



## Letter to the Editor

## Beta-blockade intolerance in anthracyclin-induced cardiomyopathy

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**Abstract**

Beta-blockade efficiency and safety in Anthracyclin Induced cardiomyopathy (AIC) are poorly documented. Cardiac Heart Failure (CHF) due to an AIC has haemodynamic and histologic particularities: only mild ventricular dilatation, restriction pattern and myocardial and endocardial fibrous thickening. Therefore, beta blockade therapy initiation may cause heart failure decompensation by absence of the usual left ventricular adaptation (improvement of left ventricular compliance allowing maintenance of stroke volume). We describe an AIC patient in whom a first beta-blockade initial administration caused a global cardiac failure; after stabilisation, one month later, a second attempt caused a new cardiac failure. We raise the question of beta-blockade safety in restrictive cardiomyopathies.

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Beta-blockade has been shown to improve prognosis and to reduce cardiovascular hospitalisations in patients with chronic heart failure (CHF) [1,2]. On the basis of clinical trials, beta-blocker treatment has been included in the guidelines of CHF therapy and is strongly recommended as standard therapy for all patients with CHF and left ventricular systolic dysfunction [3]. However, safety and benefit of beta-blockade treatment in anthracyclin-induced cardiomyopathy (AIC) have been poorly documented.

**1. Clinical case**

A 52-year-old woman presented in 1997 a breast carcinoma treated by radical mastectomy followed by radiotherapy. A pleural metastatic localisation in April 2003 led to 8 courses of anthracyclin administration with a total

cumulative dose of 300 mg and 776 mg of theprubicin and doxorubicin, respectively.

The patient was hospitalised for a first acute heart failure decompensation in November 2003, related to AIC. At discharge, spironolactone, furosemide, fluindione and enalapril were administered at dosages of 25, 60, 10 and 2.5 mg daily, respectively.

One month later, she was in NYHA functional class III, her heart rate was 100/min, and blood pressure was 90/60 mm Hg without sign of congestion. Echocardiography revealed an aspect of global dilated cardiomyopathy (left ventricular end diastolic diameter 58 mm) with severe diffuse hypokinesia with left ventricular ejection fraction (LVEF) of 25%–30%, low cardiac output (3 l/min), and a moderate mitral regurgitation. Mitral inflow pattern was restrictive and E/Ea ratio by DTI was 16, in relation with high left ventricular filling pressures. (Figs. 1 and 2). Systolic pulmonary arterial pressure was estimated at 45 mm Hg.

Beta-blocker treatment was instaured. The administration of bisoprolol (1.25 mg/day) was poorly tolerated with an

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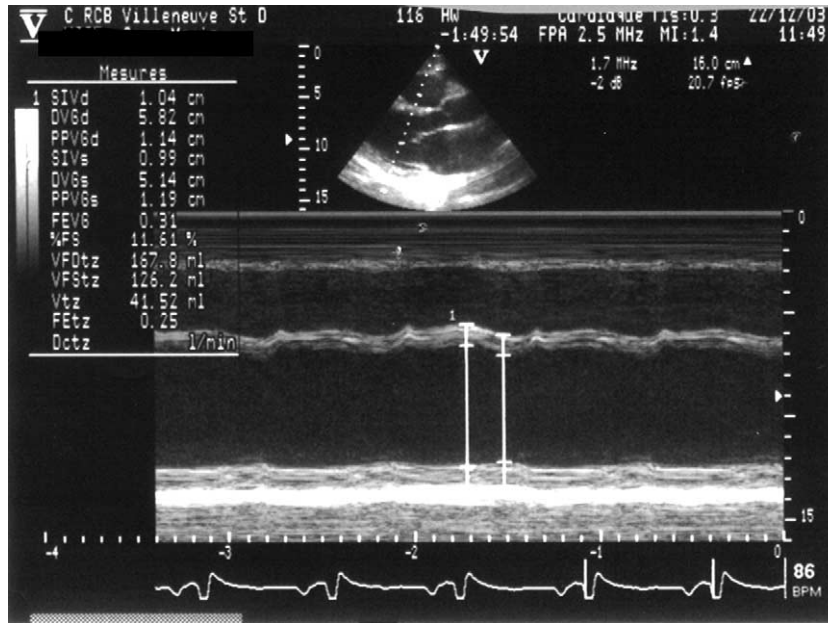


Fig. 1. Aspect of global dilated cardiomyopathy with a modest left ventricular dilation but with a severe diffuse hypokinesia.

increase of NYHA functional class from III to IV, a decrease in systolic blood pressure from 90 to 80 mm Hg without significant change in heart rate and an increase of plasma creatinine level from 130 to 230 mmol/l was observed after one week leading to beta-blocker treatment cessation.

One month later, the patient was in NYHA functional class III again, blood pressure was 95/60 mm Hg and plasma creatinine level had returned to the baseline values.

A new beta-blocker introduction attempt (carvedilol 3.125 mg the first day and 6.25 mg/day the days after) was again poorly tolerated, leading to the same clinical and biological consequences. No further attempt of beta-blocker initiation was done.

Beta-blocker treatment has been shown to be effective in the treatment of patients with dilated cardiomyopathy but large scale clinical trials have not specifically reported tolerance and benefit of beta-blocker therapy in heart failure

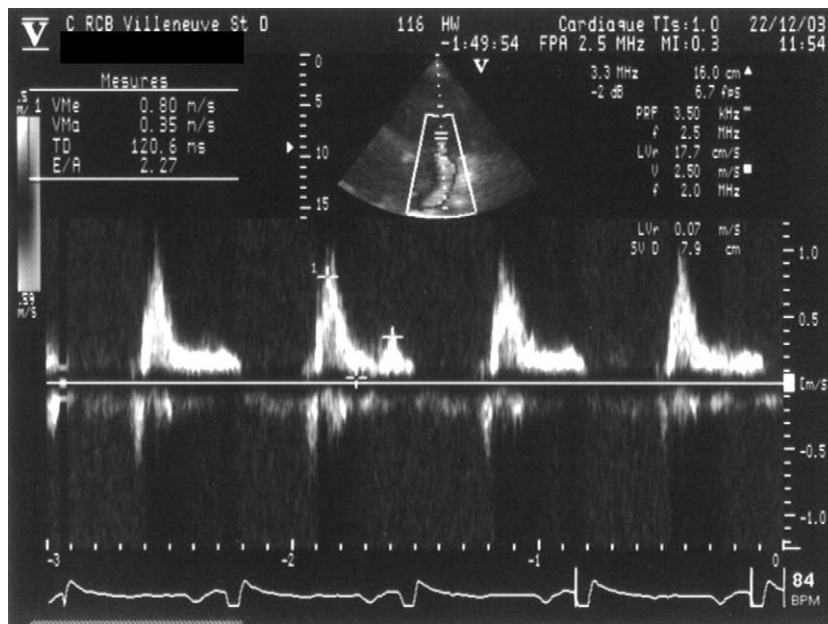


Fig. 2. Mitral inflow profile: restrictive pattern with  $E/A > 1$  and a short E wave deceleration time (120 ms) in relation with high left ventricular filling pressures.

related to AIC, and whether they are similar as in other causes of cardiomyopathy remains unknown.

To date, only 3 clinical studies have evaluated the value of beta-blocker therapy in AIC. Fazio et al [5] reported a case of complete clinical recovery after carvedilol treatment in a 35-year old woman with AIC. Shaddy et al. [6] examined the efficacy and safety of metoprolol in three pediatric patients with AIC, referred for heart transplantation. All patients improved symptoms and LVEF at 5–30 months. The last and largest study is a retrospective case-control design study that included only 8 patients with AIC and 16 control patients with idiopathic dilated cardiomyopathy. The degree of improvement of LVEF was not significantly different in patients with or without AIC [7]. However, these results are limited by their retrospective nature and the lack of control group of AIC patients not treated with beta-blocker, especially as cases of spontaneous improvement in LV function with time have been reported in these patients. [8,9]. In summary, the available data about safety and efficacy of beta-blocker therapy in AIC are limited. Although prevalence of this etiology is small, it would be important to know if data obtained in other forms of heart failure can be extrapolated to AIC-related heart failure.

In fact, pathophysiology of AIC is still unclear and probably multifactorial. Hemodynamic profile is often characteristic with sinus tachycardia, only mild ventricular dilation and a pattern of restriction at invasive or non-invasive hemodynamic evaluation with a pseudo-dip and plateau aspect. Histologic studies often show considerable fibrous thickening of both the myocardium and endocardium [4]. Beta-blockade therapy initiation may cause heart failure decompensation in stable CHF, but use of the Frank–Starling mechanism and progressive remodelling with improvement in left ventricular chamber compliance generally allows maintenance of stroke volume and lessening of diastolic pressures increase in most of the cases of dilated cardiomyopathy. In restrictive cardiomyopathy, such as in AIC or cardiac amyloidosis, the mechanisms are often ineffective; decrease in heart rate and inotropy with beta-blockade therapy oblige the left ventricle to operate the vertical part of a steep pressure–volume curve, leading to pulmonary congestion.

In this case report, we describe repetitive poor tolerance of beta-blockade initiation in a stable AIC patient probably in relation with a specific profile of restrictive cardiomyopathy. Although it is possible that with increase in diuretic dosage prior to a third attempt of beta-blockade therapy, the latter may have been successful, and although generalization from one single case cannot obviously be done, it is striking to see that the tolerance of beta-blocker therapy in these patients remains largely unknown. Given the very specific hemodynamic profile in this disease, registries on the tolerance and the efficacy of beta-blocker therapy in these patients are, in our opinion, warranted.

## References

- [1] The cardiac insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- [2] 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] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101–13.
- [4] Mortensen SAOH, Baandrup U. Chronic anthracycline cardiotoxicity: haemodynamic and histopathological manifestations suggesting a restrictive endomyocardial disease. *Br Heart J* 1986;55:274–82.
- [5] Fazio S, Palmieri EA, Ferravante B, Bone F, Biondi B, Sacca L. Doxorubicin-induced cardiomyopathy treated with carvedilol. *Clin Cardiol* 1998;21:777–9.
- [6] Shaddy RE, Olsen SL, Bristow MR, Taylor DO, Bullock EA, Tani LY, et al. Efficacy and safety of metoprolol in the treatment of doxorubicin-induced cardiomyopathy in pediatric patients. *Am Heart J* 1995;129:197–9.
- [7] Noori A, Lindenfeld J, Wolfel E, Ferguson D, Bristow MR, Lowes BD. Beta-blockade in adriamycin-induced cardiomyopathy. *J Card Fail* 2000;6:115–9.
- [8] Cohen M, Kronzon I, Lebowitz A. Reversible doxorubicin-induced congestive heart failure. *Arch Intern Med* 1982;142:1570–1.
- [9] Saini J, Rich MW, Lyss AP. Reversibility of severe left ventricular dysfunction due to doxorubicin cardiotoxicity. Report of three cases. *Ann Intern Med* 1987;106:814–6.