Adrenomedullin Plasma Levels Predict Left Ventricular Reverse Remodeling after Cardiac Resynchronization Therapy

MARIA-AURORA MORALES, M.D., MARISTELLA MALTINTI, MARCELLO PIACENTI, M.D., STEFANO TURCHI, DANIELA GIANNESSI, Sc.D., and SILVIA DEL RY, Sc.D.
From the CNR Institute of Clinical Physiology and G. Monasterio Foundation, Pisa, Italy

Background: *Increase in adrenomedullin (ADM) plasma levels in congestive heart failure (HF) patients is due to many cardiac and systemic factors, particularly to greater fluid retention and to activation of sympathetic nervous system. Aim of this study was to assess the role of plasma ADM levels in HF patients treated by cardiac resynchronization therapy (CRT).*

Methods: *50 patients, mean age 70 years, 34 male, New York Heart Association (NYHA) Class III–IV HF, left ventricular ejection fraction (LVEF) < 35%, underwent CRT. All patients were in sinus rhythm and with complete left bundle branch block (QRS duration 138 ± 6 msec). A complete echoDoppler exam, blood samples for brain natriuretic peptide (BNP), and ADM were obtained from 2 to 7 days before implantation.*

Results: *At 16 ± 6 months follow-up, ≥1 NYHA Class improvement was observed in 38 patients. However, a >10% reduction in end-systolic dimensions (ESD) was reported in 21 patients (Group I): −16.6 ± 1.8%; in the remaining 29 patients ESD change was almost negligible: −2.0 ± 1.03% (Group II), P < 0.0001. The two groups were comparable for age, sex, cause of LV dysfunction, therapy, QRS duration at baseline, preimplantation ESD, LVEF%, and BNP. Significantly higher pre implantation ADM levels were present in Group I than in Group II (27.2 ± 1.8 pmol/l vs 17.9 ± 1.4, P = 0.0003).*

Conclusions: *Significantly higher ADM levels indicate a subgroup of patients in whom reverse remodeling can be observed after CRT. Patients with lower ADM basal values before CRT could represent a group in whom the dysfunction is so advanced that no improvement can be expected. (PACE 2010; 33:865–872)*

adrenomedullin, natriuretic peptides, cardiac resynchronization therapy, heart failure

Introduction

Heart failure (HF) remains one of the most common, costly, disabling, and deadly medical conditions despite great improvements in diagnostic techniques and treatment.[1]

In this complex clinical syndrome, structural and hemodynamic abnormalities are accompanied by a series of hormonal alterations of systemic, renal, and neurological origin.[2,3] Activation of neurohormones such as catecholamines, natriuretic peptides, and renin-angiotensin system, and inflammatory cytokines has both pathophysiological and prognostic implications.[2–7] In the last years, much attention has been paid to nonpharmacological treatments of HF; in this respect, cardiac resynchronization therapy (CRT) based on correction of electro-mechanical dyssynchrony by biventricular pacing in patients with severe chronic HF and ventricular conduction disturbances has been developed. This treatment has been shown to improve symptoms and exercise capacity, to reduce ventricular tachyarrhythmias and rate of hospitalization for worsening HF, as well as to improve survival.[8–12]

However, even today, up to 30% of patients do not respond either clinically or functionally to CRT, despite selection for implantation based on current guidelines.[13]

The effects of CRT on specific neurohormones, as norepinephrine, brain natriuretic peptide (BNP), N-terminal pro-BNP, and atrial natriuretic peptide (ANP) are well documented.[14–17] In particular, several studies suggest that plasma concentration of natriuretic peptides may represent a useful parameter for evaluation and monitoring of patients undergoing CRT; however, conflicting results on the role of the single peptides have been published.[14–23]

Recent studies report that adrenomedullin (ADM), another member of the natriuretic peptides family, may play an important role in the pathophysiology of chronic HF[24,25]; it is believed to have potent endogenous natriuretic and vasodilating actions, increasing cardiac output and regulating local and systemic vascular tone.[26–29]

Financial support: None.

Address for reprints: Maria-Aurora Morales, M.D., CNR Clinical Physiology Istitute, Via G Moruzzi, 1, 56125 Pisa, Italy. Fax: 039 0503152166; e-mail: morales@ifc.cnr.it

Received August 4, 2009; revised November 3, 2009; accepted January 18, 2010.

doi: 10.1111/j.1540-8159.2010.02723.x

ADM could function as an atrial natriuretic peptide in the control of cardiorenal homeostasis thus influencing cardiovascular function.[24]

In animal experiments, chronic ADM administration attenuates the progression of cardiac dysfunction and improves the prognosis in rats developing HF.[25,28]

The aim of this study was to assess the possible role of ADM as predictor of response to CRT in chronic HF patients undergoing CRT for clinical reasons.

Materials and Methods

Patient Population

The study enrolled 50 consecutive patients (34 male, mean age 70 years, range 52 to 85 years) treated with resynchronization therapy for clinical reasons. Before device implantation, 46 patients were in New York Heart Association (NYHA) Class III and four in NYHA Class IV. Underlying cause of cardiac dysfunction was post ischemic cardiomyopathy in 29 patients, idiopathic dilated cardiomyopathy in 21. At surface ECG, QRS duration was 138 ± 6 msec (range 120 to 200 msec) with a left bundle branch block pattern. All patients were in optimal medical therapy for HF including angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, beta blockers, furosemide, and spironolactone or potassium canreonate, if not contraindicated. Exclusion criteria were represented by acute coronary syndrome or acute inflammation (within 6 months), significant peripheral occlusive artery disease, neoplastic disease, and renal failure (serum creatinine value above 1.5 mg/dl). Thirty subjects of comparable age and sex with no history of cardiovascular disease, normal regional and global left ventricular function assessed by two dimensional echocardiography, and under no medical treatment were evaluated as control group. A group of 40 HF patients, 36 in NYHA Class III and four in NYHA Class IV, under optimal medical treatment and not undergoing CRT, was also studied. Patients were matched with those undergoing CRT for NYHA class and age (using quinquennial age classes) and, whenever possible, cause of dysfunction.

Study Protocol

At time of the study patients were in stable clinical conditions under oral therapy. All patients underwent blood samples, clinical and echocardiographic examination from 2 to 7 days before implantation.

Patients returned for clinical, functional, and pace-maker follow-up on average every 6 months after implantation; clinical and echocardiographic data collected at a mean of 16 ± 6 months after CRT (FU) were considered for the present analysis. HF patients were also periodically followed in our out-patient laboratory. Clinical and echocardiographic data obtained at 13 ± 4 months (FU) after stable beta-blockers and ACE-inhibitors or angiotensin receptor blockers dosages were considered for analysis. Three months after FU, patients or strict relatives were interviewed to obtain information on mortality and hospitalization.

The investigation conforms with the principles outlined in the Declaration of Helsinki.[30] The study was approved by the local Ethical Committee and all patients provided signed informed consent before entering in the study.

Plasma Samples

Blood samples (8–10 mL) were put into ice-chilled disposable polypropylene tubes containing aprotinin, 500 KIU/mL, and EDTA, 1 mg/mL. Plasma samples were rapidly separated by centrifugation for 15 min at 4°C and then stored frozen at −20°C in aliquots.

Assay Method

Plasma ADM was measured with a radioimmunoassay (RIA) method (Human Adrenomedullin 1–52, Phoenix Pharmaceuticals, Belmount, CA, USA), with some modifications, after sample extraction, as reported in a previous work.[31]

Plasma BNP was measured by an IRMA method (Shionoria BNP, Shionogi & Co. Ltd, Osaka, Japan), which does not require a preliminary step of extraction or purification of plasma samples. This method has been previously reported in detail in literature.[32,33]

Echocardiographic Examination

Patients underwent a complete echocardiographic and Doppler examination at baseline and at follow-up using commercially available instruments (Acuson Sequoia, Acuson Corporation, Mountain View, Ca, USA, and Vivid system 7, GE/Vingmed, Milwakee, WI, USA). Simultaneously a lead II surface electrocardiogram was recorded. Left ventricular (LV) end-diastolic (EDD), and end-systolic (ESD) dimensions were obtained from the parasternal long axis view; left ventricular (LV) volumes and derived ejection fraction (LVEF) were calculated from apical four-chamber and two-chamber view by the biplane summation method.[34]

Statistical Analysis

All the sample concentrations and other data for quality control of the RIA system were calculated by a previously described computer program; the interpolation of the dose–response

curves was computed using a four-parameter logistic function.[35] The unpaired Student's *t*-test was used to compare the results of the independent groups studied. The results are expressed as mean ± standard error of the mean.

Results

All patients completed the protocol. In all 50 CRT patients baseline ADM and BNP levels were significantly higher than controls: ADM: 21.8 ± 1.3 versus 13.3 ± 0.7 pmol/L, P < 0.0001; BNP: 572.3 ± 55.9 versus 12.8 ± 1.9 pg/mL, P < 0.0001.

In the 40 HF patients, ADM baseline values were comparable to the CRT patients: (23.5 ± 1.6, vs 21.8 ± 1.3 pmol/L-NS).

In CRT patients, no differences were observed between coronary artery disease and dilated cardiomyopathy (n. 29 and n. 21, respectively) as far as ADM values: 23.7 ± 2.1 versus 21.3 ± 1.6, pmol/L and BNP values: 634.7 ± 125.1 versus 548.9 ± 58.2 pg/mL, NS.

At 16 ± 6 months FU, in patients treated with CRT, a NYHA Class improvement ≥1 was observed in 38/50 patients; in the remaining population NYHA Class was unchanged. No significant differences in baseline ADM, BNP, EDD, ESD, and LVEF could be found in the two groups.

At FU, the 38 patients which improved in NYHA Class showed changes in EDD (−4.5 ± 1.3%), ESD (−10.8 ± 1.5%), and LVEF (+24.7 ± 3.9%) while no significant changes of the same parameters could be observed in patients without clinical improvement.

LV inverse remodeling, as a >10% reduction in ESD at two-dimensional echocardiography, independent of clinical improvement at FU, was observed in 21/50 patients (Group I): −16.36 ± 1.8% while in the remaining 29 patients (Group II) ESD changes were almost negligible: −2 ± 1.03% (P < 0.0001).

The two groups of CRT patients and the HF group treated with medical therapy only were comparable for age, sex, cause of LV dysfunction, ongoing therapy, and LVEF% (Table I).

As far as neurohormonal assessment, BNP was comparable in basal conditions in the two groups of patients under resynchronization therapy (476 ± 73 vs 640 ± 79 pg/mL, NS); significantly higher preimplantation ADM levels were present in Group I than in Group II (27.2 ± 1.8 vs 17.9 ± 1.4 pmol/L, P = 0.0003) (Fig. 1).

In Table IIa and IIb individual CRT patient data relative to Group I (21 patients) and Group II (29 patients), respectively, are reported.

None of the CRT patients died during the FU; 9/50 patients were hospitalized for worsening heart failure, two in Group I and seven in Group II.

Table I.

Clinical Characteristics and Drug Treatment in Patients with ≥10% Reduction in ESD after CRT (Group I), in Those with No ESD Reduction (Group II) and in HF Patients under Medical Therapy

	Age	NYHA III/IV	DCM/ CAD	Diabetes	QRS (msec)	Beta-blockers	ACEI or ARB	Diuretics	Spironolactone or K Canreonate	Amiod	Digit	LVEF%
Group I n.21	71.1 ± 1.5	20/1	15/6	16	136 ± 14	20	21	21	12	2	0	25.6 ± 1.0
Group II n.29	69.9 ± 1.2	26/3	18/11	18	134 ± 12	26	25	29	13	1	1	25.5 ± 1.0
HF patients n.40	68.3 ± 1.9	36/4	23/17	30	100 ± 9	34	38	40	30	0	0	26.0 ± 0.7

NYHA = New York Heart Association; DCM = primitive cardiomyopathy; CAD = coronary artery disease; ACEI = ACE inhibitors; ARB = angiotensin receptor blockers; K canreonate = potassium canreonate; Amiod. = amiodarone; Digit = digitalis; LVEF = left ventricular ejection fraction.

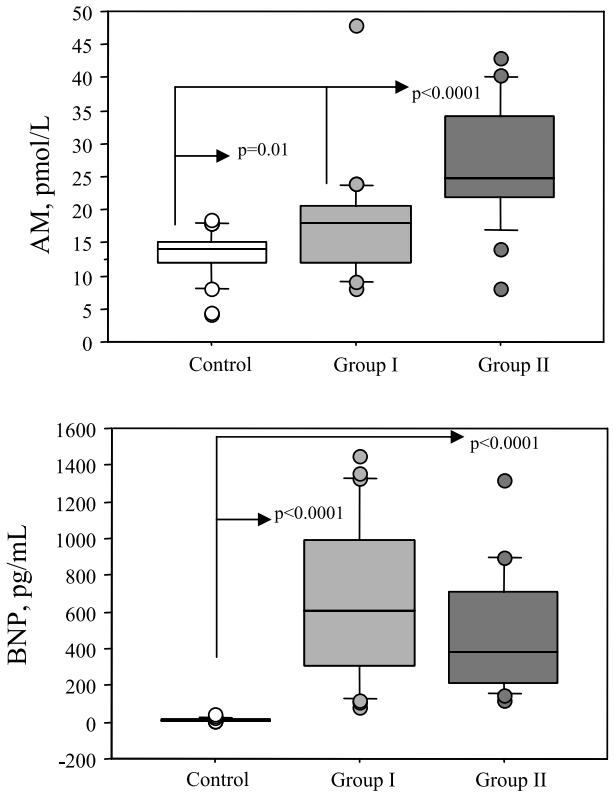

Figure 1. *Adrenomedullin and BNP plasma levels in controls and in patients with >10% decrease in ESD (Group I) and in those with negligible changes in ESD at FU (Group II).*

Lower ADM values were observed at baseline in those patients who had major cardiovascular events at FU: 16.5 ± 1.9 vs 27.3 ± 1.6 pmol/L, P < 0.0001) while the same patients showed higher—although not significant—baseline BNP plasma levels (736.11 ± 161.7 vs 529.9 ± 56.9 pg/mL, NS).

In HF patients under conventional treatment, higher ADM levels were observed in the 13 patients who showed a >10% reduction in ESD at a 13 ± 4 months FU compared to those who did not show any change (28.8 ± 2.6 vs 20.5 ± 1.8 pmol/L, P = 0.02).

Of these patients under conventional treatment, mortality was reported in two (both with <10% reduction in ESD at FU) and hospitalization for worsening heart failure in 12 patients (10 with <10% reduction in ESD). ADM levels resulted lower in patients with major events at FU (15.6 ± 1.8 vs 27.3 ± 1.6 pmol/L, P < 0.0001).

Discussion

This study shows that in patients undergoing CRT higher ADM levels may represent an index of positive LV remodeling at FU. To our knowledge, this is the first time that this peptide is assessed as a predictor of LV inverse remodeling in patients treated with biventricular stimulation.

A series of trials have demonstrated that CRT is able to improve symptoms and functional capacity and to reduce hospitalizations for worsening HF.[12,36–40] These favorable effects are associated with reduction of LV volumes and reduction of mitral regurgitation; more importantly, a burden of evidence suggests that CRT can reverse the progression of HF in terms of reverse remodeling of the left ventricle.[11,41–43]

Several studies have reported a decrease in natriuretic peptide levels among responders to CRT and percentage change in plasma BNP levels from baseline to variable FU has been considered as a strong predictor of long-term response to CRT and positive outcome.[16,21,44]

It was also demonstrated that patients with an improvement in clinical status showed a reduction in ANP plasma concentrations after CRT, suggesting the usefulness of natriuretic peptides as an objective and quantitative marker to evaluate response to CRT.[16]

In our population no statistically significant differences between responders and non responders to CRT could be observed for BNP although BNP baseline values were lower in the responder group. Until now, the potential role of preimplantation BNP to predict outcome in patients undergoing CRT is not clear. In fact, some studies have shown that patients with high BNP levels before implantation have a worse prognosis at FU[19] while other AA have shown that high BNP levels before CRT identify patients with better response to device implantation and improvement in LVEF.[18] In terms of LV remodeling, lower BNP values seem to predict significant LV reverse remodeling.[22] A possible explanation of these variable results may be related to the fact that BNP is secreted by the ventricles in response to end-diastolic pressure and volume and can reflect the actual hemodynamic status of the patient.

As far as NT-proBNP, the CARE-HF substudy showed that it was the best baseline predictor of outcome,[41] bettered only by NT-proBNP measured 3 months after randomization, but neither value predicted the long-term response to CRT.[44,45] Moreover, the absolute improvement in prognosis with CRT was similar in patients with values above and below the median NT-proBNP; on the other hand, patients who have extreme elevations of NT-proBNP have a poor prognosis, suggesting that the disease is too advanced to improve after CRT.[20, 45]

To our knowledge, the role of ADM in patients undergoing CRT for clinical reasons has not been elucidated so far.

Table IIa.

Individual Data of 21 Patients Who Showed a >10% Reduction in ESD at Baseline (Pre) and at FU (Post)

Name	Age (Years)	ADM, pmol/L	NYHA Pre/Post	EDD Pre/Post	ESD Pre/Post	LVEF Pre/Post
GD	79	22.0	III/II	65/56	52/48	32/33
GC	76	22.0	III/II	73/62	65/49	21/32
LG	76	19.0	III/II	65/63	56/50	25/30
MG	66	43.0	III/II	68/67	58/42	31/48
MA	62	40.0	III/II	64/64	52/44	34/43
MB	72	23.2	III/II	74/69	71/56	25/32
CS	71	34.0	IV/III	73/69	63/54	26/30
AE	75	40.4	III/II	65/63	58/52	25/33
PE	69	30.0	III/II	70/74	64/58	28/30
BG	78	34.0	III/II	57/55	48/42	25/35
ZA	58	27.0	III/II	70/70	64/58	20/27
GC	66	22.0	III/II	82/83	78/68	20/26
RA	68	24.8	III/II	65/55	56/42	20/24
RD	61	22.0	III/II	66/49	54/30	28/60
MG	72	27.0	III/II	78/63	70/53	20/33
DG	72	21.0	III/II	68/66	64/56	31/30
GA	67	14.0	III/II	73/68	60/54	27/32
SG	72	23.0	III/II	78/81	74/66	21/25
CC	81	40.0	III/II	68/66	57/50	30/35
VA	71	22.0	III/III	72/65	60/50	27/33
RG	67	23.2	III/II	63/66	51/45	20/27

ADM = adrenomedullin measured in basal conditions; EDD = end diastolic dimensions; ESD = end systolic dimensions; LVEF = LV ejection fraction.

ADM, in contrast to other natriuretic peptides, has a multi-tissue origin but being that its production is enhanced by mechanical stretching, it may reflect progressive cardiac impairment.[28,46]

Specifically, in the early phase of acute myocardial infarction, plasma ADM concentrations correlate closely with the severity of heart failure[47] and may offer important prognostic information regarding the risk of mortality also in chronic ischemic dysfunction.[46]

Other data suggest that plasma ADM is related to indices of LV contractility as the noninvasively derived dP/dt[31] also in patients with non ischemic cardiomyopathy can be considered as an independent predictor of the deterioration of left ventricular systolic function.[48] In this study both CRT patients and HF patients of comparable NYHA Class showed significantly higher ADM values than the control group of subjects with normal LV function.

In the subset of patients undergoing CRT studied in the present work, ADM values may reflect a situation of increased neurohumoral activation which could be important for the improvement in LV function at FU. In other words, patients who show at baseline low levels of this peptide could represent a group in whom the dysfunction is so advanced that no improvement, in particular in terms of reverse remodeling, can be expected despite CRT.

Similarly, also in the group of 40 HF patients under conventional drug therapy, the—although small—group who showed reduction in ESD was the one with higher baseline ADM levels.

Moreover, when outcome is considered, both CRT and HF patients under conventional treatment who show major events at FU present lower baseline ADM levels.

It is interesting to note that in the patients studied, 38 showed NYHA Class improvement while ESD reduction was found in 21 patients only. This result is not surprising; other reports have shown that after CRT, improvement in NYHA class without reductions in LV end-systolic volume may occur and this observation can be explained by the presence of a placebo effect after the procedure.[36,49]

Limitations of the Study

The main limit of this observational work is represented by the small number of patients

Table IIb.

Individual Data of 29 Patients Who Showed a <10% Reduction in ESD at Baseline (Pre) and at FU (Post)

Name	Age (Years)	ADM, pmol/L	NYHA Pre/Post	EDD Pre/Post	ESD Pre/Post	LVEF Pre/Post
BA	78	18.0	III/III	68/70	52/51	18/17
LR	68	24.0	III/III	61/63	48/52	26/26
AF	79	12.0	III/III	61/64	54/54	28/27
GF	62	15.9	III/III	67/69	52/53	32/32
DM	67	16.2	III/III	64/59	49/48	30/38
RM	70	9.0	III/III	84/88	80/78	25/20
MM	52	17.5	III/III	76/80	71/75	25/10
CA	55	20.0	III/III	72/74	64/68	15/16
MA	72	22.6	IV/IV	79/83	68/72	20/17
LS	58	9.0	III/III	59/56	54/48	16/22
CS	75	20.0	III/III	77/80	70/74	18/15
SM	68	32.0	III/III	70/71	55/49	32/35
BF	62	18.0	III/I	62/60	57/52	24/34
MG	77	14.0	III/II	72/68	62/58	25/30
SL	74	12.0	III/I	60/57	52/50	30/31
ML	74	16.0	III/I	62/58	50/47	25/33
PG	61	12.0	IV/III	63/73	66/63	25/27
PC	79	23.4	III/II	65/71	60/63	21/18
RB	69	19.0	III/II	68/68	56/59	32/28
SA	71	19.0	III/II	63/57	50/50	30/31
CA	77	16.0	III/II	58/54	42/40	34/38
FR	71	22.3	III/II	72/68	65/60	30/36
BA	82	20.0	IV/II	78/80	69/63	20/24
DG	79	20.0	III/II	68/61	52/49	35/36
GD	75	12.0	III/II	71/69	60/57	25/31
DR	68	23.2	III/I	60/58	50/48	32/37
CR	65	8.0	III/I	67/68	57/58	28/30
LM	85	24.0	III/II	61/50	48/44	18/30
LS	78	24.0	III/II	62/59	50/47	28/40

ADM = adrenomedullin measured in basal conditions; EDD = end-diastolic dimensions; ESD = end-systolic dimensions; LVEF = LV ejection fraction.

studied; therefore, since no other data are available in literature on CRT patients, more extensive studies are needed to confirm our observations. We cannot provide clinically valuable data on the changes of ADM during FU due to the limited number of patients enrolled; changes in NYHA Class which were documented in our population after CRT could by itself be related to changes in ADM levels. Also, in the HF group only a minority of patients had plasma levels assay for ADM at FU. Therefore, prospective, multicenter studies may be specifically tailored for this purpose.

Conclusions

Until present, we should be considerate in asserting whether or not a patient may respond to CRT; sticking to the guidelines when selecting patients for CRT is still highly recommended.

However, despite the small group of patients enrolled in this study, the assessment of baseline ADM may provide a better definition of patients who could show significant LV reverse remodeling after CRT.

Acknowledgement: The Authors wish to thank Giuseppe Rossi, B. Sc., for his help in statistical analysis.

References

1. McMurray JV, Pfeffer MA. Heart failure. Lancet 2005; 365:1877–1888.
2. Ferrari R, Ceconi C, Curello S, Visioli O. The neuroendocrine and sympathetic nervous system in congestive heart failure. Eur Heart J 1998; 19:F45–F51.
3. Francis GS. Pathophysiology of chronic heart failure. Am J Med 2001; 110:37S–46S.
4. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998; 351:9–13.
5. Stanek B, Frey B, Hülsmann M, Berger R, Sturm B, Strametz-Juranek J, Bergler-Klein J, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. J Am Coll Cardiol 2001; 38:436–442.
6. Angermann CE, Ertl G. Natriuretic peptides—new diagnostic markers in heart disease. Herz 2004; 29:609–617.
7. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997; 96:509–516.
8. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001; 104:3026–3029.
9. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–1549.
10. Saxon LA, Ellenbogen KA. Resynchronization therapy for the treatment of heart failure. Circulation 2003; 108:1044–1048.
11. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003; 107:1985–1990.
12. Rossi A, Rossi G, Startari U, Panchetti L, Piacenti M, Morales MA. The current role of cardiac resynchronization therapy in reducing mortality and hospitalization in heart failure patients. A meta-analysis from clinical trials. Heart Vessels 2008; 23:217–223.
13. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2007; 18:2256–2295.
14. Braun MU, Rauwolf T, Zerm T, Schulze M, Schnabel A, Strasser RH. Long term biventricular resynchronisation therapy in advanced heart failure: Effect on neurohormones. Heart 2005; 91:601–605.
15. Kubanek M, Malek I, Bytesnik J, Fridl P, Riedlbauchova L, Karasova L, Lanska V, et al. Decrease in plasma B-type natriuretic peptide early after initiation of cardiac resynchronization therapy predicts clinical improvement at 12 months. Eur J Heart Failure 2006; 8:832–840.
16. Molhoek SG, Bax JJ, Van Erven L, Bootsma M, Steendijk P, Lenties E, Boersma E, et al. Atrial and brain natriuretic peptides as markers of response to resynchronisation theraphy. Heart 2004; 90:97–98.
17. Ricciardi C, Pieragnoli P, Colella A, Giaccardi M, Padeletti L, Abbate R, Gensini GF, et al. Role of natriuretic peptides in heart failure patients with special reference on cardiac resyncronization therapy. Minerva Cardioangiol 2006; 54:743–752.
18. Lellouche N, De Diego C, Cesario DA, Vaseghi M, Natterson Horowitz B, Mahajan A, Wiener I, et al. Usefulness of preimplantation B-type natriuretic peptide level for predicting response to cardiac resynchronization therapy. Am J Cardiol 2007; 99:242–246.
19. Pitzalis MV, Iacoviello M, Di Serio F, Romito R, Guida P, De Tommasi E, Luzzi G, et al. Prognostic value of brain natriuretic peptide management of patients receiving cardiac resynchronization therapy. Eur J Heart Fail 2006; 8:509–514.
20. Fruhwald FM, Fahrleitner-Pammer A, Berger R, Leyva F, Freemantle N, Erdmann E, Gras D, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. Eur Heart J 2007; 28:1592–1597.
21. Maeda K, Tsutamoto T, Wada A, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol 2000; 36:1587–1593.
22. Cappola TP, Harsch MR, Jessup M, Abraham WT, Young JB, Petersen-Stejskal S, Plappert T, et al. Predictors of remodeling in the CRT era: Influence of mitral regurgitation, BNP, and gender. J Card Fail 2006; 122:182–188.
23. Wang RX, Guo T, Li XR. BNP/NT-ProBNP and cardiac pacing: A review. Pace 2009; 32:794–799.
24. Pousset F, Masson F, Chaviroskaia O, Isnard R, Carayon A, Golmard JL, Lechat P, et al. Plasma adrenomedullin, a new independent predictor of prognosis in patients with chronic heart failure. Eur Heart J 2000; 21:1009–1014.
25. Ishimitsu T, Ono H, Minami J, Matsuoka H. Pathophysiologic and therapeutic implications of adrenomedullin in cardiovascular disorders. Pharmacol Therapet 2006; 111:909–927.
26. Parkes DG. Cardiovascular actions of adrenomedullin in conscious sheep. Am J Physiol 1995; 268:H2574–H2578.
27. Tian Q, Zhao D, Tan DY, Zhao YT, Li QH, Qiu JX, Song LW, et al. Vasodilator effect of human adrenomedullin (13–52) on hypertensive rats. Can J Physiol Pharmacol 1995; 73:1065–1069.
28. Nishikimi T, Saito Y, Kitamura K, Ishimitsu T, Eto T, Kangawa K, Matsuo H, et al. Increased plasma levels of adrenomedullinin patients with heart failure. J Am Coll Cardiol 1995; 26:1424–1431.
29. Jougasaki M, Rodeheffer RJ, Redfield MM, Yamamoto K, Wei CM, McKinley LJ, Burnett JC Jr., et al. Cardiac secretion of adrenomedullin in human heart failure. J Clin Invest 1996; 97:2370–2376.
30. World Medical Organization. Declaration of Helsinki. Br Med J 1996; 313:1448–1449.
31. Morales M-A, Del Ry S, Startari U, Maltinti M, Prontera C, Emdin M, Giannessi D. Plasma adrenomedullin relation with Doppler derived dP/dt in patients with congestive heart failure. Clin Cardiol 2006; 29:126–130.
32. Clerico A, Iervasi G, Del Chicca MG, Emdin M, Maffei S, Nannipieri M, Sabatino L, et al. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. J Endocrinol Invest 1998; 21:170–179.
33. Del Ry S, Clerico A, Giannessi D, Andreassi MG, Caprioli R, Iascone MR, Biagini A, et al. Measurement of BNP in plasma samples in cardiac tissue extracts by means of an IRMA method. Scand J Clin Lab Invest 2000; 60:81–90.
34. Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman NH, et al. Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation 1979; 60:547–555.
35. Pilo A, Zucchelli GC, Malvano R, Masini S. Main features of computer algorithms for RIA data reduction. Comparison of same different approaches for the interpolation of dose-response curve. J Nucl Med All Sci 1982; 26:235–248.
36. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845–1853.
37. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350:2140–2150.
38. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, et al. Systematic review: Cardiac resynchronization in patients with symptomatic heart failure. Ann Int Med 2004; 141:381–390.
39. Boriani G, Biffi M, Martignani C, Fallani F, Greco C, Grigioni F, Corazza I, et al. Cardiac resynchronization by pacing: An electrical treatment of heart failure. Int J Cardiol 2004; 94:151–161.
40. Cleland JG, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, et al. Predicting the long-term effects of cardiac resynchronisation therapy on mortality from baseline variables and the early response: A report from CARE-HF (Cardiac Resynchronisation in Heart Failure). J Am Coll Cardiol 2008; 52:438–445.
41. Sitges M, Vidal B, Delgado V, Mont L, Garcia-Alvarez A, Tolosana JM, Castel A, et al. Long-term effect of cardiac resynchronization therapy on functional mitral valve regurgitation. Am J Cardiol 2009; 104:383–388.
42. Marsan NA, Bleeker GB, Ypenburg C, Van Bommel RJ, Ghio S, Van de Veire NR, Delgado V, et al. Real-time three-dimensional

echocardiography as a novel approach to assess left ventricular and left atrium reverse remodeling and to predict response to cardiac resynchronization therapy. Heart Rhythm 2008; 5:1257–1264.
43. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E; VIGOR Congestive Heart Failure Investigators. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodelling. Circulation 2002; 105:1304–1310.
44. Sinha AM, Filzmaier K, Breithardt OA, Kunz D, Graf J, Markus KU, Hanrath P, et al. Usefulness of brain natriuretic peptide release as a surrogate marker of the efficiency of long-term cardiac resynchronization therapy in patients with heart failure. Am J Cardiol 2003; 91:755–758.
45. Cleland JGF, Tavazzi L, Daubert JC, Tageldien A, Freemantle N. CRT: Are modern myths preventing appropriate use? J Am Coll Cardiol 2009; 53:608–611.
46. Richards AM, Doughty R, Nicholls MG, MacMahon S, Sharpe N, Murphy J, Espiner EA, et al. Plasma N-Terminal Pro-Brain natriuretic peptide and adrenomedullin. J Am College Cardiol 2001; 37:1781–1787.
47. Miyao Y, Nishikimi T, Goto Y, Miyazaki S, Daikoku S, Morii I, Matsumoto T, et al. Increased plasma adrenomedullin levels in patients with acute myocardial infarction in proportion to the clinical severity. Heart 1998; 79:39–44.
48. Katayama T, Nakashima H, Honda Y, Suzuki S, Yano K. Relationship between adrenomedullin and left-ventricular systolic function and mortality in acute myocardial infarction. Angiology 2005; 56:34–52.
49. Bleeker GB, Bax JJ, Wing-Hong Fung J, van der Wall EE, Zhang Q, Schalij MJ, Yat-Sun Chan J, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. Am J Cardiol 2006; 97:260–263.