Cardiac resynchronization therapy increases plasma levels of the endogenous inotrope apelin

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Received 20 February 2006; received in revised form 1 May 2006; accepted 15 June 2006
Available online 7 August 2006

Abstract

Background: Cardiac resynchronization therapy (CRT) has been introduced to treat drug refractory chronic heart failure (CHF). Apelin, the endogenous ligand of the APJ receptor, is under evaluation for its potential role in human CHF pathophysiology. This study aims to assess whether biventricular pacing affects plasma apelin levels in patients with severe CHF.

Methods and results: Fourteen patients (9 men, 5 women, mean age 68±13 years) undergoing biventricular pace-maker/ICD implantation were studied. Patients underwent baseline clinical and echocardiographic evaluation, and assessment of plasma apelin and NT-proBNP levels. The evaluation was repeated 48 h and 9±2 months after device implantation to assess the acute and chronic effects of CRT on apelin and NT-proBNP levels. Eight healthy age- and sex-matched subjects served as controls.

In CHF patients, baseline apelin levels were reduced and NT-proBNP increased compared to control subjects (apelin: 0.47±0.2 vs. 0.97±0.3 ng/mL, p<0.001; NT-proBNP: 2007±114 vs. 229±72 pmol/L, p<0.001). Short-term evaluation did not reveal any effect of CRT on apelin or NT-proBNP levels. By contrast, at 9±2 months follow-up, CRT responders showed left ventricular reverse remodelling and an increase in ejection fraction, together with a significant increase in plasma apelin levels (0.99±0.1 vs. 0.47±0.2 ng/mL, p<0.001) and decrease in NT-proBNP (938±591 vs. 2007±114 pmol/L, p<0.05).

Conclusions: Long-term CRT increases plasma levels of the endogenous inotrope apelin in patients with CHF.

Keywords: Apelin; Resynchronization; Heart failure; NT-proBNP; APJ; Neurohormones

1. Background

Cardiac resynchronization therapy (CRT) improves electromechanical abnormalities that result from intra- and inter-ventricular conduction delay, a common feature of patients with chronic heart failure (CHF). Recent studies have reported that the effects of biventricular pacing on haemodynamic variables, functional status and quality of life in patients with CHF are mirrored by substantial changes in tissue and circulating levels of peptides and neurohormones involved in the pathogenesis of CHF [1,2].

Apelin, the endogenous ligand of the APJ receptor, is currently under evaluation for its potential role in human CHF pathophysiology. Indeed, the mature peptide is expressed in the cardiovascular system and exerts a potent cardiac positive inotropic effect [3–5]. Notably, it has recently been reported that plasma apelin concentrations are decreased in patients with CHF [6,7].

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doi:10.1016/j.ejheart.2006.06.005
2. Aims

To assess whether biventricular pacing affects peripheral apelin levels in patients with severe CHF.

3. Methods

Fourteen consecutive patients (9 men, 5 women, mean age 68±13 years) undergoing biventricular pace-maker/ICD implantation based on strictly defined selection criteria (NYHA class III–IV, left ventricular ejection fraction (LVEF) <35%, left bundle branch block with QRS duration >120 ms) were studied. All patients underwent baseline clinical and echocardiographic evaluation, and blood sample collection for assessment of plasma apelin and NT-proBNP levels. The evaluation was repeated 48 h and 9±2 months after device implantation in order to assess acute and chronic effects of CRT on apelin and NT-proBNP levels.

Echocardiography was performed using a commercially available system (Acuson Sequia C512). Intra- and interventricular dysynchrony were evaluated respectively as septal-to-posterior wall motion delay (SPWMD) in M-mode recordings, and interventricular mechanical delay (IVMD), expressed as the difference between left and right ventricular pre-ejection intervals. Plasma apelin concentration was assessed by a commercially available enzyme immunoassay kit (Apelin-12 EIA Kit, Phoenix Pharmaceuticals, Inc.). This kit presents a 100% cross-reactivity against Apelin-12, Apelin-13 and Apelin-36, the minimum detectable concentration being 0.08 ng/mL. All samples were tested in duplicate using 50 μL of plasma. NT-proBNP plasma levels were measured using a competitive immunoassay (Biomedica Gruppe), the detection limit being 5 pmol/L. All samples were tested in duplicate using 100 μL of plasma. Blood samples from 8 healthy age- and sex-matched normotensive subjects with normal LV dimensions and EF served as controls.

Data are presented as mean±S.D. Comparison of data was performed using one-way ANOVA for repeated measures with Bonferroni’s correction or χ² test for categorical variables, as appropriate. For all tests a p value <0.05 was considered significant. The study was approved by the ethics committee of our institution and all patients gave written informed consent to participate.

4. Results

Clinical and echocardiographic variables of patients are presented in Table 1. As shown, all patients had left ventricular dilation and markedly impaired LVEF at baseline. The majority of patients showed a SPWMD ≥130 ms (8/14) and/or an IVMD ≥40 ms (9/14). In the CHF patients, baseline circulating apelin levels were significantly reduced...
and NT-proBNP increased compared to control subjects (apelin: $0.47 \pm 0.2$ vs. $0.97 \pm 0.3$ ng/mL, $p<0.001$; NT-proBNP: $2007 \pm 114$ vs. $229 \pm 72$ pmol/L, $p<0.001$) (Fig. 1).

Two days after device implantation, SPWMD and IVMD were significantly reduced, and patients showed a slight and borderline significant improvement of LVEF (Table 1). At that time, both apelin and NT-proBNP levels did not change compared to baseline (Fig. 1). At 9±2 months follow-up, one patient was classified as a CRT non-responder based on lack of improvements in CHF symptoms and the need for repeated hospitalisations for decompensated CHF. In the CRT responders, improvements of echocardiographic variables observed 48 h after biventricular device implantation persisted over time (Table 1). Ejection fraction showed a further significant increase, and left ventricular reverse remodelling was observed (Table 1). Drug therapy remained unchanged during the entire follow-up in all CRT responders. The single non-responder patient failed to show left ventricular reverse remodelling, increase in ejection fraction, or reduction in NT-proBNP levels; drug therapy was continuously implemented with higher dosages of diuretics. At 9±2 months follow-up, plasma apelin levels in the CRT responders were doubled compared to baseline values ($0.99 \pm 0.1$ vs. $0.47 \pm 0.2$ ng/mL, $p<0.001$). These changes in apelin were mirrored by significant reductions in NT-proBNP levels ($938 \pm 591$ vs. $2007 \pm 114$ pmol/L, $p<0.05$) (Fig. 1). The non-responder patient displayed a marked increase in NT-proBNP levels, while apelin changes paralleled those observed in the CRT responders (Fig. 1).

5. Discussion

We report here for the first time that CRT increases circulating levels of the potent endogenous inotrope apelin in patients with CHF. Indeed, CRT-induced improvements in clinical and echocardiographic variables were reflected by changes in plasma apelin.

Changes in plasma apelin concentrations in CHF patients have already been described with conflicting results. Indeed, while apelin concentrations have been reported to be significantly lower in CHF patients regardless of NYHA class and impairment of systolic function [6], Chen et al. reported that plasma apelin levels are increased in the early phases of CHF and fall in more advanced stages of the disease [8]. Although the mechanism responsible for this phenomenon has not been elucidated, it could be speculated that induction of apelin gene expression and protein synthesis represents an adaptive mechanism triggered by cardiac overload. Thus, the decline of apelin levels in severely sick patients may reflect the inability of the failing heart to compensate for the decline of left ventricular systolic performance. Consistent with this hypothesis, Chen et al. demonstrated that left ventricular unloading with mechanical ventricular support increases apelin cardiac tissue levels in patients with CHF [8]. However, a direct effect of left ventricular unloading on peripheral concentrations of apelin in CHF patients has never been demonstrated.

Although we could not find any correlations between apelin levels and remodelling indexes or NT-proBNP,
plasma levels of the inotrope peptide displayed a trend which was virtually opposite to that shown by NT-proBNP, a marker of left ventricular function that has been successfully used to monitor the effects of CRT [9]. Surprisingly, we found that the single non-responder patient in our population displayed an increase in plasma apelin levels at follow-up. Conversely, increased plasma NT-proBNP levels reflected the lack of benefits of CRT in this patient. An explanation for the discrepant behaviour of apelin in this patient cannot be provided by our current data, and might be related to the influence of the aggressive therapeutic measures that were adopted in this individual.

Finally, it is noteworthy that in responder patients, CRT restored plasma apelin to levels which were not different from controls. This intriguing observation may promote further studies in larger populations to better identify the pathophysiological significance and the clinical relevance of apelin in CHF.

References


