Effect of Cardiac Resynchronization Therapy on Left Atrial Reverse Remodeling and Spontaneous Echo Contrast

AHMET VURAL, AYSEN AĞAÇDIKEN, DILEK URAL, TAYFUN ŞAHİN, GULİZ KOZDAĞ, GÖKSEL KAHRAMAN, ERTAN URAL, HALUK AKBAŞ,¹ KAYA SÜZER¹ and BAKİ KOMSUOĞLU

Department of Cardiology, and ¹Department of Cardiovascular Surgery, Kocaeli University Medical Faculty, Kocaeli, Turkey

VURAL, A., AĞAÇDIKEN, A., URAL, D., ŞAHİN, T., KOZDAĞ, G., KAHRAMAN, G., URAL, E., AKBAŞ, H., SÜZER, K. and KOMSUOĞLU, B. *Effect of Cardiac Resynchronization Therapy on Left Atrial Reverse Remodeling and Spontaneous Echo Contrast.* Tohoku J. Exp. Med., 2004, **202** (2), 143-153 — Recent studies revealed reverse remodeling in left ventricle with cardiac resynchronization therapy (CRT). However, effects on left atrial remodeling, left atrial total emptying fraction and left atrial spontaneous echo contrast (SEC) have not been adequately evaluated. The aim of this study was to investigate the long-term changes in SEC, left atrial reverse remodeling, and left atrial total emptying fraction after CRT. Twenty patients with systolic heart failure and complete left bundle-branch block underwent implantation of biventricular pacemaker devices. Transthoracic and transesophageal echocardiography were performed one week before and one and six months after pacemaker implantation. After biventricular pacemaker implantation, significant clinical improvement was observed in all patients. Left atrial maximal and minimal volumes showed a significant progressive decline after CRT (reverse remodeling). Left atrial total emptying ejection fraction (LATEF) was $33\pm 19\%$ at baseline and increased to $37\pm 10\%$ and $41\pm 11\%$ at the 1st and 6th months respectively ($p=0.01$ and $p=0.04$). SEC was detected in 18 of 20 patients (90%) at the beginning of the study. After six months SEC disappeared in 5 patients and frequency of SEC reduced to 45%. Decrease in the intensity of the SEC was also statistically significant (at the 1st and 6th months; $p=0.001$ and $p<0.001$ respectively). Long-term CRT results in atrial reverse remodeling, increases LATEF, and reduces both frequency and intensity of atrial SEC. ——— cardiac resynchronization; atrial reverse remodeling; SEC

© 2004 Tohoku University Medical Press

Received October 22, 2003; revision accepted for publication January 5, 2004.

Address for reprints: Ahmet Vural, M.D., Fatih Mahallesi, Seymen Doktorlar Sitesi, B-Blok No: 7, 41100 Kuruçeşme/Kocaeli, Turkey.

e-mail: drahmetvural@superonline.com

In patients with heart failure, the most frequent type of interventricular conduction delay is left bundle-branch block (Doval et al. 1994; Aaronson et al. 1997). Conduction delay leads to abnormal ventricular depolarization and disturbance of the synchrony between inter- and intraventricular contraction and relaxation (Hardarson et al. 1987; Grines et al. 1989; Xiao et al. 1992; Fahy et al. 1996; Nelson et al. 2000; Saxon et al. 2000). Disturbance of ventricular synchrony causes a shortening in diastolic filling and effective ejection time, reduces stroke volume, prolongs mitral regurgitation and leads to an increase in global and regional wall stress (Grines et al. 1989; Xiao et al. 1992; Nelson et al. 2000). Previous studies have shown that interventricular conduction delay is also an independent predictor of deteriorated functional capacity and cardiac mortality in these patients (Doval et al. 1994; Xiao et al. 1996; Aaronson et al. 1997).

Although not specifically studied for this particular group of patients, left atrial spontaneous echo contrast (SEC) is frequently observed by transesophageal echocardiography in patients with left ventricular systolic dysfunction (Balck et al. 1991; Bilge et al. 1999). In patients with dilated cardiomyopathy (CMP) SEC is strongly related to left ventricular ejection fraction, cardiac output, left atrial diameter and left atrial flow velocities and is an indicator for subsequent thromboembolic events (Daniel et al. 1988; Castello et al. 1990; Siostrzonek et al. 1993).

Cardiac resynchronization therapy leads to an acute and sustained improvement in left ventricular systolic function (Auricchio et al. 1999; Kass et al. 1999; Kerwin et al. 2000). Restoration of ventricular synchrony increases functional capacity, lengthens exercise duration and improves life quality (Gras et al. 1998; Abraham 2000; Zardini et al. 2000; Cazeau et al. 2001).

Recent studies revealed a reverse remodeling in left ventricle with cardiac resynchronization therapy (Saxon et al. 1998; Lau et al. 2000; Stellbrink et al. 2001; Sogaard et al. 2002; Pitzalis et al. 2002). However, changes in left atrial

remodeling and effects on SEC have not been adequately evaluated. The aim of this study was to investigate the long-term effects of cardiac resynchronization therapy on left atrial SEC, left atrial reverse remodeling, left atrial total emptying fraction, left ventricular remodeling and systolic function in patients with dilated CMP and left bundle branch block.

METHODS

Patients

The study group consisted of 20 patients with dilated CMP who had been referred to our clinic for biventricular pacemaker implantation (Table 1). All cases had PR interval ≥ 160 milliseconds, QRS duration ≥ 150 milliseconds and left bundle branch block pattern. On echocardiographic examination, all patients had ejection fraction $<35\%$, left ventricular end-diastolic diameter >56 mm and asynchronous left ventricular contraction. Functional capacity was NYHA III in 13 cases and NYHA IV in 7 cases.

Exclusion criteria were age younger than 18 years, history of a recent acute coronary syndrome (<3 months), recent coronary by-pass operation (<3 months), terminal disease other than cardiovascular diseases, expected survival less than 1 year, right bundle branch block and incomplete left bundle branch block.

All patients received optimal pharmacological treatment before and after pacemaker implantation. Oral anticoagulation therapy was given to three patients because of atrial fibrillation and one patients because of high-grade SEC before and after implantation. Betablockers were started to all patients and continued in those who could tolerate them.

Pacemaker implantation

All patients underwent ambulatory ECG (electrocardiography) monitoring before pacemaker implantation. Electrophysiological study was performed in patients with complex ventricular arrhythmias. Medtronic InSync ICD (implantable cardioverter defibrillator) (model

TABLE 1. *Baseline clinical characteristics of the patients*

Patient (=n)	20
Female/Male	7 / 13
Etiology of cardiomyopathy (ischemic/nonischemic)	7 / 13
NYHA III/IV	13 / 7
Rhythm (sinus/atrial fibrillation)	17 / 3
QRS (msec)	172±14
Baseline PR interval (msec)	193±17
LBBB (%)	100
Diuretic (%)	90
ACE-I (%)	75
Digoxin (%)	40
Beta-blocker (%)	45
Spironolactone (%)	50
Warfarin (%)	20
Amiodarone (%)	35

Fig. 1. Standard orthogonal apical four and two chamber views

7272, Medtronic Inc., Minneapolis, MN, USA) was implanted in three patients with a history of presyncope-syncope, clinically detected complex ventricular arrhythmias, and monomorphic ventricular tachycardia induced by electrophysiologi-

cal study. Three patient with permanent atrial fibrillation received Medtronic VVIR biventricular pacemaker. In the other 14 patients Medtronic InSync III biventricular pacemaker (model 8042, Medtronic Inc.) was implanted.

Right atrial and right ventricular stimulation leads were implanted using a transvenous approach. In three patients, the left ventricular epicardial lead was placed using a limited thoracotomy. One week after the implantation atrio-ventricular delay optimization was performed by transthoracic echocardiographic examination (TTE).

Echocardiography

Transthoracic and transesophageal echocardiography (TEE) were performed with Toshiba SSA-390A ultrasound machine (Tokyo). TTE examinations were performed with a 2.5 MHz transducer from standard parasternal and apical views one week before pacemaker implantation. Left ventricular wall thickness, left atrial and left ventricular dimensions were measured from parasternal long axis M-mode tracings according to standard criteria (Sahn et al. 1978). Left ventricular ejection fraction was estimated from the apical four-chamber view using Simpson method (Schiller et al. 1989).

Left atrial maximum and minimum areas, maximum and minimum long diameters at mitral valve opening and mitral valve closure were measured from apical views (Gutman et al. 1983; Basnight et al. 1991). Left atrial maximum and minimum volumes (LAV_{max} and LAV_{min}) were determined from orthogonal apical views using the biplane area-length method (Fig. 1). Left atrial total emptying fraction (LATEF) was estimated as follows: $100 \times (LAV_{max} - LAV_{min}) / LAV_{max}$.

Mitral regurgitation was evaluated by color-Doppler echocardiography. Gradient of regurgitation was assessed as follows: Grade-0=none; grade-1=mild; grade-2=moderate and grade-3=severe.

Transesophageal echocardiography was performed with a 5 MHz multiplane probe (PEF-S1 OMA) while the patients were in left lateral position (Seward et al. 1990). TEE procedure was explained to all patients. Hypopharynx analgesia was achieved with 10% xylocain spray.

Two observers without regard to the clinical

and transthoracic echocardiographic data determined presence and severity of left atrial SEC independently. Left atrial SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artifact (Castello et al. 1990). Grade of SEC was classified in 4 classes as follows: Grade-0=none (absence of echogenicity); grade-1=mild (minimal echogenicity located in the left atrial appendage or sparsely distributed in the main cavity of the left atrium; may be detectable only transiently during the cardiac cycle; barely visible at operating gain settings for two-dimensional echocardiographic analysis); grade-2=moderate (dense swirling pattern in the left atrial appendage; generally associated with somewhat lesser intensity in the main cavity; detectable constantly throughout the cardiac cycle without increased gain settings); grade-3=severe (intense echodensity and very slow swirling patterns in the left atrial appendage, usually with similar density in the main cavity) (Balck et al. 1991; Fatkin et al. 1994a, b).

TTE and TEE examinations were repeated at the 1st and 6th months after pacemaker implantation. Written informed consent was obtained from all patients. The study was approved by the Local Ethical Committee.

Statistical analysis

Data is given as mean and standard deviation. Echocardiographic findings in pre-implantation period, at 1st and 6th months were compared with each other using Wilcoxon signed-rank test. A *p*-value less than 0.05 was accepted as statistical significance.

RESULTS

After biventricular pacemaker implantation, significant clinical improvement was observed in all patients. Class of functional capacity decreased in 1st and 6th months after implantation compared to basal levels ($p < 0.05$). Exercise testing performed with Naughton protocol revealed a significant increase in exercise duration ($p < 0.001$

TABLE 2. *Exercise duration and functional capacity of the patients before and after implantation*

	Baseline	1 Month	6 Month
NYHA-functional capacity	3.1±0.5	2.4±0.5*	2.2±0.5*
Exercise duration (Naughton protocol)	9.2±3.4	12.5±3.6*	13.6±5*

* $p<0.001$. Baseline parameters compared with 1st and 6th month parameters after implantation.

TABLE 3. *Echocardiographic parameters of the patients before and after CRT*

	Baseline	1 Month	6 Month	P1 (B -1)	P2 (B-6)	P3 (1-6)
LVEDD	70±9	66±8	64±10	<0.001	<0.001	NS
LVESD	60±9	54±10	52±12	<0.001	0.001	NS
LVEDV	228±70	196±60	187±55	<0.001	0.001	0.04
LVESV	180±71	139±58	132±51	<0.001	0.002	NS
EF	23±7	31±8	32±10	<0.001	<0.001	NS
FS	12.4±3	16±5	17±5	0.002	<0.001	NS
CI	2.1±0.5	2.5±0.5	2.7±0.5	0.007	<0.001	0.02
LAD	44±3.2	42.4±3	41±3	0.003	0.001	0.007
LALD _{max}	58±16	61±8	60±9	NS	NS	NS
LALD _{min}	56±9	53±9	52±10	0.02	0.01	NS
LAV _{max}	91±38	74±20	69±21	0.003	0.005	NS
LAV _{min}	56±21	47±15	42±16	0.004	0.001	0.03
LA SEC	1.75±1	1.1±0.8	0.8±0.7	0.001	<0.001	0.03
LATEF	33±19	37±10	41±11	0.01	0.04	NS

P1 (B-1): Baseline and 1 month (m) after the CRT, P2 (B-6): baseline and 6 m, P3 (1-6) 1 m and 6 m. LVEDD: Left ventricular end-diastol dimension (mm), LVESD: Left ventricular end systolic dimension (mm), LVEDV: Left ventricular end-diastolic volume (ml), LVESV: Left ventricular end systolic volume, EF: Left ventricular ejection fraction (%), FS: Fractional shortening (%), CI: Cardiac index L/dk/m², LAD: Left atrial dimension from parasternal long axis (mm), LALD_{max} and LALD_{min}: Left atrial longitudinal maximum and minimum dimension from apical four chamber views (mm), LAV_{max}: Left atrial maximum volume (ml), LAV_{min}: Left atrial minimum volume (ml).

and $p<0.001$) (Table 2).

In echocardiographic examination, left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV) decreased significantly 1 and 6 months after implantation when compared to baseline values (Table 3).

Decrease in left ventricular volumes and diameters continued between the 1st and 6th months, however while the decrease in left ventricular end-diastolic volume was statistically

significant ($p=0.04$), reduction in end-systolic volume remained statistically insignificant ($p=0.06$).

Ejection fraction, fractional shortening and cardiac index showed a significant increase after biventricular pacemaker implantation. Increase in cardiac index continued between the 1st and 6th months; however difference for the other parameters was not statistically significant.

Left atrial diameter measured from parasternal long axis view and left atrial minimum diameter measured from apical view decreased

Fig. 2a-c. Changes in left atrial volumes and total emptying fraction before and after implantation. *: $p < 0.05$, baseline parameters compared with 1st and 6th months parameters.

progressively in the follow-up period. There was not any significant change in left atrial maximum diameter.

Significant changes were observed in LAV_{max}

Fig. 3. Intensity of the left atrial SEC. *: $p < 0.05$, baseline parameters compared with 1st and 6th months parameters. LA SEC: Left atrial spontaneous echocontrast.

and LAV_{min} . Both of them showed a progressive decrease in 6 months after cardiac resynchronization therapy. Together with the changes in size and volume of left atrium, LATEF increased also significantly in the 1st and 6th months when compared to baseline values. Left atrial changes continued between 1st and 6th months, however difference was not statistically significant except LAV_{min} values (Figs. 2 a-c) (Table 3).

Mitral regurgitation was detected in 19 of the patients (95%) before biventricular pacemaker implantation. Severity of mitral regurgitation was grade 1 in 7, grade 2 in 7 and grade 3 in 5 patients. One month after biventricular stimulation, severity of mitral regurgitation changed as follows: grade 1 in 9, grade 2 in 6 and grade 3 in 3 patients. In the 6th month, mitral regurgitation was grade 1 in 8, grade 2 in 4 and grade 3 in 2 patients. Change in the severity of mitral regurgitation in the follow-up period was statistically significant ($p < 0.05$).

Left atrial SEC was detected in 18 patients (90%) before pacemaker implantation. Severity of SEC was grade 1 in 5 (25%), grade 2 in 9 (45%) and grade 3 in 4 (20%) of the patients. Grade 3 SEC has not been observed in any patient one month after cardiac resynchronization. In the 6th month, SEC disappeared in 5 of the cases. Before

Fig. 4. Frequency and intensity of the left atrial SEC.

■, Grade-3; ■, Grade-2; ■, Grade-1; □, Grade-0.

implantation, mean grade of left atrial SEC was 1.75 ± 1 ; in the 1st and 6th months it decreased to 1.1 ± 0.8 and 0.8 ± 0.7 respectively ($p=0.001$ and $p<0.001$ compared to pre-implantation). Decrease in the intensity of the SEC also was statistically significant between 1st and 6th months ($p=0.03$) (Figs. 3 and 4).

Oral anticoagulation treatment had no significant additional effect on the decrease of SEC. Changes in the frequency and severity of SEC were similar between patients with and without anticoagulation therapy.

DISCUSSION

Improvement in clinical status, left ventricular systolic function and left ventricular reverse remodeling has been observed in various studies after cardiac resynchronization therapy (Saxon et al. 1998; Kerwin et al. 2000; Lau et al. 2000; Stellbrink et al. 2001; Pitzalis et al. 2002; Sogaard et al. 2002). However, effects of cardiac resynchronization therapy on atrial remodeling, left atrial function and SEC have not been evaluated. The objectives of this study was to investigate the effects of biventricular pacing on left atrial reverse remodeling, left atrial total emptying fraction and SEC in association with left ventricular reverse remodeling.

Left ventricular systolic function and reverse remodeling

In our study, we observed a significant improvement in left ventricular systolic function after cardiac resynchronization therapy. This improvement was apparent in the first month after treatment, and continued until 6th month. Parallel to the increase in left ventricular systolic function, a significant decrease in left ventricular end-diastolic and end-systolic volumes was detected after 1 and 6 months compared to baseline values.

Increase of left ventricular systolic function is a well-known effect of biventricular pacing (Kass et al. 1990; Blanc et al. 1997; Gras et al. 1998; Saxon et al. 2000). However, studies about left ventricular remodeling have been published only in recent years. In a 3 months follow-up study, Lau et al. (2000) showed a progressive decrease in left ventricular end-systolic and end-diastolic diameters and volumes in 11 patients after cardiac resynchronization therapy. In a study consisted of 53 patients, Saxon et al. (1998) got similar findings after a 12 weeks follow-up period. Results of our study are consistent with these previous findings and showed further that, significant changes in left ventricular volumes start already in the first month, and although slower, continue at least until 6 months after biventricular pacing.

Left ventricular reverse remodeling may be attributed to the improvement in left ventricular wall motion asynchrony, increase in contraction, and decrease in mitral regurgitation in addition to the decrease in left ventricular filling pressures. Decrease in peripheral resistance following the increase in cardiac output may also have decreased the left ventricular afterload and augmented the favorable remodeling in left ventricle (Capomolla et al. 2000).

The finding of progressive reduction in left ventricular volumes supports the previous data, that reverse remodeling observed after cardiac resynchronization is not solely a result of correction of conduction delay, but is a change emerging in a time-dependent manner (Saxon et al. 1998; Lau et al. 2000).

Left atrial reverse remodeling and LATEF

After resynchronization treatment, left atrial diameters shortened and left atrial volumes diminished significantly. LATEF has also showed a significant enhancement. Similar to the changes in left ventricle, left atrial changes were also more evident in the 1st month and slowed down in the following period.

Saxon et al. (1998) reported a significant reduction in atrial volume index simultaneous with reverse ventricular remodeling 12 weeks after resynchronization treatment. Findings of our study support the results of Saxon et al. and shows that changes in left atrium starts earlier after implantation and continues at least until the 6th month. In our study, we also detected a significant increase in LATEF.

Atrial reverse remodeling and increase in the LATEF may be related to the improvement in left ventricular contraction, reduction of left ventricular end-systolic and end-diastolic volumes, decrease in mitral regurgitation and subsequently to the diminish in left atrial volume and pressure.

Rossi et al. (2002) showed an independent prognostic value of LAV_{max} in patients with dilated CMP. Determinants of LAV were low ejection fraction, large left ventricular end-diastolic vol-

ume, degree of mitral regurgitation, atrial fibrillation, and mitral flow E to A ratio. Patients with a LAV higher than 68.5 ml/m^2 had a 3.8 times higher prognostic risk compared to patients with lower volumes. Decrease in LAV_{max} and reverse atrial remodeling achieved with biventricular pacing treatment may exert favorable effects on prognosis of patients with dilated CMP.

Effect of biventricular pacing on left atrial SEC

Left atrial SEC is a frequent finding in patients with left ventricular systolic dysfunction (Siostrzonek et al. 1993; Bilge et al. 1999). Although it represents a relatively common event, underlying etiology is still not clear. In-vitro studies revealed that low blood flow velocity and erythrocyte aggregation play an important role in SEC development (Sigel et al. 1981).

Siostrzonek et al. (1993) showed that, in patients with dilated CMP, left atrial SEC occurs more frequently in those with larger left atrial diameters, lower cardiac output and left atrial flow velocities. In the same study, left ventricular systolic function and atrial fibrillation appeared as the most important determinants atrial flow velocity. In the study of Shiari and Mark (2000) left atrial diameter was an independent risk factor for the development of left atrial SEC in patients with sinus rhythm. Erythrocyte aggregation abnormalities in dilated CMP patients may also play a facilitating role for development of SEC (Siostrzonek et al. 1992).

In our study, left atrial SEC was detected in 18 (90%) of the patients before resynchronization treatment. The higher frequency of SEC observed in our study compared to previous reports (Vigna et al. 1992; Siostrzonek et al. 1993; Bilge et al. 1999) can be explained by more severe left ventricular systolic dysfunction and larger cardiac chambers of our cases.

After cardiac resynchronization treatment, frequency of SEC decreased gradually and in the 6th month it disappeared in 5 of 18 patients (28%). Grade 3 SEC detected in 20% of the patients

before resynchronization treatment has not been observed in any patient after 1 month.

Decrease in frequency and intensity of SEC may also be explained by left atrial and ventricular reverse remodeling, and improved cardiac function. An enhanced left ventricular systolic function decreases the left ventricular end-diastolic pressure, and augments the rapid filling of the left ventricle. Decrease in left atrial pressure and the reverse remodeling of the left atrium improves the left atrial systolic function. These changes contribute to the decrease in blood stasis in left atrium and lead to decrease in SEC.

The relation between left atrial SEC, thrombus formation and thromboembolic events has been confirmed in many studies (Daniel et al. 1988; Castello et al. 1990). The favorable effect of biventricular pacing on SEC suggests that a decrease in thromboembolic events may be achieved by this new treatment.

References

- Aaronson, K.D., Schwartz, J.S., Chen, T.M., Wong, K.L., Goin, J.E. & Mancini, D.M. (1997) Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*, **95**, 2260-2267.
- Abraham, W.T. (2000) Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J. Card. Fail.*, **6**, 369-380.
- Auricchio, A., Stellbrink, C., Block, M., Sack, S., Vogt, J., Bakker, P., Klein, H., Kramer, A., Ding, J., Salo, R., Tockman, B., Pochet, T. & Spinelli, J. (1999) Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation*, **99**, 2993-3001.
- Balck, I.W., Hopkins, A.P., Lee, L.C., Walsh, W.F. & Jacobson, B.M. (1991) Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. *J. Am. Coll. Cardiol.*, **18**, 398-404.
- Basnight, M.A., Gonzalez, M.S., Kershenovich, S.C. & Appleton, C.P. (1991) Pulmonary venous flow velocity: relation to hemodynamics, mitral flow velocity and left atrial volume and ejection fraction. *J. Am. Soc. Echocardiogr.*, **4**, 547-558.
- Bilge, M., Güler, N., Eryonucu, B. & Aşker, M. (1999) Frequency of left atrial thrombus and spontaneous echocardiographic contrast in acute myocardial infarction. *Am. J. Cardiol.*, **84**, 847-849.
- Blanc, J.J., Etienne, Y., Gilard, M., Mansourati, J., Munier, S., Bosch, J., Benditt, D.G. & Lurie, K.G. (1997) Evaluation of different ventricular pacing sites in patients with severe heart failure. Results of an acute hemodynamic study. *Circulation*, **96**, 3273-3277.
- Capomolla, S., Febo, O., Gnemmi, M., Riccardi, G., Opasich, C., Caporotondi, A., Mortara, A., Pinna, G.D. & Cobelli, F. (2000) Beta-blockade therapy in chronic heart failure. Diastolic function and mitral regurgitation improvement by carvedilol. *Am. Heart J.*, **139**, 596-608.
- Castello, R., Pearson, A.C. & Labovitz, A.J. (1990) Prevalence and clinical implications of atrial spontaneous echo contrast in patients undergoing transesophageal echocardiography. *Am. J. Cardiol.*, **65**, 1149-1153.
- Cazeau, S., Leclercq, C., Lavergne, T., Walker, S., Varma, C., Linde, C., Garrigue, S., Kappenberger, L., Haywood, G.A., Santini, M., Bailleul, C. & Daubert, J.C. (2001) Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effect of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N. Eng. J. Med.*, **344**, 873-880.
- Daniel, W.G., Nellessen, U., Schröder, E., Nonnast-Daniel, B., Bednarski, P. & Lichtlen, P.R. (1988) Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. *J. Am. Coll. Cardiol.*, **11**, 1204-1211.
- Doval, H.C., Nul, D.R., Grancelli, H.O., Perrone, S.V., Bortman, G.R. & Curiel, R. (1994) Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet*, **344**, 493-498.
- Fahy, G.J., Pinski, S.L., Miller, D.P., McCabe, N., Pye, C., Walsh, M.J. & Robinson, K. (1996) Natural history of left bundle branch block. *Am. J. Cardiol.*, **77**, 1185-1190.
- Fatkin, D., Herbert, E. & Feneley, M.P. (1994a) Hematologic correlates of spontaneous echo contrast in patients with atrial fibrillation and implications for thromboembolic risk. *Am. J. Cardiol.*, **73**, 672-676.
- Fatkin, D., Kelly, R.P. & Feneley, M.P. (1994b) Relations between left atrial appendage blood flow

- velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J. Am. Coll. Cardiol.*, **23**, 961-969.
- Gras, D., Mabo, P., Tang, T., Luttikuis, O., Chatoor, R., Pedersen, A.K., Tscheliessnigg, H.H., Deharo, J.C., Puglisi, A., Silvestre, J., Kimber, S., Ross, H., Ravazzi, A., Paul, V. & Skehan, D. (1998) Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc Sync study. *Pacing Clin. Electrophysiol.*, **21**, 2249-2255.
- Grines, C.L., Bashore, T.M., Boudoulas, H., Olson, S., Shafer, P. & Wooley, C.F. (1989) Functional abnormalities in isolated left bundle branch block: the effect of interventricular asynchrony. *Circulation*, **79**, 845-853.
- Gutman, J., Wang, Y.S., Wahr, D. & Schiller, N.B. (1983) Normal left atrial function determined by 2-dimensional echocardiography. *Am. J. Cardiol.*, **51**, 336-340.
- Hardarson, T., Arnason, A., Eliasson, G.J., Palsson, K., Eyjolfsson, K. & Sigfusson, N. (1987) Left bundle branch block: prevalence, incidence, follow-up and outcome. *Eur. Heart J.*, **8**, 1075-1079.
- Kass, D.A., Chen, C.H., Curry, C., Talbot, M., Berger, R., Fetis, B. & Nevo, E. (1999) Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*, **99**, 1567-1573.
- Kerwin, W.F., Botvinick, E.H., O'Connell, J.W., Merrick, S.H., DeMarco, T., Chatterjee, K., Scheibly, K. & Saxon, L.A. (2000) Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. *J. Am. Coll. Cardiol.*, **35**, 1221-1227.
- Lau, C.P., Yu, C.M., Chau, E., Fan, K., Tse, H.F., Lee, K., Tang, M.O., Wan, S.H., Law, T.C., Lee, P.Y., Lam, Y.M. & Hill, M.R. (2000) Reversal of left ventricular remodeling by synchronous biventricular pacing in heart failure. *PACE*, **23**, 1722-1725.
- Nelson, G.S., Berger, R.D., Fetis, B.J., Talbot, M., Spinelli, J.C., Hare, J.M. & Kass, D.A. (2000) Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*, **102**, 3053-3059.
- Pitzalis, M.V., Iacoviello, M., Romito, R., Massari, F., Rizzon, B., Luzzi, G., Guida, P., Andriani, A., Mastropasqua, F. & Rizzon, P. (2002) Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J. Am. Coll. Cardiol.*, **40**, 1615-1622.
- Rossi, A., Ciccoira, M., Zanolli, L., Sandrini, R., Golia, G., Zardini P. & Enriquez-Sarano, M. (2002) Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J. Am. Coll. Cardiol.*, **40**, 1425.
- Sahn, D.J., De Maria, A., Kisslo, J. & Weyman, A. (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*, **58**, 1072-1083.
- Saxon, L.A., Kerwin, W.F., Cahalan, M.K., Kalman, J.M., Olgin, J.E., Foster, E., Schiller, N.B., Shinbane, J.S., Lesh, M.D., Merrick, S.H. (1998) Acute effects of intraoperative multisite ventricular pacing on left ventricular function and activation/contraction sequence in patients with depressed ventricular function. *J. Cardiovasc. Electrophysiol.*, **9**, 13-21.
- Saxon, L.A., Kumar, K.N. & De Marco, T. (2000) Heart failure and cardiac resynchronization therapies: US experience in the year 2000. *Ann. Noninvas. Electrocardiol.*, **5**, 188-194.
- Seward, J., Khandheria, B.K., Edwards, W.D., Oh, J.K., Freeman, W.K. & Tajik, A.J. (1990) Biplanar transesophageal echocardiography: anatomic correlations, image orientation and clinical applications. *Mayo. Clin. Proc.*, **65**, 1193-1213.
- Schiller, N.B., Shah, P.M., Crawford, M., DeMaria, A., Devereux, R., Feigenbaum, H., Gutgesell, H., Reichek, N., Sahn, D. & Schnittger, I. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography. Committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J. Am. Soc. Echocardiography.*, **2**, 358-367.
- Shiari, S. & Mark, V. (2000) Clinical and echocardiographic characteristics of left atrial spontaneous echo contrast in sinus rhythm. *J. Am. Coll. Cardiol.*, **35**, 1932-1938.
- Sigel, B., Coelho, J.C., Spigos, D.G., Flanagan, D.P., Schuler, J.J., Kasprisin, D.O., Nyhus, L.M. & Capek, V. (1981) Ultrasonography of blood during stasis and coagulation. *Invest Radiol.*, **16**, 71-76.
- Siostrzonek, P., Koppensteiner, R., Kreiner, G., Madl, C., Gossinger, H.D., Heinz, G., Stumpf, A.,

- Wendelin, B., Mossbacher, H. & Ehringer, H. (1992) Abnormal blood rheology in idiopathic dilated cardiomyopathy. *Am. J. Cardiol.*, **69**, 1497-1499.
- Siostrzonek, P., Koppensteiner, R., Gossinger, H., Zangeneh, M., Heinz, G., Kreiner, G., Stumpfien, A., Buxbaum, P., Ehringer, H. & Mossbacher, H. (1993) Hemodynamic and hemorheologic determinants of left atrial spontaneous echo contrast and thrombus formation in patients with idiopathic dilated cardiomyopathy. *Am. Heart J.*, **125**, 430-434.
- Sogaard, P., Egeblad, H., Kim, W.Y., Jensen, H.K., Pedersen, A.K., Kristensen, B.O. & Mortensen, P.T. (2002) Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J. Am. Coll. Cardiol.*, **40**, 723-730.
- Stellbrink, C., Breithardt, O.A., Franke, A., Sack, S., Bakker, P., Auricchio, A., Pochet, T., Salo, R., Kramer, A. & Spinelli, J. (2001) The PATH-CHF (Pacing THERapies in Congestive Heart Failure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J. Am. Coll. Cardiol.*, **38**, 1957-1965.
- Vigna, C., Russo, A., De Rito, V., Perna, G., Villella, A., Testa, M., Sollazzo, V., Fanelli, R. & Loperfido, F. (1992) Frequency of left atrial thrombi by transesophageal echocardiography in idiopathic and in ischemic dilated cardiomyopathy. *Am. J. Cardiol.*, **70**, 1500-1501.
- Xiao, H.B., Brecker, S.G. & Gibson, D.G. (1992) Effects of abnormal activation on the time course of left ventricular pressure pulse in dilated cardiomyopathy. *Br. Heart J.*, **68**, 403-407.
- Xiao, H.B., Roy, C., Fujimoto, S. & Gibson, D.G. (1996) Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. *Int. J. Cardiol.*, **53**, 163-170.
- Zardini, M., Tritto, M. & Bargiggia, G. (2000) The InSync Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronization. *Eur. Heart J.*, **2**, Suppl, 16-22.