

Digoxin Withdrawal in Patients with Dilated Cardiomyopathy Following Normalization of Ejection Fraction with Beta Blockers

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Summary

Background: The effect of withdrawal of digoxin on left ventricular function in patients with a history of idiopathic dilated cardiomyopathy (IDCM) following normalization of left ventricular ejection fraction (LVEF) with beta blockers remains unknown.

Hypothesis: This study was undertaken to determine the effect of digoxin withdrawal on left ventricular function in patients with IDCM.

Methods: In 8 consecutive patients with IDCM (5 men, 3 women) who had normalization of LVEF following beta-blocker treatment, digoxin was withdrawn as part of an office protocol, and LVEF was followed. Baseline EF prior to beta blocker initiation (carvedilol = 6, atenolol = 1, metoprolol = 1) was measured with isotope ventriculography (IVG), echocardiography, or left ventriculography. Post beta blocker ejection fraction (post BB EF) was measured in all patients with IVG at a mean of 17.25 ± 5.38 months. Follow-up EF was measured using IVG after digoxin withdrawal at a mean of 6.99 ± 4.34 months.

Results: An experienced blinded reader interpreted the IVG scans. Baseline EF was 28.5 ± 8.26 ; post BB EF and follow-up EF were 56.1 ± 4.65 and 51.0 ± 7.35 , respectively ($p = 0.05$).

Conclusion: These data provide potential evidence that digoxin withdrawal can result in a small but significant reduction in LVEF in patients with IDCM who had normalization of LVEF after treatment with beta blockers. Mean LVEF, however, remained within normal (> 50%) on beta-blocker therapy and without digitalis. Large, randomized controlled trials are needed to confirm these findings.

Key words: beta blockers, cardiomyopathy, digoxin, ejection fraction

Introduction

The standard treatment of patients with idiopathic dilated cardiomyopathy (IDCM) is currently a combination of an angiotensin-converting enzyme (ACE) inhibitor, digoxin, beta blockers, and diuretics.¹ Beta blockers have been shown to improve left ventricular ejection fraction (LVEF) and reduce morbidity and mortality.^{2–4} Angiotensin-converting enzyme inhibitors improve survival and the quality of life of patients with reduced LVEF and congestive heart failure.^{5–7} Digoxin improves symptoms and hemodynamics in patients with reduced LVEF and congestive heart failure, but it does not alter mortality.⁸ The effect of digoxin on patients with normal LVEF is questionable.⁹ At present it is unclear whether patients with IDCM with a normalized LVEF (> 50%) following conventional therapy would still derive any benefit from continued treatment with digoxin. In this study, we present a small series of patients in whom digoxin was withdrawn as part of an office protocol after normalization of LVEF with ACE inhibitors and beta blockers.

Methods

A cohort of eight consecutive patients (5 men, 3 women) with IDCM and with normalized LVEF following treatment with conventional therapy (ACE inhibitors, digoxin, and/or diuretics) and a beta blocker (carvedilol = 6, atenolol = 1, metoprolol = 1) formed the basis of this study. Baseline LVEF prior to initiation of beta blockers was measured using left ventriculography during cardiac catheterization, echocardiography, or isotope ventriculography (IVG). Beta blockers were added to conventional therapy, and LVEF was measured with IVG at a mean 17.25 ± 5.38 months. Digoxin was discontinued in all these patients as part of an office protocol adopted by the author (NWS) when LVEF normalized (> 50%). The rationale for adopting this protocol was an expected neutral effect of digoxin on LVEF in patients with normalized LV systolic function. Isotope ventriculography was then repeated at a mean of 6.99 ± 4.34 months. All patients had normal coronary arteries except for one who had single-vessel coronary disease treated by angioplasty with subsequent follow-up normal myocardial perfusion scan. The global nature of the LV hypokinesia in this patient could not be explained by his history of coronary artery disease (CAD). Left ventricular EF after beta-

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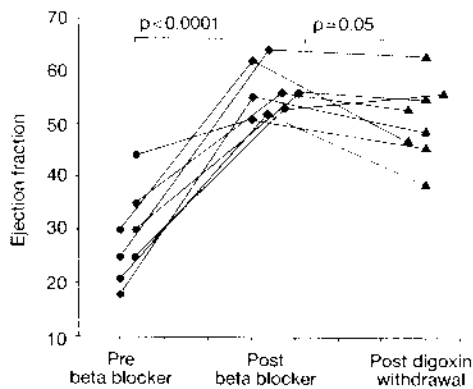


FIG. 1 Ejection fraction at baseline, prior to beta-blocker administration, after beta-blocker treatment, and following digoxin withdrawal. Ejection fraction markedly improved with beta blockers and remained stable despite digoxin withdrawal.

blocker administration and digoxin withdrawal were quantitatively measured with IVG by an experienced blinded reader.

Data Analysis

Paired *t*-tests were performed to test for significant differences between baseline LVEF (on conventional therapy), post BB EF, and follow-up LVEF after digoxin withdrawal.

Results

The study comprised 5 men and 3 women, with a mean age of 55.7 ± 9.8 . All patients had documented normal coronaries by angiography, except for one patient who had a history of CAD (one treated vessel) but with normal subsequent myocardial perfusion. This patient had global hypokinesia unexplained by his history of CAD. Figure 1 illustrates the change in EF of individual patients at baseline, following beta-blocker administration, and after digoxin withdrawal. Mean baseline EF was measured at 28.5 ± 8.26 ; post BB EF significantly improved to 56.1 ± 4.65 ($p < 0.0001$) at a mean follow-up of 17.25 ± 5.38 months. When digoxin was withdrawn, follow-up EF at a mean of 6.99 ± 4.34 months was reduced significantly to 51.0 ± 7.35 ($p = 0.05$). The mean LVEF, however, continued to be within normal ($> 50\%$) despite digoxin withdrawal ($p < 0.001$ compared with baseline), indicating that beta-blocker therapy continues to have a significant positive impact on LVEF despite digoxin withdrawal.

Discussion

Beta blockers have been shown to be beneficial in patients with congestive heart failure, leading to improvement in EF and survival.¹⁻⁴ In our study, EF normalized in eight patients following conventional therapy with the addition of beta blockers. At present, digoxin is thought to add no significant benefit in patients with normal LV systolic function.⁹ It is unclear, however, whether patients with a history of IDCM and

subsequent normalization of LV function after beta-blocker therapy represent an exception. In this study we hypothesized that digoxin withdrawal will have no significant impact on LVEF in patients with IDCM and normalized EF following beta-blocker therapy. To our surprise, this study provides evidence that withdrawal of digoxin could lead to a small but significant reduction in LVEF in this group of patients. However, the reduction of LVEF following digoxin withdrawal occurred within the defined range of normal EF ($> 50\%$). This indicates a minor role of digoxin in maintaining the stability of EF in IDCM after its normalization following beta-blocker therapy. In fact, beta-blocker therapy continues to provide a significant protective effect on EF compared with baseline ($p < 0.001$).

Conclusion

The clinical significance of this finding is as yet unclear. Digoxin is a neurohumoral modulator even in patients with mild congestive heart failure.¹⁰ Although it might not have a dominant role in altering LVEF in patients with a history of cardiomyopathy and a normalized EF after beta-blocker therapy, digoxin could still exert some clinical benefit through its modulation of the neurohumoral system. Large randomized and controlled trials are needed to confirm this observation. The major limitations of this report are its small number of patients and lack of control subjects.

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