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ORIGINAL ARTICLE

Differential Effects of Prevention and Reversal Treatment with Lisinopril on Left Ventricular Remodelling in a Rat Model of Heart Failure

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Background Angiotensin converting enzyme (ACE) inhibitors such as lisinopril, represent the front line pharmacological treatment for heart failure, which is characterised by marked left ventricular (LV) dilatation and hypertrophy. This study sought to determine whether initiating treatment with ACE inhibitors at different stages in the remodelling process would alter the efficacy of treatment.

Methods To this end, LV size and function were determined in the aortocaval (AV) fistula model of volume overload-induced heart failure. Sprague-Dawley rats were assigned to sham, untreated AV fistula (21 weeks), AV fistula treated with lisinopril (21 weeks), or AV fistula treated with lisinopril from six to 21 weeks post-fistula groups.

Results Administration of lisinopril for the entire 21-week period prevented LV dilatation, attenuated myocardial hypertrophy and prevented changes in myocardial compliance and contractility, whereas delaying initiation of treatment until six weeks post-fistula attenuated LV dilatation and hypertrophy, however, the delayed onset of treatment had no beneficial effect on ventricular compliance or systolic function.

Conclusions The results demonstrate differential effects that can occur with ACE inhibitors depending on the stage during the remodelling process at which treatment is administered.

Keywords Angiotensin converting enzyme inhibitor • Volume overload • Hypertrophy • Heart failure

Introduction

Angiotensin converting enzyme (ACE) inhibitor therapy has become standard practice for the treatment of heart failure [1], in large part due to the success of clinical trials such as SOLVD, in which enalapril prevented left ventricular (LV) dilatation and improved systolic function in mild to moderate heart failure patients [2], and SAVE, where survival following myocardial infarction was improved by captopril treatment [3]. Previously, we demonstrated in the aortocaval (AV) fistula model of volume overload-induced heart failure, that treatment with the ACE inhibitor lisinopril, initiated at the time volume overload was imposed, prevented LV dilatation and maintained normal LV compliance [4]. The beneficial effects of lisinopril were attributable to its ability to inhibit matrix metalloproteinase (MMP) activity by directly

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binding to MMPs [4]. While this was an important observation, in clinical practice ACE inhibitor treatment is often not initiated until the patient becomes symptomatic, at which point the myocardial remodelling process is already well underway and frequently the heart has already begun to decompensate. Thus, this study sought to determine if the time at which ACE inhibitor treatment is initiated during the remodelling process may have differing effects and, thus, be critical to determining the degree of success. The current study used the AV fistula model of volume overload-induced congestive heart failure to compare the effects of lisinopril on LV structure and function, where lisinopril treatment was initiated either at the time of creation of volume overload (prevention), or six weeks after the creation of volume overload (regression). We hypothesised that lisinopril treatment initiated six weeks after the creation of volume overload would be less beneficial on myocardial remodelling and function than prevention treatment. Herein we report that both prevention and regression treatments with lisinopril markedly attenuated LV dilatation, as well as LV and right ventricular (RV) hypertrophy, while only preventative lisinopril treatment was able to prevent increased myocardial compliance and loss of intrinsic systolic function.

Materials and Methods

All experiments were performed using adult male Sprague-Dawley (Hsd:SD) rats housed under standard environmental conditions and maintained on commercial rat chow and tap water *ad libitum*. All studies conformed to the principles of the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. The protocol was also approved by the University's Animal Care and Use Committee. Anaesthesia for surgical procedures and subsequent euthanasia at the experimental endpoint was induced by intraperitoneal injection of sodium pentobarbital (50 mg/kg). Post-operative analgesia was achieved by administration of buprenorphine HCl (0.025 mg/kg, s.c).

Experimental Design

These experiments were designed to determine whether lisinopril administered six weeks after the induction of a sustained cardiac volume overload could achieve improved structural and functional adaptations in a manner comparable to prevention treatment with lisinopril. Prior to surgery, rats were randomly divided into sham (n=10), 21-week untreated AV fistula (n=14), 21-week AV fistula continually treated with lisinopril (n=9, prevention) and AV fistula treated with lisinopril where treatment was initiated six weeks following the creation of an AV fistula and continued through to 21 weeks post-fistula (n=12, regression). Lisinopril (Sigma, St Louis Missouri) was administered in the drinking water at a concentration of 100 mg/L. The time-point of six weeks post-fistula was chosen to begin lisinopril treatment in the regression group because it represents a period in the remodelling process where there is already ventricular dilatation and increased myocardial compliance. Thus, this would represent a time where the hearts of patients are already decompensated when they first begin ACE inhibitor therapy.

Surgical Preparation

An AV fistula was created as previously described [5]. Briefly, the aorta and caudal vena cava were exposed via ventral abdominal laparotomy. Both vessels were occluded proximal and distal to the intended puncture site before an 18-gauge needle was inserted into the abdominal aorta and advanced through the medial wall of the vena cava and subsequently withdrawn. The ventral aortic puncture was sealed with cyanoacrylate and flow restored. Successful creation of a fistula was confirmed by the presence of pulsatile oxygenated blood flow in the vena cava. Incisions to the musculature and skin were closed with absorbable sutures and autoclips, respectively.

Ventricular Function

At the conclusion of the study period, each rat was weighed, anaesthetised, fistula patency visually confirmed, and the heart removed and attached to a perfusion apparatus for evaluation of LV function. LV volume and function were assessed using a blood-perfused isolated heart preparation as previously described [4–10]. Briefly, the apparatus consisted of a pressurised (100-105 mmHg) perfusion reservoir and a collection reservoir connected in circuit with a support rat. LV volumes and pressures from unpaced hearts were recorded using a latex balloon inserted into the LV through the mitral valve orifice. Once the heart developed stable isovolumetric contractions, the balloon volume (V_0) producing a LV end diastolic pressure (EDP) of 0 mmHg was determined. Balloon volume was then increased in 20 µl increments until an LVEDP of 25 mmHg was attained. The EDP and peak isovolumetric pressure, which were recorded following each increase in balloon volume, were then used to assess LV diastolic function and intrinsic contractility (i.e. slope of the linear isovolumetric pressure-volume relationship; P_{max}-V) Following completion of the experiment the RV was dissected away and the LV plus septum and RV were weighed.

Statistical Analysis

Grouped data comparisons were made by one-way analysis of variance (ANOVA) using SPSS 11 software (SPSS Inc., Chicago, IL). When a significant F test ($P \leq 0.05$) was obtained, intergroup comparisons were analysed using Fisher's protected least significant difference post-hoc testing.

Results

Biometric Parameters

Body weight, LV weight and RV weight are reported in Table 1. Body weight was significantly increased in the 21-week untreated fistula group, indicative of oedema secondary to heart failure. This was prevented by lisinopril