

# Should Angiotensin-Converting Enzyme Inhibitors Be Continued Over the Long Term in Patients Whose Left Ventricular Ejection Fraction Normalizes After an Episode of Acute Myocarditis?

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It is well established that long-term administration of angiotensin-converting enzyme (ACE) inhibitors has a favorable effect in patients with chronic heart failure and dilated cardiomyopathy. However, less information is available on patients whose left ventricular ejection fraction normalizes after an episode of systolic dysfunction secondary to acute myocarditis. We followed 35 patients who were diagnosed at our center between 1987 and 1995 with acute myocarditis and an ejection fraction <45%. All were taking ACE inhibitors. After 34 (23) months of follow-up, the left ventricular ejection fraction was >50% in all 35 patients. Treatment with ACE inhibitors was discontinued in 15 of the 35 patients, while the other 20 continued ACE inhibitor therapy. After 3 years of follow-up, no death had occurred, but the incidence of new episodes of heart failure with a left ventricular ejection fraction <45% was higher in patients who stopped taking ACE inhibitors (33% vs 5%,  $P=0.064$ ), and their ejection fraction was lower (47 [12%] vs 57 [11%],  $P=0.002$ ). These results suggest that ACE inhibitors should be continued over the long term in these patients.

## ¿Se deben mantener los inhibidores de la enzima de conversión de la angiotensina a largo plazo en pacientes que normalizan la fracción de eyección tras un episodio de miocarditis aguda?

El efecto favorable de la administración de los inhibidores de la enzima de conversión de la angiotensina (IECA) a largo plazo en pacientes con insuficiencia cardiaca crónica y fracción de eyección deprimida está bien establecido, pero no hay tanta evidencia en pacientes con disfunción sistólica secundaria a miocarditis aguda que normalizan la contracción ventricular. Hemos seguido a 35 pacientes con miocarditis aguda y fracción de eyección < 45% estudiados entre 1987 y 1995, todos tratados con IECA; a los 34 ± 23 meses de seguimiento, la fracción de eyección era > 50% en los 35 casos. De esos 35, en 15 se suspendieron los IECA, mientras que 20 continuaron tomándolos. A los 3 años de seguimiento no hubo ninguna muerte, pero los pacientes en los que se suspendieron los IECA tuvieron una mayor incidencia de nuevos episodios de insuficiencia cardiaca con fracción de eyección < 45% (el 33 frente al 5%;  $p = 0,064$ ) y menor fracción de eyección (47 ± 12 frente a 57 ± 11%;  $p = 0,002$ ), lo que indica que estos fármacos se deben mantener a largo plazo también en estos pacientes.

**Key words:** Acute myocarditis. ACE-inhibitors. Prognosis.

**Palabras clave:** Miocarditis aguda. IECA. Pronóstico.

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## INTRODUCTION

Numerous studies have been performed on the long-term prognosis of patients with chronic heart failure due to left ventricular systolic dysfunction (dilated cardiomyopathy) of different etiology, and much evidence has been collected on the benefits of drugs such as angiotensin converting enzyme inhibitors (ACE inhibitors) and beta-blockers with respect to this prognosis.<sup>1</sup> However, the natural history of patients with systolic dysfunction and recently developed heart failure due to acute myocarditis<sup>2</sup> is less well known. Neither is it known

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## ABBREVIATIONS

LVEF: left ventricular ejection fraction  
NYHA: New York Heart Association

whether treatment with ACE inhibitors should be maintained over the long term in patients whose left ventricular ejection fraction (LVEF) normalizes after the period of dysfunction. To investigate this, the data for 35 consecutive patients diagnosed at our center between 1987 and 1995 with severe left ventricular systolic dysfunction due to acute myocarditis, and in whom the LVEF normalized after treatment, were reviewed.

## METHODS

The characteristics of the patients, the inclusion criteria, the study protocol, and the results after five years of follow-up have been published elsewhere.<sup>2</sup> Clinical, echocardiographic and radioactive isotope criteria were used to arrive at a diagnosis of acute myocarditis, ie, recently developed heart failure (less than two weeks), an LVEF of <45%, a non-dilated left ventricle (end-diastolic diameter normal for patient age and body surface area), diffuse distribution of necrosis markers in the myocardium (anti-myosin antibodies labeled with indium-111), and the exclusion (via echocardiography, myocardial perfusion gammagraphy, and coronary angiography) of any other cause of left ventricular dysfunction. The LVEF was determined by echocardiography (initial LVEF 27 [8%]) using the Simpson method. All patients initially received ACE inhibitors, diuretics and digoxin.

At 34 (23) months the LVEF had normalized in all 35 patients (mean LVEF 57 [7%]); all continued to receive ACE inhibitors. None of the patients received diuretics at this time, and only those with atrial fibrillation (five patients, 16%) were administered digoxin. At this point the patients were released from attending further appointments at our center, although they were still followed by their normal cardiologists who were at liberty to decide on their continued use of ACE inhibitors. Five years later the patients again attended an appointment at our center, and a comparison was made between those who had continued with ACE inhibitors and those who had not. The  $\chi^2$  or Fisher's exact test was used to compare qualitative variables; the Student t test was used to compare quantitative variables.

## RESULTS

All 35 patients released to normal care had an LVEF >50%. The habitual cardiologists of 15 patients (42%) decided to suspend the use of ACE inhibitors; the

remaining 20 patients (58%) continued to take them. The demographic and clinical characteristics of both groups of patients were similar (Table), as was the treatment they received (with the exception of ACE inhibitors). The LVEF in both eventual groups of patients was similar at the time of release from our center (56 [8] and 57 [8%]), all were asymptomatic, and the prevalence of atrial fibrillation in both was similar (13% and 15%) (Table). At that moment of release no patient was being treated with diuretics or beta-blockers; digoxin was used for the control of atrial fibrillation in two patients who would eventually no longer receive ACE inhibitors (13%) and in three patients who would continue to receive them (15%).

No patient died during follow-up. However, the incidence of new episodes of heart failure with LVEF<45% was higher in the group that stopped using ACE inhibitors (33% compared to 5%;  $P=.064$ ). In all cases this heart failure was moderate (four patients fell into NYHA functional class functional II and two into class III). None of these patient needed to be readmitted to hospital and all improved with diuretics and ACE inhibitors. These six patients were also administered beta-blockers. The mean LVEF during the decompensation period in these patients was 37 (7%), but was seen to have increased to 52 (8%) during echocardiographic tests performed six months later. In only one of these six patients - a patient who had stopped taking ACE inhibitors - did the LVEF fail to normalize after the reintroduction of these drugs and beta-blockers; at the 5 year follow-up examination it was still at 35%. No important differences were seen between the characteristics of these six patients and the remainder, except in terms of the suspension of treatment with ACE inhibitors. At the final examination (at five years), the LVEF was significantly lower among the patients in whom ACE inhibitor treatment had been suspended (47 [12%] compared to 57 [11%];  $P=.002$ ).

## DISCUSSION

The long-term progress of patients with chronic dilated cardiomyopathy is well known, and there is much

**TABLE 1. Demographic, Clinical and the Most Important Treatment Characteristics of the Patients in Whom ACE Inhibitor Treatment Was Suspended or Continued**

	No ACEi n=15	With ACEi n=20
Age (years)	23 (12)	24 (13)
males	10 (66%)	14 (70%)
NYHA class I	15 (100%)	20 (100%)
Previous LVEF	56 (8%)	57 (8%)
Atrial fibrillation	2 (13%)	3 (15%)

LVEF: left ventricular ejection fraction; ACEi: angiotensin converting enzyme inhibitors; NYHA: New York Heart Association.

evidence regarding the need for their chronic treatment with ACE inhibitors and beta-blockers.<sup>1</sup> However, the natural history of patients with left ventricular systolic dysfunction due to myocarditis is less well known.<sup>3</sup> A large percentage of these patients may see their LVEF normalize after the initial period of dysfunction,<sup>2</sup> but it is unknown whether ACE inhibitors should be administered over the long term or even indefinitely. The present results suggest that up to one third of patients in whom ACE inhibitor treatment is suspended could suffer another episode of heart failure, while such events are rare in patients who continue with this treatment (only 5% suffered a new episode over the five year experimental period). Similarly, the LVEF was significantly lower at five years among those who had ceased to take ACE inhibitors. This might indicate that it is better to continue with these drugs after an initial episode of acute myocarditis even when progress is favorable. The mechanism via which ACE inhibitors provide their benefit in these patients is not well understood although several suggestions have been made, including their modulatory effect on the neurohormonal axis, the inhibition of fibrosis and the remodeling of the left ventricle,<sup>4,5</sup> and the reduction in the number of small blood vessel spasms.<sup>6</sup>

The present study has a number of limitations; it was observational and non-randomized, and the study population was small (due to the infrequency of this health problem). The decision to suspend treatment with ACE inhibitors was taken by the clinician normally in charge of each patient, and this could have originated some bias. However, the characteristics of both groups of patients were identical, as shown in Table, which reduces the likelihood of this. Given the time when the initial study was performed, no patient was administered beta-blockers. It is also possible that some of these patients did not suffer true myocarditis given the diagnostic criteria followed; some could have suffered other uncommon

problems such as apical ballooning. Although the incidence of new heart failure was greater among those who had ceased to take ACE inhibitors, these events were rarely serious; no patient died, none needed to be readmitted to hospital, and all progressed well after the reintroduction of these drugs. Despite these limitations, the present results indicate that the suspension of ACE inhibitors may be associated with poorer progress and a reduction in the LVEF in this kind of patient. It would be interesting to determine which patients are at greater risk of suffering a deterioration in their LVEF after the suspension of ACE inhibitors. A randomized study with a larger numbers of patients will probably be required to confirm the present findings.

## REFERENCES

1. Grupo de Trabajo de diagnóstico y tratamiento de la insuficiencia cardiaca crónica de la Sociedad Europea de Cardiología. Guías de práctica clínica sobre el diagnóstico y tratamiento de la insuficiencia cardiaca crónica (versión resumida, actualización 2005). *Rev Esp Cardiol.* 2005;58:1062-92.
2. Torres F, Anguita M, Jiménez D, Mesa D, Tejero I, Franco M, et al. Evolución a largo plazo de la miocarditis aguda. Estudio prospectivo de una serie de 99 pacientes (1987-1995). *Rev Esp Cardiol.* 1996;49:723-31.
3. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med.* 2000;342:1077-84.
4. Godsel LM, León JS, Engman D. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists in experimental myocarditis. *Curr Pharm Des.* 2003;9:723-35.
5. Nakazawa JW, Watanabe K, Ma M, Wahed MI, Hasegawa G, Natio M, et al. Quinapril inhibits progression of heart failure and fibrosis in rats with dilated cardiomyopathy after myocarditis. *Mol Cell Biochem.* 2003;251:77-82.
6. Rezkalla S, Kloner RA, Khatib G, Khatig R. beneficial effects of captopril in acute coxsackievirus B3 murine myocarditis. *Circulation.* 1990;81:1039-46.