CARDIOVASCULAR MEDICINE

Longitudinal myocardial contraction improves early during titration with metoprolol CR/XL in patients with heart failure

B Andersson, B Grüner Sveälv, M Scharin Täng, R Mobini

Heart 2002;**87**:23–28

See end of article for authors' affiliations

Correspondence to: Dr B Andersson, Department of Cardiology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden; bert.andersson@hjl.gu.se

Accepted 8 October 2001

Objective: To investigate diastolic and systolic left ventricular recovery during titration with metoprolol CR/XL (controlled release/extended release).
Design: Placebo run in, followed by an open study.
Setting: University hospital.
Patients: 14 patients with chronic heart failure.
Interventions: Metoprolol CR/XL titrated from 12.5 mg once daily to 200 mg once daily.
Main outcome measures: M mode recordings of atrioventricular (AV) plane displacement, Doppler measurement of transmitral flow and pulmonary venous flow, two dimensional ejection fraction, and measurement of venous plasma concentration of noradrenaline. Patients were investigated after 2, 4, 6, and 24 weeks of treatment.
Results: A reduction of heart rate was observed on the first dose (12.5 mg once daily), from a mean (SD) of 74 (11) to 67 (11) beats/min, $p < 0.05$. This was accompanied by prominent effects on AV plane filling parameters, including an increase in early diastolic filling period from 87 (28) to 105 (33) ms ($p < 0.05$), and in the lateral AV plane fractional shortening from 8.7 (2.7)% to 10.2 (2.8)% ($p < 0.05$). An early trend towards improvement in global systolic left ventricular function was also seen, although this was not significant until six weeks. Ejection fraction increased from 33 (7.5)% to 38 (11)% ($p < 0.05$).
Conclusions: First effects of left ventricular recovery during β blocker treatment were seen in recordings of longitudinal performance, as expressed by AV plane displacement. Doppler flow dynamics as well as global systolic recovery appeared several weeks later, emphasising the importance of longitudinal performance in evaluating left ventricular function.

In terms of survival benefit and improvement in left ventricular systolic function, adrenergic β blockers have proved to be the most successful of all medical treatments for patients with congestive heart failure.[1 2] Although it is well known that a majority of patients experience improvement of symptoms and in ejection fraction within several months, early effects of β blockade are poorly documented. Acute administration of β blockers might cause adverse haemodynamic effects and sometimes precipitate heart failure. We have proposed that positive effects on myocardial metabolism and diastolic function are the prerequisite for future improvement in systolic ventricular function.[3 4] The acute effects of β blockade have been reported in a few studies, whereas most clinical trials have reported the effect of treatment for three months or longer.[5] In one study the effect on ejection fraction after 24 hour metoprolol treatment was reported.[6] However, the mode of action regarding systolic and diastolic events during the first weeks and months of treatment have not been studied with modern non-invasive techniques.

We recently reported that the left ventricular longitudinal contraction pattern recovered early after three months of treatment with metoprolol in a substudy of the metoprolol in dilated cardiomyopathy (MDC) trial.[7] It was also shown that this early recovery was strongly associated with future global recovery in left ventricular function. It was suggested that subendocardial effects of β blockade caused improvement in longitudinal myocardial fibres that enhanced the movements of the atrioventricular (AV) plane.

We studied diastolic and systolic longitudinal as well as global ventricular function during the early titration phase of metoprolol CR/XL (controlled release/extended release). The aim was to investigate the time course of diastolic and systolic recovery during the early phase of treatment.

PATIENTS AND METHODS

Patients

Patients with stable congestive heart failure in New York Heart Association (NYHA) functional class II–IV were eligible for the study. The entry criteria were adopted from the survival study MERIT-HF (metoprolol CR/XL randomised intervention trial in congestive heart failure) that was conducted simultaneously with the present study.[2] Seventeen patients fulfilled the study criteria and were enrolled and 14 patients completed the study (nine men). Patient mean (SD) age was 59 (9.3) years. At inclusion the ejection fraction was 33 (7.5)%. Eight patients had ischaemic heart disease and six had idiopathic dilated cardiomyopathy. Eight patients were in NYHA functional class II, five were in class III, and one was in class IV. Twelve patients were being treated with angiotensin converting enzyme inhibitors or with angiotensin receptor antagonists, 10 were on loop diuretics, and six were treated with digoxin. Duration of heart failure symptoms was 18 (22) months (range 1–66 months).

Abbreviations: AV, atrioventricular; AVP-FS, atrioventricular plane fractional shortening; CR/XL, controlled release/extended release; MDC, metoprolol in dilated cardiomyopathy; MERIT-HF, metoprolol CR/XL randomised intervention trial in congestive heart failure; NYHA, New York Heart Association

Study protocol

Metoprolol CR/XL was titrated in the following steps: 12.5 mg once daily, 25 mg once daily, 50 mg once daily, 100 mg once daily, and 200 mg once daily, with increments in each dose after two weeks of treatment. Echocardiography was performed on the last day of each period, for the first three doses (12.5 mg, 25 mg, and 50 mg). Echocardiography was repeated after 24 weeks of treatment (200 mg). All echocardiographic examinations were performed during the expected maximum plasma concentration of metoprolol CR/XL, four hours after intake of the morning dose.

Echocardiography

Two dimensional echocardiography was performed with the patient in the left lateral position and recordings were obtained during relaxed end expiratory apnoea. Longitudinal contractions were registered by directing the M mode beam from the apex to the fibrous tissue of the AV plane at the angle of the left ventricular wall and the insertion of the mitral valve apparatus as previously described.[7] The ultrasound beam was adjusted to obtain a continuous echo without interfering echoes from the mitral valve. Four recordings of the AV plane were obtained, in the standard apical four chamber view (septal and left lateral portions of the AV plane) and in the two chamber view (anterior and posterior portions). All data were registered with magnification of the structures (using the zoom function). The AV plane movements were recorded on video tape and on strip charts at 50–100 mm/s. Using zoom, the movements of the pericardial contour of left ventricular apex in relation to the thoracic wall were registered. Diastolic mitral flow was recorded by pulsed wave Doppler with the sampling volume between the tips of the mitral valve in the four chamber view. Pulmonary venous flow was recorded with the sampling volume inside the medial pulmonary vein. An ECG signal and a phonocardiogram was recorded on all echocardiographic tracings for timing of cardiac events.

Measurements

M mode tracings were evaluated and calculated off line on a digitiser. Data were acquired by a software program (CAS Cardiac Analysis Software, Sahlgrenska University Hospital, Göteborg, Sweden), which we developed. The program generated calculations of velocities, maximal speed of contraction and relaxation, and time intervals.

Six points in the curve of the AV plane were identified: (1) the start of systolic contraction; (2) end of systolic contraction; (3) start of rapid filling; (4) end of rapid filling; (5) start of atrial contraction; and (6) end of atrial contraction (fig 1). The systolic AV plane amplitude was calculated as the difference between points 1 and 2. The diastasis period was measured as the time from point 4 to point 5. In cases of tachycardia, the diastasis is abolished and there is a continuous downslope from point 3 to point 6. In these cases the software extrapolated a midpoint between points 3 and 6, which was substituted for point 4. In our present study, only one patient had such a short filling time at baseline. All patients had a point 4 at the follow up at 24 weeks. The systolic fractional shortening of the AV plane (AVP-FS) was calculated as the total systolic amplitude divided by the length of the long axis from the epicardial contour of the ventricular apex to point 5 (end of diastasis) in the AV plane curve, expressing the total systolic amplitude normalised for the end diastolic length of the left ventricular long axis. The performance of the AV plane was calculated as the average of at least three beats. Where not stated otherwise, all results are reported as the average performance of the septal, lateral, anterior, and posterior AV plane recordings. The average of the diastolic and systolic distances from the transducer to the apical contour were used in the formula for AVP-FS calculation. Normal values in our laboratory have been presented previously.[7] Left ventricular volumes and ejection fraction were determined from biplane recordings (four chamber and two chamber views) using Simpson's rule. Mitral flow data were analysed from strip charts at 100 mm/s and recordings were digitised.[8] Pulmonary venous flow registrations were analysed from strip charts at 100 mm/s and the recordings were digitised. Data on the amplitude and velocity time integral of the S and D wave were generated as well as ratios and time intervals.

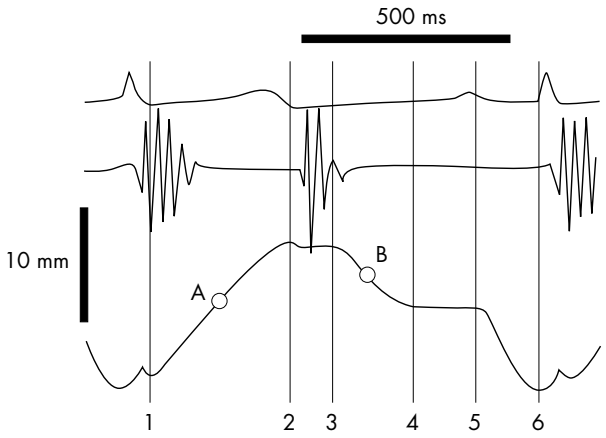


Figure 1 Schematic curve depicting the movements of the atrioventricular plane and delineation of measured periods: (1) start of left ventricular contraction and ejection; (2) end of left ventricular contraction; (3) start of early rapid diastolic filling; (4) end of rapid filling, beginning of diastasis; (5) end of diastasis, beginning of atrial contraction; (6) end of atrial contraction. (A) Maximal derivative of systolic ejection; (B) maximal derivative of early rapid filling.

Determination of plasma catecholamines

An intravenous cannula was inserted and the patients were allowed to rest for 30 minutes in a quiet room before their blood was sampled. Blood samples were collected in ice cold tubes containing EDTA and reduced glutathione (Amersham, Little Chalfont, UK) and were immediately centrifuged at 1500 *g* for 10 minutes at 4°C. The plasma was moved to a new plastic tube and was frozen at −70°C. Plasma catecholamines were purified and concentrated by extraction with acid washed aluminium oxide. Four concentrations between 0.01–1 ng/ml of external standard solutions in 0.1 M perchloric acid were used for calibration. Plasma catecholamines, including noradrenaline, were determined by means of high performance liquid chromatography with electrochemical detection.

Statistical analysis

A repeated measurement analysis of variance on ranks was used to evaluate differences over time, followed by comparison of changes in relation to baseline data (Dunnett's method). The investigation at run in (two weeks before active treatment) was also incorporated into the analysis of variance. To compare changes in different variables, incremental changes (percentages) were evaluated. A probability value of $p < 0.05$ was considered significant.

The study was approved by the ethics committee of the medical faculty, Göteborg University. Participating patients gave informed consent before inclusion in the study.

RESULTS

During the study one patient developed atrial fibrillation. One patient developed severe diabetes mellitus and died suddenly in the hospital after three weeks of treatment. One patient was withdrawn from the study before entering active treatment

Table 1 Two dimensional echocardiographic volume data during titration with metoprolol CR/XL (controlled release/extended release)

	Baseline	2 weeks	4 weeks	6 weeks	24 weeks	RM ANOVA
Metoprolol dose (mg)		12.5	25	50	200	
End diastolic volume (ml)	168 (46)	165 (51)	161 (52)	156 (55)	142 (46)	0.006
95% CI		–17 to 11	–24 to 9.7	–29 to 5.5	–50 to –2.9	
End systolic volume (ml)	112 (32)	110 (43)	104 (42)	99 (43)	86 (42)	0.01
95% CI		–16 to 13	–22 to –5.8	–28 to 2.0	–46 to –5.5	
Ejection fraction (%)	33 (7.5)	35 (11)	37 (10)	38 (11)	41 (12)	0.008
95% CI		–1.7 to 5.4	–0.6 to 7.8	0.4 to 8.9	2.1 to 14	

Values are mean (SD). 95% confidence intervals (CI) are of differences versus baseline.
RM ANOVA, repeated measurements analysis of variance on ranks within respective group.

because of non-compliance. These three patients were not included in the present report. There were no significant changes in the measured variables between the run in investigation and the baseline investigation after two weeks of placebo treatment.

Global ventricular function

There were gradual improvements in global ejection fraction and left ventricular volumes, with changes observed already after four weeks of active treatment (table 1). The magnitude of change in ejection fraction was proportional to the change in Q_1-Q_2 interval and was similar to the decreases in end diastolic and end systolic volumes.

Longitudinal contraction pattern

The AVP-FS displayed an increase that was comparable with the increase in global ejection fraction and that in Q_1-Q_2 interval. Small, but non-significant, changes were observed in systolic and early diastolic filling amplitudes already on the first dose of metoprolol (table 2). The absolute values of AVP-FS were significantly increased after six weeks of treatment. The rapid filling amplitude increased to an extent similar to that of AVP-FS (fig 2). The most obvious changes in recorded data were the prolongation of filling times in the AV plane recordings. Whereas the Q_1-Q_2 interval increased by 22% after six months, the early rapid filling time increased by 54% and the diastasis by 76% (fig 3). These diastolic filling events were significantly altered already after the initial dose of 12.5 mg metoprolol. The atrial wave duration increased by 18%. The changes in AV plane at the septal, lateral, anterior, and posterior registrations were comparable, although the changes in the lateral position were significantly greater during all follow up examinations. As an example, at the lateral

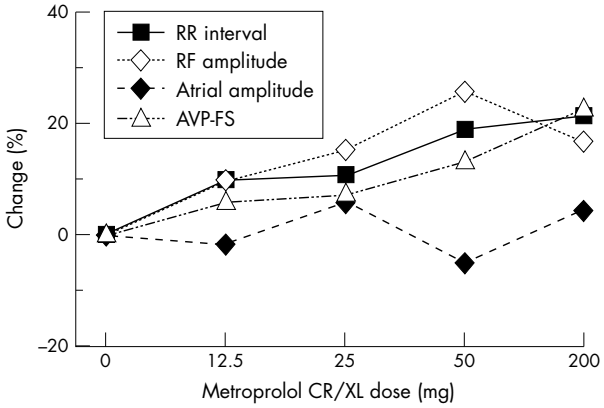


Figure 2 Relative changes in left ventricular atrioventricular plane amplitudes during titration with metoprolol in 14 patients with congestive heart failure. Changes are expressed as mean changes (%) relative to baseline investigation. AVP-FS, atrioventricular plane fractional shortening; RF, rapid filling.

Table 2 Atrioventricular plane amplitudes and time intervals during titration with metoprolol CR/XL

	Baseline	2 weeks	4 weeks	6 weeks	24 weeks	RM ANOVA
Metoprolol dose (mg)		12.5	25	50	200	
Heart rate (beats/min)	74 (11)	67 (11)	67 (13)	62 (10)	61 (11)	<0.001
95% CI		–10 to –2.9	–13 to 0.3	–16 to –6.7	–17 to –7.7	
AVP-FS (%)	7.8 (2.0)	8.2 (2.4)	8.2 (2.0)	8.9 (2.8)	9.5 (3.1)	<0.001
95% CI		–0.2 to 1.0	–0.3 to 1.1	0.4 to 1.8	0.7 to 2.8	
Rapid filling amplitude (mm)	3.1 (1.0)	3.5 (1.4)	3.5 (1.5)	4.0 (1.8)	3.8 (1.8)	0.001
95% CI		–0.1 to 0.7	–0.4 to 1.1	0.2 to 1.5	–0.3 to 1.6	
Rapid filling maximal velocity (cm/s)	39.9 (11)	38.6 (11)	40.3 (11)	44.0 (11)	41.8 (11)	NS
95% CI		–4.9 to 2.3	–3.2 to 3.9	0.6 to 7.5	–3.5 to 7.3	
Atrial contraction amplitude (mm)	4.7 (0.9)	4.6 (1.1)	4.9 (1.2)	4.7 (0.9)	4.7 (1.0)	NS
95% CI		–0.6 to 0.4	–0.5 to 0.9	–0.8 to 0.2	–0.6 to 0.8	
Atrial filling fraction (%)	71 (26)	64 (12)	66 (15)	60 (18)	59 (13)	0.001
95% CI		–17 to 3.0	–19 to 9.3	–20 to –5.9	–24 to –0.5	
Q_1-Q_2 interval (ms)	836 (130)	920 (155)	922 (160)	989 (140)	1010 (148)	<0.001
95% CI		42 to 125	13 to 159	98 to 207	105 to 243	
Ejection time (ms)	237 (35)	249 (32)	249 (27)	263 (29)	268 (32)	<0.001
95% CI		–2.1 to 26	–3.1 to 28	17 to 36	14 to 48	
Rapid filling time (ms)	87 (28)	105 (33)	103 (34)	124 (33)	128 (39)	<0.001
95% CI		5.2 to 31	–2.4 to 35	25 to 50	22 to 61	
Diastasis (ms)	161 (76)	212 (99)	198 (90)	263 (91)	269 (107)	<0.001
95% CI		9.1 to 84	–0.9 to 76	71 to 124	60 to 155	
Atrial contraction time(ms)	107 (19)	117 (25)	114 (22)	120 (16)	125 (18)	<0.001
95% CI		3.3 to 16	–2.5 to 15	3.3 to 23	8.9 to 27	

Values are mean (SD). 95% confidence intervals are of differences versus baseline.
AVP-FS, Atrioventricular plane fractional shortening; NS, not significant.

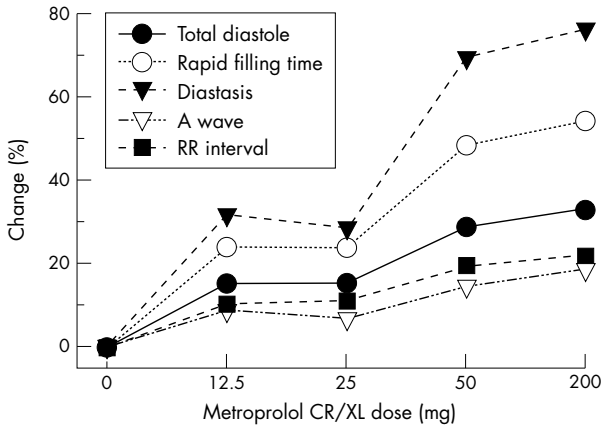


Figure 3 Relative changes in left ventricular atrioventricular plane diastolic time intervals during titration with metoprolol in 14 patients with congestive heart failure. Changes are expressed as mean changes (%) relative to baseline investigation.

position AVP-FS increased significantly on the first dose of metoprolol CR/XL from 8.7 (2.7)% to 10.2 (2.8)%, $p < 0.05$.

Mitral flow and pulmonary venous flow

The majority of patients had signs of disturbed diastolic filling at baseline with an E:A ratio below 1.0 (table 3). None of the patients had a pseudonormal pattern (E:A ratio > 2 or > 1 with subnormal E wave deceleration time). During metoprolol treatment the E:A ratio increased gradually from 0.86 (0.39) to 1.15 (0.78), and the alterations were significant after four weeks of treatment. Pulmonary venous flow was not significantly altered during the study, although there was a tendency to an increase in the S:D ratio that was comparable with the increase in Q_1-Q_2 interval.

Peripheral noradrenaline concentration

During the first metoprolol dose venous noradrenaline (norepinephrine) concentration increased in some patients. The mean concentration was slightly reduced during six months of follow up, although not significantly, from 0.425 (0.26) at baseline to 0.449 (0.41), 0.436 (0.24), 0.448 (0.28), and 0.382 (0.23) ng/ml with metoprolol CR/XL 12.5 mg, 25 mg, 50 mg, and 200 mg, respectively.

DISCUSSION

This is the first study to provide detailed information about systolic and diastolic events during the first weeks of β blocker titration in heart failure. Prominent diastolic effects were observed already with the first dose of metoprolol, whereas systolic improvements were seen later.

Diastolic effects by β blockade

A common misinterpretation of β blocking effects during heart failure treatment is that all effects are mediated through slowing of the heart rate and prolongation of diastole. The reduction of heart rate is probably an important positive consequence during β blocker treatment. However, we and others have shown that there are other important effects, including metabolic actions promoting a more efficacious consumption of carbohydrates with less energy expenditure[3 4 9] and an enhancement of myocardial high energy content.[10] We have also shown that improvements in early filling, as expressed by a less restrictive filling pattern in the mitral Doppler flow, were induced by β blockade and not fully paralleled by slowing of the heart rate.[8] Further, if the heart rate was increased by atrial pacing after a period of chronic treatment with β blockers, an improvement in systolic function was maintained, implying that restoration of myocardial function enables the heart to work more efficiently even at higher heart rates.[11] Other interesting effects might be that β blockade attenuates apoptosis and inflammation.[12–14] Digoxin and calcium channel blockers with heart rate reducing effects do not appear to share these positive effects of β blockers and have not been found to increase survival expectancy in patients with heart failure.

The effects on heart rate were observed already with the first dose of metoprolol, 12.5 mg given once daily. However, all diastolic time intervals were not prolonged homogeneously. Whereas the magnitude of prolongation of the Q_1-Q_2 interval and of the atrial contraction period was similar, the most prominent effects were observed in the prolongation of the rapid filling time and the diastasis period. These first two diastolic periods were increased more than the Q_1-Q_2 interval in terms of percentage. It may be argued that the diastasis does not contribute to left ventricular filling. However, myocardial metabolic events—as described above— as well as myocardial perfusion can take place during this diastolic phase and thereby be important for myocardial recovery. Measurement of the longitudinal contraction pattern has not been used extensively, although some studies have reported on diastolic events.[15–19] The detailed analysis that we used in our study has not been reported by others and it enabled us to observe diastolic events already after two weeks of treatment. Changes in conventional recordings, such as Doppler and global two dimensional left ventricular volumes, were seen several weeks later. We have recently published results showing that AV plane effects during the first months of β blocker treatment could predict later recovery of global ventricular function.[7] It is therefore suggested that the importance of left ventricular longitudinal motions might be underestimated.[20] It is also intriguing to compare the short term effects of intravenous milrinone in a study by Brecker and colleagues[21] with the chronic effects of metoprolol in our study. Similar effects

Table 3 Doppler flow recordings during titration with metoprolol CR/XL

	Baseline	2 weeks	4 weeks	6 weeks	24 weeks	RM ANOVA
Metoprolol dose (mg)		12.5	25	50	200	
Transmitral flow						
E:A velocity ratio	0.86 (0.39)	0.9 (0.40)	1.0 (0.43)	1.09 (0.51)	1.15 (0.78)	0.009
95% CI		–0.15 to 0.05	0.04 to 0.22	0.11 to 0.34	–0.08 to 0.67	
E deceleration time (ms)	221 (61)	210 (59)	215 (88)	221 (61)	211 (73)	NS
95% CI		–52 to 31	–54 to 44	–16 to 61	–71 to 48	
Pulmonary venous flow						
S peak velocity (m/s)	0.51 (0.099)	0.54 (0.063)	0.53 (0.061)	0.56 (0.079)	0.54 (0.078)	NS
95% CI		–0.062 to 0.12	–0.040 to 0.023	–0.020 to 0.12	–0.022 to 0.13	
D peak velocity (m/s)	0.42 (0.082)	0.41 (0.080)	0.42 (0.10)	0.42 (0.084)	0.43 (0.12)	NS
95% CI		–0.060 to 0.071	–0.047 to 0.092	–0.034 to 0.071	–0.086 to 0.084	
S:D velocity ratio	1.26 (0.33)	1.38 (0.35)	1.35 (0.49)	1.4 (0.34)	1.39 (0.50)	NS
95% CI		–0.17 to 0.37	–0.27 to 0.24	–0.13 to 0.33	–0.26 to 0.68	

Values are mean (SD). 95% confidence intervals are of differences versus baseline.

were seen with respect to increases in AV amplitudes and increases in the early diastolic filling parameters with no effects on atrial filling characteristics. This would imply that intrinsic myocardial contractility is improved by β blockade treatment.

Transmitral pulsed wave Doppler is the conventional method of studying diastolic function. We found signs of less compromised diastolic function with an *increase* in E:A ratio during treatment. A shift of diastolic filling from late to early diastole was also in accordance with the findings in the AV plane pattern with increase in early filling amplitude but not in the atrial wave amplitude. It might be of interest to compare our present results with a previous substudy from the MDC trial, in which the patients on average were sicker than in this study.[8] Whereas none of our patients had a restrictive filling pattern, many patients in the previous report had a pseudonormal filling pattern. In patients with a restrictive filling pattern metoprolol caused a *decrease* in E:A ratio. Thus, it is intriguing that β blocker treatment improves diastolic filling at both ends of the spectrum, promoting normalisation of the filling pattern. Pulmonary venous flow registration is technically more difficult than AV plane recording, which may explain why we could not observe significant changes. In one of the early β blocker studies it was found that the rapid filling wave in the apex cardiogram was reduced after only one month of treatment.[22] The apex cardiogram is probably influenced by the AV plane and longitudinal movements of the heart. A less prominent rapid filling wave in the apex cardiogram would represent less restrictive left ventricular filling. Also, it is likely that the balance between diastolic and systolic recovery differs depending on the severity of left ventricular dysfunction. The patients in this report had higher ejection fractions than those in the MERIT-HF study and in the MDC study.

Negative inotropic effects and catecholamines

In the present study, echocardiography was performed during the peak plasma concentration of metoprolol CR/XL. This is in contrast to most previous studies reporting β blockade effects where investigations were done during plasma trough concentration. Kukin and colleagues[23] showed that each dose of β blocker induced a negative inotropic effect. Investigations during plasma peak and trough could therefore produce very different results. Our study is the first to present serial data in patients on peak concentrations of β blockers. This could explain why we found such prominent early diastolic effects. It is possible that the negative inotropic action of the drug causes a short term reflex increase in peripheral noradrenaline, obscuring any decrease in concentration over time. We did not observe any decrease in noradrenaline concentration in this study. However, we have preliminary data showing that nerve fibre recordings and evaluation of myocardial noradrenaline kinetics were capable of detecting a reduction in sympathetic activity during long term treatment with metoprolol.[24] β Blockers with intrinsic activity and a less negative inotropic effect have shown poor results and are useless in the treatment of heart failure.[25 26] On the other hand, there were small but non-significant positive findings in global left ventricular function already with the first dose of metoprolol, including a reduction in end systolic volumes in particular. This is in contrast with other investigations showing improvement after 3–6 months of treatment.[6 8] However, besides differences in methods and in the timing of investigations, we here report on a period not previously studied. Improvement in systolic performance might be detected early, after one to two weeks of treatment.

Limitations of the study

This was an open study. A lot of previous studies have now been published, all showing consistent positive findings regarding cardiac function during β blocker treatment. We therefore considered it unethical to perform another placebo controlled study with the aim of studying left ventricular function. Patients with a short history of heart failure sometimes have a greater tendency towards spontaneous improvement. Six patients had a history of heart failure not exceeding six months and these patients had an increase in AVP-FS of 2.1 units on average during the study, in comparison with 1.5 units for patients with a longer duration. However, the first two weeks of placebo treatment enabled us to ensure that the patients were in a stable condition and there were no significant differences in recorded data during the placebo period.

Conclusion

In this study of the early effects on left ventricular function during metoprolol titration, it was clearly shown that the first recorded events occurred in the longitudinal contraction pattern. The changes in diastolic filling were more prominent than changes in heart rate. Even though investigations were performed during peak plasma concentration of β blockade, there were also trends towards improvement in systolic function on the first titration dose. Recordings of left ventricular longitudinal contraction are sensitive to β blocking effects and changes in performance precede those in Doppler indices and left ventricular global function.

Authors' affiliations

B Andersson, B Grüner Sveälv, M Scharin Täng, R Mobini, Department of Cardiology and Wallenberg Laboratory of Cardiovascular Research, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden

REFERENCES

1 **CIBIS-II investigators and committees**. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
2 **The MERIT-HF study group**. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999;**353**:2001–7.
3 **Andersson B**, Lomsky M, Waagstein F. The link between acute haemodynamic adrenergic beta-blockade and long-term effects in patients with heart failure. *Eur Heart J* 1993;**14**:1375–85.
4 **Andersson B**, Hamm C, Persson S, *et al*. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol* 1994;**23**:1397–404.
5 **Haber HL**, Simek CL, Gimple LW, *et al*. Why do patients with congestive heart failure tolerate the initiation of beta-blocker therapy? *Circulation* 1993;**88**:1610–9.
6 **Hall SA**, Cigarroa CG, Marcoux L, *et al*. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol* 1995;**25**:1154–61.
7 **Andersson B**, Waagstein F, Caidahl K, *et al*. Early changes in longitudinal performance predict future improvement in global left ventricular function during long term beta adrenergic blockade. *Heart* 2000;**84**:599–605.
8 **Andersson B**, Caidahl K, Di Lenarda A, *et al*. Changes in early and late diastolic filling patterns induced by long-term adrenergic beta-blockade in patients with idiopathic dilated cardiomyopathy. *Circulation* 1996;**94**:673–82.
9 **Eichhorn EJ**, Heesch CM, Barnett JH, *et al*. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1994;**24**:1310–20.
10 **Omerovic E**, Bollano E, Mobini R, *et al*. Selective beta(1)-blockade improves cardiac bioenergetics and function and decreases neuroendocrine activation in rats during early postinfarct remodeling. *Biochem Biophys Res Commun* 2001;**281**:491–8.
11 **Andersson B**, Strömblad S-O, Lomsky M, *et al*. Heart rate dependency of cardiac performance in heart failure patients treated by metoprolol. *Eur Heart J* 1999;**20**:575–83.
12 **Yue TL**, Ma XL, Wang X, *et al*. Possible involvement of stress-activated protein kinase signaling pathway and Fas receptor expression in prevention of ischemia/reperfusion-induced cardiomyocyte apoptosis by carvedilol. *Circ Res* 1998;**82**:166–74.
13 **Communal C**, Singh K, Sawyer DB, *et al*. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. *Circulation* 1999;**100**:2210–2.
14 **Irwin MW**, Mak S, Mann DL, *et al*. Tissue expression and immunolocalization of tumor necrosis factor-alpha in postinfarction dysfunctional myocardium. *Circulation* 1999;**99**:1492–8.

15 **Alam M**, Höglund C. Assessment by echocardiogram of left ventricular diastolic function in healthy subjects using the atrioventricular plane displacement. *Am J Cardiol* 1992;**69**:565–8.
16 **Henein MY**, Gibson DG. Abnormal subendocardial function in restrictive left ventricular disease. *Br Heart J* 1994;**72**:237–42.
17 **Henein MY**, Gibson DG. Suppression of left ventricular early diastolic filling by long axis asynchrony. *Br Heart J* 1995;**73**:151–7.
18 **Henein MY**, Anagnostopoulos C, Das SK, *et al*. Left ventricular long axis disturbances as predictors for thallium perfusion defects in patients with known peripheral vascular disease. *Heart* 1998;**79**:295–300.
19 **Willenheimer R**. Assessment of left ventricular dysfunction and remodeling by determination of atrioventricular plane displacement and simplified echocardiography. *Scand Cardiovasc J Suppl* 1998;**48**:1–31.
20 **Brecker SJ**. The importance of long axis ventricular function. *Heart* 2000;**84**:577–9.
21 **Brecker SJD**, Xiao HB, Mbaissouroum M, *et al*. Effects of intravenous milrinone on left ventricular function in ischemic and idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993;**71**:203–9.
22 **Waagstein F**, Hjalmarson A, Swedberg K, *et al*. Beta-blockers in dilated cardiomyopathies: they work. *Eur Heart J* 1983;**4**:173–8.
23 **Kukin ML**, Kalman J, Mannino MM, *et al*. Beta blockade in congestive heart failure: persistent adverse haemodynamic effects during chronic treatment with subsequent doses. *Heart* 1997;**78**:444–9.
24 **Rundquist B**, Friberg P, Andersson B, *et al*. Metoprolol treatment reduces sympathetic nerve activity in patients with heart failure. *Eur Heart J* 1999;**20**:200.
25 **The Xamoterol in Severe Heart Failure Study Group**. Xamoterol in severe heart failure. *Lancet* 1990;**336**:1–6.
26 **Witchitz S**, Cohen-Solal A, Dartois N, *et al*. Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD group. *Am J Cardiol* 2000;**85**:1467–71.

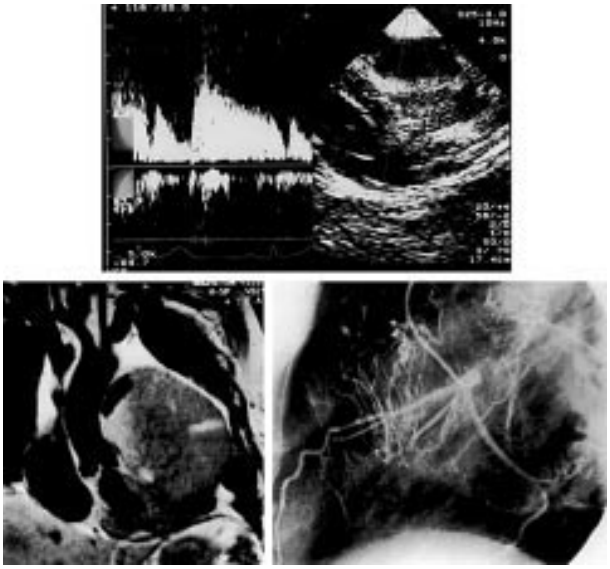
IMAGES IN CARDIOLOGY

Transthoracic Doppler flow images detect cardiac angiosarcoma earlier than other imaging modalities

A 48 year old man visited our hospital because of fatigue. Transthoracic echocardiography demonstrated a capsulated mass in the pericardial space with pericardial effusion. Doppler flow velocity signal during diastole was detected, indicating epicardial left coronary artery running into the tumour (upper panel). This finding suggested that arteries were running from the coronary artery to feed the tumour, most likely an angiosarcoma. Thus, the patient was hospitalised immediately. Pericardial fluid containing blood was collected by pericardiocentesis but was cytologically negative for malignant cells. Enhanced computed tomography (CT) scan revealed a tumour measuring 14 × 10 cm of inhomogeneous density compressing the left ventricle. Gated cardiac magnetic resonance imaging showed an extensive mass of heterogeneous signal intensity in the pericardial space (lower left panel). A coronary angiogram revealed a massive supply artery from the left coronary artery to the tumour with contrast retention (lower right panel).

Histological examination of the open chest biopsy samples showed multiple anastomosing vascular channels lined with malignant endothelial cells, comparable with angiosarcoma. Surgical resection and irradiation were not applicable. Chemotherapy with adriamycin, cyclophosphamide, and dacarbazine was prescribed, but the patient died 12 months after the initiation of the treatment.

Angiosarcoma are usually diagnosed postmortem. Both clinical course and physical examination are non-specific. If time and cost do not matter, enhanced CT or magnetic resonance imaging could offer more precise and detailed information than echocardiography. However, non-invasive, prompt, and less expensive imaging techniques are required on a daily outpatient basis. Doppler flow velocity imaging seems to be useful for the earlier diagnosis of cardiac angiosarcoma.



Kazuo Komamura
Kunio Miyatake
kkoma@hsp.ncvc.go.jp