastolic augmentation ratio	1.1±0.4	1.2±0.4	0.1±0.2	<0.01
CCS class	2.6±0.4[a]	2.0±0.4[a]	−0.6±0.4[a]	<0.01[a]
6-min walk distance	409.0±79.9	444.5±77.1	25 (5–65)	<0.01
Perceived exertion (Borg's scale)	12.4±2.6	11.5±3.1	−0.9±3.2	<0.05
Chest pain (visual analog scale)	2.1±1.8	1.6±2.0	−0.5±2.0	0.07
N-terminal pro-brain natriuretic peptide	244 (96–509)	216 (72–542)	7 (−34 to 57)	0.79

Data are shown as mean±SD or median (interquartile range).
CCS, Canadian Cardiovascular Society; EECP, enhanced external counterpulsation.
[a]Data for CCS class were available for a subgroup of 39 patients.

Fig. 2



Difference in levels of N-terminal pro-brain natriuretic peptides (NT-proBNP) between EECP nonresponders (light gray) and responders (dark gray). EECP, enhanced external counterpulsation.

a diuretic (6/8 vs. 8/45; $P = 0.01$) but less frequently a calcium channel blocker (1/8 vs. 17/45; $P = 0.06$). This group was also characterized by higher levels of NT-proBNP [696 (317–976) vs. 239 (57–472) ng/l; $P = 0.03$], shorter baseline 6MW (367±82 vs. 423±68 m; $P = 0.04$), and a greater increase in 6MW distance post EECP both in absolute [56 (44–81) vs. 17 (2–58) m; $P = 0.02$] and relative [14.9 (12.2–21.1) vs. 3.9 (0.4–14.3)%; $P = 0.02$] terms.

There were 37 patients in whom the DA ratio increased during the EECP treatment course (70%; 1.1±0.3 to 1.3±0.4) and 16 patients with unchanged or decreased DA ratio (30%; 1.2±0.6 to 1.1±0.5). Patients with an increase in DA ratio had significantly shorter 6MW distance at baseline (392±82 vs. 449±60 m; $P = 0.01$) and tended to exhibit a greater increase in 6MW post EECP (12±14 vs. 5±9%; $P = 0.07$).

The population was dichotomized into two subgroups by applying the pre-hoc determined cut-off for 6MW distance improvement of at least 5%, corresponding to an increase of 26 m. There were 28 EECP responders [53%; 6MW distance change, absolute: +64 (45–93) m; relative: +16.6 (11.6–23.4)%] and 25 EECP nonresponders [47%; +4 (−11 to 10) m; +0.9 (−2.8 to 2.6)%; P for both < 0.01]. Responders tended to rate the perceived exertion at 6MW test as heavier than failures (12.3±2.4 vs. 10.6±3.6; $P = 0.06$), had higher levels of NT-proBNP (Table 1 and Fig. 2) and more commonly demonstrated an increase in DA ratio (23/28 vs. 14/25 in nonresponders; $P = 0.04$). In multivariate analysis, the two independent baseline predictors of EECP response were (a) a short 6MW distance and (b) a high NT-proBNP at baseline. There was no multicollinearity between DA ratio or LVEF and either 6MW distance or NT-proBNP (variance inflation factors < 1.4, condition indices < 1.3). On the basis of the model shown in Table 3, EECP response was predicted in 30 patients of whom 23 did indeed respond (sensitivity: 82%), and, inversely, nonresponse was predicted in 23 patients of whom 19 did indeed fail to respond (specificity: 72%; positive predictive value: 77%; negative predictive value: 78%; overall model accuracy: 79%). The ability of this model to predict response in individual patients is further demonstrated as a surface plot in Fig. 3; probability of response is shown on the *z*-axis as a function of the two independent variables (NT-proBNP and baseline 6MW distance) shown on the *x*-axis and *y*-axis.

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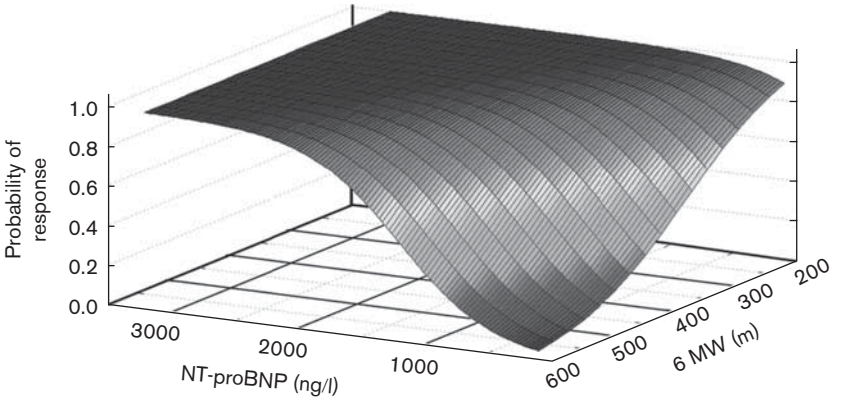
Table 3 Predictors of response to enhanced external counterpulsation treatment

	Univariate analysis		Multivariate analysis		
	B	OR (95% CI)	*B*	Wald	OR (95% CI)
Constant	–	–	−3.24	7.70	0.04
NT-proBNP	0.27	1.13 (1.05–1.64)*	0.26	5.55	1.30 (1.05–1.61)*
6-min walk distance	0.60	1.81 (1.19–2.77)**	0.55	5.43	1.73 (1.09–2.76)*
Increase in DA ratio	1.35	3.84 (1.13–13.09)*	–	–	–
Left ventricular ejection fraction ≤ 45%	2.35	10.5 (1.16–94.9)*	–	–	–
Serum creatinine	0.58	1.79 (0.99–3.69)	–	–	–
Random plasma glucose	−0.63	0.53 (0.22–0.93)	–	–	–

Intervals for independent variables: NT-proBNP, increments of 100 ng/l; 6-min walk distance, decrements of 50 m; increase in DA ratio was modeled as a dichotomous variable (increase = 1, decrease = 0); depressed LVEF was modeled as a dichotomous variable (LVEF > 45% = 0, LVEF ≤ 45% = 1); creatinine, increments of 20 μmol/l; serum glucose, increments of 1 mmol/l.
CI, confidence interval; DA, diastolic augmentation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio.
In univariate analysis, *P*-values for creatinine and serum glucose were 0.08 and 0.10, respectively.
*$P<0.05$.
**$P<0.01$.

Fig. 3



Probability of response is shown as predicted from baseline distance on 6-min walk (6MW) and baseline levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) using the expression: $p(\text{response}) = e^{(4.359-0.0129\,6\text{MW}+0.003\,\text{NTproBNP})}/[1+e^{(4.359-0.0129\,6\text{MW}+0.003\,\text{NTproBNP})}]$, as derived from logistic regression. Unit for 6MW is meters; unit for NT-proBNP is ng/l.

Discussion

The present study investigated predictors of treatment response in patients undergoing EECP for severe refractory angina pectoris. Although available data in this field indicate that most patients do respond to EECP, a minority do not. This suggests that some patients are treated unnecessarily and perhaps inappropriately. The purpose of the present study was to identify, in a real-world population of EECP-treated patients, whether and how it is possible to predict treatment response in individual patients. Our first finding was that the two independent predictors of EECP response were (a) baseline levels of NT-proBNP and (b) baseline 6MW distance. This is important for several reasons. First, our data offer a way to identify those patients with the highest probability of EECP response, which opens up the possibility that this group should preferentially be prescribed EECP. A second perspective offered by this study is related to the higher levels of NT-proBNP seen in EECP responders. This is incremental to earlier reports in this field as natriuretic peptides are not only central to the detrimental neurohormonal activation that occurs in coronary artery disease, but also strongly predictive of cardiovascular risk [15]. Against this background, our data suggest that EECP response occurs in patients with neurohormonal activation and high cardiovascular risk.

In the large body of data published on EECP treatment to date, there is surprisingly little reported about which patients do respond to EECP. Some efforts have been directed at clarifying the role of the DA ratio for clinical response. This is logical as a high DA ratio indicates greater augmentation of diastolic pressure, which is believed to be a key factor behind the treatment effect of EECP [7]. In the first of two large registry studies from the International EECP Patient Registry [18], the study by Michaels *et al.* [18]showed that patients in whom a higher DA ratio

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is achieved during EECP are more likely to be young, male nonsmokers without extracardiac vascular disease, and this subgroup tended to have greater angina pectoris reduction ($P = 0.07$). In a subsequent report by Lakshmi *et al.* [19], the change over time in DA ratio during an EECP treatment course was examined, in a population of 2486 patients whose median DA ratios at the beginning and end were 0.7 and 1.0, respectively. Among patients whose DA ratio changed from low to high during EECP, there was a mean decrease in angina pectoris class by 1.7, and 49% decreased by at least two classes. In contrast, patients whose DA ratio changed from high to low during EECP exhibited a smaller decrease in angina pectoris class of only 1.4, and 37% experienced a reduction of at least two classes ($P < 0.05$) [19]. In the present study, we were able to confirm and extend these observations, as EECP responders commonly had a low-to-high change in DA ratio during EECP. However, when NT-proBNP was added to the model, the DA ratio change was excluded in the multivariate analysis. A putative explanation may be that low-to-high change occurred in EECP responders by a mechanism of 'reverse causality', that is it was produced by the same pathophysiological mechanism that made patients improve. Indeed, as shown by Michaels and colleagues, a low DA ratio tends to occur in older patients with vascular disease. This group can be assumed to have greater arterial and left ventricular (LV) stiffening and remodeling, both of which have been suggested to improve with EECP [20,21]. By entering into the model NT-proBNP, which is upregulated in arterial and chamber stiffening due to, for example heart failure and old age, we correct for these biological changes and make the DA ratio redundant.

The fact that natriuretic peptide levels are strongly predictive of EECP response merits consideration, given that NT-proBNP is a marker of more extensive cardiovascular remodeling and neurohormonal activation, and closely related to cardiovascular risk [15,22,23]. Interestingly, Lawson *et al.* [13] reported in a larger population ($n = 4592$) that patients who derived subjective benefit were predominantly nonsmokers without diabetes, heart failure, or previous by-pass surgery, that is patients with less cardiovascular remodeling and presumably also a lower risk. This leads to the following questions. First, does EECP response occur predominantly in patients with highest risk? Second, is EECP able to modify this risk? Unfortunately, the small population size of the present study does not allow hard endpoints to be studied, and there are few reports of clinical endpoints in EECP patients in other articles. Soran *et al.* [24] reported both outcome data and clinical EECP response as judged based on Canadian Cardiovascular Society class, in a population of exclusively high-risk patients (LVEF in all patients < 35%; 45% were diabetic and 68% hypertensive) but found similar event rates in patients with versus without angina pectoris reduction during a 2-year follow-up. Lawson *et al.* [25] described in a registry study of 2007 patients that the incidence of death and myocardial infarction during follow-up was similar between patients with versus without angina pectoris reduction. In a smaller cohort, fewer major adverse cardiovascular events during 5 years' follow-up were found in patients with versus without scintigraphic improvement in myocardial perfusion (6/23 vs. 6/7 patients; $P < 0.01$). Of note, however, there were no differences in antianginal medication between patients with improved versus unchanged perfusion, suggesting that change in perfusion did not necessarily equate to clinical EECP response [26].

An associated question is whether EECP is able to modify cardiovascular risk. A number of previous publications have reported a favorable impact of EECP on indirect measures of risk (including a 25% increase in endothelial function [27], a 29% reduction in levels of tumor necrosis factor-α [28], a 75% increase in endothelial progenitor cells [29], and a 14% increase in maximal oxygen uptake [2]). LV catheterization data have demonstrated that the acute increase that occurs in LV end-diastolic volume during EECP is paralleled by a decrease in end-diastolic pressure, corresponding to a net increase in LV chamber compliance and presumably a reduction in wall stress [30]. This suggests that one may expect on mechanistic grounds that cardiomyocyte stretch should lessen after EECP, producing a decrease in natriuretic peptide levels and conceivably a decrease in risk. At variance with this, however, we did not observe a change in levels of NT-proBNP taken before versus after treatment in the present study. Similarly, Taguchi *et al.* [31] found that EECP did induce acute elevations of atrial pressure and atrial natiuretic peptide levels but unchanged levels of BNP. Analogously, an uncontrolled study by Lawson *et al.* [1] showed a persisting high rate of death in high-risk patients treated with EECP. The exact impact of EECP on LV wall stress and natriuretic peptide levels, as well as cardiovascular risk, remains uncertain and must be established in future research conducted prospectively and longitudinally. In planning such studies, however, it is likely that our finding that EECP response is associated with elevated NT-proBNP is of importance. After all, if this should translate into a higher risk being present in responders, this would obscure treatment effects achieved by EECP in a prospective interventional study.

Lastly, the definition of response as chosen in this study merits discussion. We dichotomized the population prehoc on the basis of whether a 5% improvement occurred in 6MW distance. This corresponded to a lengthening of distance by 26 m. This degree of improvement, which may at first appear to be relatively minor, has actually been shown to be meaningful both to patients and to managing clinicians: Gremeaux and colleagues studied a cohort of 81 patients with coronary artery disease and analyzed changes in patients' 6MW distance with regard to the so-called MCID ('the smallest difference in score [...] that patients perceive as beneficial and which would mandate [...] a change in patient management') [32].

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MCID was determined for 6MW distance using two different techniques and was found to be 25 m, which is in fact virtually identical to the cut-off used in the present study [17].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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