μg/kg/min) infusion, which did not alter hemodynamics, as compared with a higher dose (0.015 μg/kg/min) infusion, which reduced BP.

In conclusion, further prospective randomized controlled studies are warranted to test the efficacy of non-hypotensive low-dose nesiritide such as 0.005 μg/kg/min and the current dose of 0.01 μg/kg/min without the bolus of 2 μg/kg/min in enhancing renal function in patients with acute decompensated CHF and renal dysfunction as well as defining the mechanisms of the renal-enhancing actions of such a strategy.

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A Biomarker of Myocardial Fibrosis Predicts Long-Term Response to Cardiac Resynchronization Therapy

To the Editor: Serum concentrations of the carboxy-terminal propeptide of procollagen type I (PICP), a peptide that is cleaved from procollagen type I during the synthesis of fibril-forming collagen type I (CTI), may provide indirect diagnostic information on both the synthesis of fibril-forming CTI molecules and the extent of myocardial deposition of CTI fibers (1). We investigated whether PICP is related to the clinical long-term response to cardiac resynchronization therapy (CRT) in heart failure (HF) patients.

Thirty-eight consecutive patients were prospectively studied. All patients received CRT for New York Heart Association (NYHA) functional class III/IV HF, left ventricular (LV) ejection fraction (EF) ≤35%, and QRS ≥130 ms. Twenty healthy subjects were included as control subjects.

Patients were evaluated at baseline and at the 1-year follow-up. Evaluation included NYHA functional class, 6-min walk test, blinded echocardiographic study with measurement of interventricular and intraventricular dyssynchrony parameters (septal-to-posterior-wall motion delay [SPWMD] and septal-to-lateral-wall motion delay [SLWMD]), and obtaining of blood samples. At 1 year, patients were categorized as nonresponders if they died of HF, were scheduled for heart transplantation, or did not increase the distance walked in 6 minutes by >10%.

Serum PICP was determined by a sandwich enzyme-linked immunosorbent assay (ELISA) (inter- and intra-assay variations were 6.3% and 6.4%, respectively). The minimum analytical detection limit was 1 μg/l. Serum amino-terminal propeptide of brain natriuretic peptide (NT-proBNP) was measured by ELISA (inter- and intra-assay coefficients of variation lower than 2%).

Differences between baseline values and between final values in the two groups of patients were analysed with the Mann-Whitney *U* test for SLWMD, interventricular dyssynchrony, and NT-proBNP and with the Student *t* test for unpaired data for the rest of the quantitative variables. Intragroup comparisons between baseline and final values were analyzed with the Wilcoxon test (SLWMD, interventricular dyssynchrony, and NT-proBNP) and with the Student *t* test for paired data for the rest of quantitative variables. Categoric variables were analyzed by chi-square test. Significant variables in univariate analysis were used in logistic regression analysis to predict the probability of positive response to CRT. A model was constructed using stepwise variable selection, verified with the Hosmer-Lemeshow test. Receiver-operating characteristic (ROC) curves allowed determination of the overall performance for predicting a positive response to CRT. The results are expressed as mean ± SD.

At 1 year, 26 patients (68%) were considered responders to CRT (Table 1). At baseline, nonresponders exhibited higher left ventricular end-diastolic diameter (LVEDD) and lower SLWMD than responders ($p < 0.05$). Baseline PICP was higher in responders than in controls ($p < 0.01$) and nonresponders ($p < 0.05$). Baseline NT-proBNP was higher ($p < 0.001$) in the two groups of patients than in controls (36 ± 5 pg/ml). Baseline NT-proBNP was increased ($p < 0.05$) in responders compared with nonresponders.

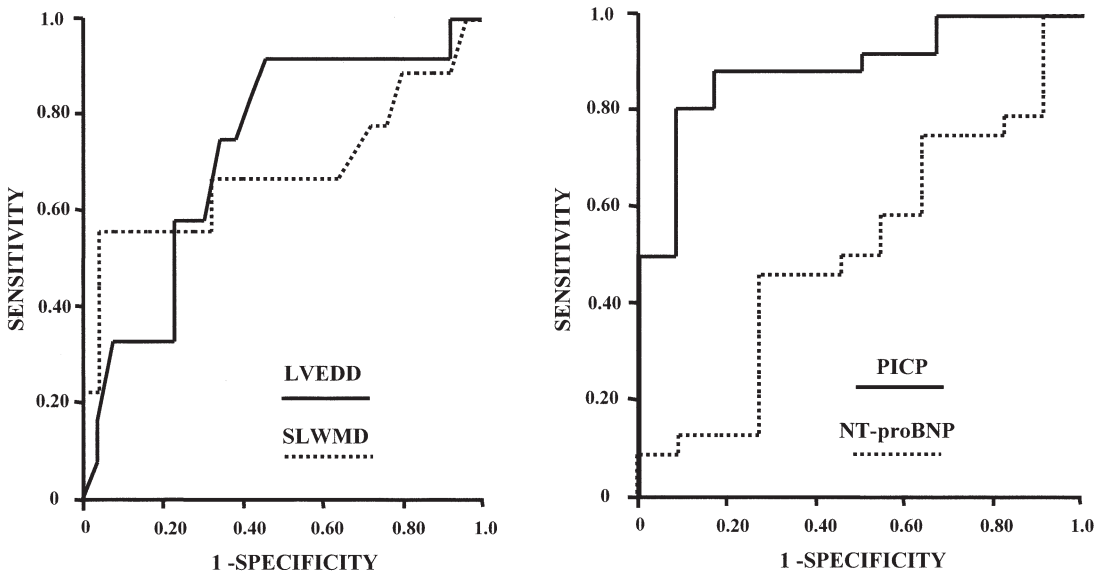
Whereas EF, LV diameters, and the dyssynchrony parameters decreased ($p < 0.05$) at 1 year in responders, they remained unchanged in nonresponders. At 1 year, PICP decreased ($p < 0.005$) in responders and increased ($p < 0.005$) in nonresponders. Whereas in responders PICP decreased in 21 patients (81%) and

Table 1. Effects of CRT in Heart Failure Patients Separated According to the Response

	Responders		Nonresponders	
	Baseline	1 yr	Baseline	1 yr
Age (yrs)	67 ± 8		69 ± 7	
NYHA functional class	3.3 ± 0.5	2.0 ± 0.6†	3.1 ± 0.7	2.9 ± 0.8
6-min walk test (m)	327 ± 129	437 ± 200†	367 ± 191	360 ± 173
Ischemic etiology (%)	46		75	
Medical treatment (%)				
RAS-I	100	100	100	100
Beta-blockers	50	58	58	58
Spironolactone	20	16	25	25
LVEDD (mm)	66.2 ± 9.5	61.5 ± 7.7†	73.9 ± 8.8*	71.3 ± 10.4
LVESD (mm)	56.1 ± 10.1	49.1 ± 10.4†	61.4 ± 9.6	58.1 ± 12.6
EF (%)	25.8 ± 6.1	37.1 ± 10.0†	25.4 ± 5.8	26.8 ± 6.6
Dyssynchrony (ms)				
SPWMD	204.8 ± 79.5	63.3 ± 43.4†	207.2 ± 80.1	173.3 ± 70.5
SLWMD	141.6 ± 82.0	39.1 ± 41.7†	89.4 ± 46.2*	60.5 ± 32.7
Interventricular	47.2 ± 23.7	25.9 ± 25.5†	49.4 ± 34.7	29.5 ± 19.4
Serum PCIP (μg/l)	101 ± 34	82 ± 21‡	57 ± 18*	91 ± 34†
Serum NT-proBNP (pg/ml)	2,926 ± 1,326	1,354 ± 1,132	1,900 ± 1,793*	1,946 ± 1,568

*$p < 0.05$ baseline values responders vs. nonresponders; †$p < 0.05$ baseline vs. 1 year in responders; ‡$p < 0.005$ baseline vs. 1 year in responders and nonresponders.

EF = ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NT-proBNP = amino-terminal propeptide of brain natriuretic peptide; PICP = carboxy-terminal propeptide of procollagen type I; RAS-I = renin-angiotensin system inhibition; SLWMD = septal-to-lateral-wall motion delay; SPWMD = septal-to-posterior-wall motion delay.



	AUC	Cutoff value	Sensitivity (%)	Specificity (%)	Odds ratio (95% CI)
PICP	0.891	73 μg/L	85	83	27.5 (4.3-175.7)
NT-proBNP	0.511	815 pg/mL	71	49	0.750 (0.15-3.62)
LVEDD	0.726	67.5 mm	75	61.5	5.6 (1.2-26.3)
SLWMD	0.684	95 ms	67	40	0.333 (0.067-1.65)

Figure 1. Receiver-operating characteristic curves for cardiac (left ventricular end-diastolic diameter [LVEDD] and septal-to-lateral-wall motion delay [SLWMD]) **(left)** and biochemical (carboxy-terminal propeptide of procollagen type I [PICP] and amino-terminal propeptide of brain natriuretic peptide [NT-proBNP]) **(right)** parameters for determining a positive response to CRT. AUC = area under curve; CI = confidence interval.

increased in 5 patients (19%), in nonresponders PICP decreased in 1 patient (8%) and increased in 11 patients (92%); these differences were significant ($p < 0.05$).

The NT-proBNP level tended to decrease in responders at 1 year, although the difference was not significant; NT-proBNP was unchanged in nonresponders.

Significant associations were observed between positive response to CRT and high baseline values of PICP (>73 μg/l) (chi square = 16.29; $p < 0.001$) and low baseline values of LVEDD (<67.5 mm) (chi square = 5.37; $p < 0.05$). The only independent predictor of a positive response to CRT was PICP (odds ratio 13.9, 95% confidence interval 7 to 97; $p < 0.001$). The accuracy of the model was confirmed by the nonsignificant Hosmer-Lemeshow goodness-of-fit-test ($p = 0.796$)

As shown in Figure 1, PICP exhibited the larger area under the ROC curve. In addition, only the area under the ROC curve for PICP and LVEDD was higher ($p < 0.001$ and $p < 0.05$, respectively) than 0.50. The cutoff value of PICP showed better sensitivity and specificity than the others parameters analyzed. The odds ratio of presenting a favorable response to CRT was higher for patients with PICP >73 μg/l than for patients with NT-proBNP >815 pg/ml, LVEDD <67.5 mm, or SLWMD >95 ms.

These findings can be summarized as follows: 1) an association exists between abnormally high baseline serum PICP and a positive long-term response to CRT in HF patients; 2) whereas the beneficial effects of CRT are associated with its ability to normalize serum PICP, the lack of benefit is associated with enhancement of serum PICP; and 3) serum PICP is more accurate than some echocardiographic parameters and NT-proBNP in the prediction of a positive long-term response to CRT.

Previous studies have shown that circulating PICP detected in HF patients is essentially of cardiac origin and that serum PICP is a reliable index of the amount of CTI present within the myocardium (2,3). Therefore, the present study suggests that ventricular dyssynchrony may induce excessive cardiac synthesis and deposition of CTI fibrils and that limitation of these alterations may be one of the mechanisms contributing to the positive effect of CRT. Our results would suggest also that stimulation of CTI synthesis and deposition may account for a negative response to CRT. Whatever are the factors determining these two patterns of response, it appears that long-term responses to this therapy are linked to its ability to interfere with myocardial fibrosis. Additional studies aimed to evaluate histologically measured myocardial collagen deposition in CRT patients are necessary to prove these hypotheses.

Some findings reported here suggest that PICP adds predictive value to other indices of response to CRT. First, serum PICP was the only independent predictor of a positive response to CRT. Second, serum PICP was a highly sensitive and specific parameter in the identification of a positive long-term response to CRT. Third, patients with serum levels of PICP >73 μg/l had an almost 28-fold higher probability of presenting a positive response to CRT, showing the highest performance for predicting a positive response to CRT.

In conclusion, the determination of serum PICP may be useful for predicting the response to CRT. However, we are aware that this was a study involving a relatively small number of patients with heterogeneous etiologies. Albeit preliminary, these findings set the stage for large-scale studies to definitively validate this approach.

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Paired Ventricular Stimulation: An Approach for Hemodynamic Stabilization During Ventricular Tachycardia

To the Editor: Despite great efforts and success in terminating ventricular tachycardia (VT) by methods like cardioversion and overdrive stimulation, there are situations in which VTs are ongoing (incessant VT) despite aggressive therapy. We assessed a stimulation technique for hemodynamic stabilization during VT.

A ventricular extrasystole occurring shortly after the effective ventricular refractory period generates a postextrasystolic pause and leads to an augmentation of the arterial pressure wave initiated by the next spontaneous beat. This phenomenon was originally described by Langendorff (1). We speculated that single premature ventricular beats during an ongoing VT might have a similar effect. The premature beats would be introduced with coupling intervals longer than the ventricular refractory period but shorter than the VT cycle length. The subsequent postextrasystolic pause should prolong the diastolic filling time, resulting in an augmented pressure wave initiated by the next spontaneous VT beat. Postextrasystolic potentiation of contractile force should contribute to hemodynamic stabilization during VT.

In 22 patients (70 ± 8 years, ejection fraction 38 ± 14%) with a history of spontaneous VT (n = 21) or ventricular fibrillation (VF) (n = 1) and inducible sustained VT during an electrophysiological study (n = 16) or ablation procedure (n = 6), paired