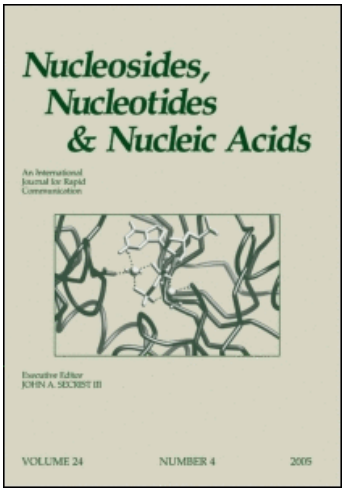

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PREVENTION OF ADRIAMYCIN INDUCED HEART FAILURE BY AN INCREASE IN ENDOGENOUS ADENOSINE PRODUCTION

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▫ *Adenosine (Ado) triggers several protective mechanisms that may attenuate development of heart failure, both locally and systemically. We developed a procedure allowing sustained increase in endogenous Ado production by the combined application of Ado metabolism inhibitors and nucleotide precursors. We found that our procedure attenuate the development of heart failure induced by adriamycin.*

Keywords Adenosine, Heart Failure, Cardiac Function, Nucleotides

INTRODUCTION

Adenosine (Ado) is a catabolite of adenine nucleotides. It regulates coronary flow, inflammation, immune response contractility and thrombosis.[1,2] Although Ado has a very short half-life, it has been proven that Ado is a cardioprotective agent during ischemia/reperfusion.[3,4] We have previously found that the application of Ado metabolism inhibitors increases Ado production but causes the depression of the adenine nucleotide pool and ATP depletion. However, if we combined the Ado metabolism inhibitors with the nucleotide precursors, it will allow to maintain the

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adenine nucleotide pool.[5] In this study, we evaluated whether this procedure will attenuate development of experimentally induced heart failure.

MATERIALS AND METHODS

Sprague-Dawley rats were used in these studies. All animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* published by the National institutes of Health. To evaluate the changes in adenosine and other purines concentration following the administration of the inhibitor/substrate solution, rats were given an intraperitoneal injection containing Ado deaminase inhibitor-deoxycoformycin, Ado kinase inhibitor-5′-aminoadenosine and nucleotide precursors-adenine and ribose. Blood samples were collected from the femoral vein at a regular interval, extracted, and analyzed by HPLC.[6] After these preliminary studies, in two experimental groups (AC, AT), heart failure was induced by repeated intraperitoneal injections of adriamycin for 2 weeks, while in two other groups saline was injected (CC, CT). Subsequently, in the following 4 weeks an inhibitor/substrate solution was administered in treated groups (AT, CT) in the form of daily intraperitoneal injections while saline was given to controls (AC, CC). Cardiac function was monitored using transthoracic echocardiography and is expressed as left ventricular ejection fraction (EF ± S.E.M).

RESULTS AND DISCUSSION

Blood adenosine concentration was increased 5 min after the injection (Figure 1). Concentration was highest at 15 min, remained elevated for 6 h, and

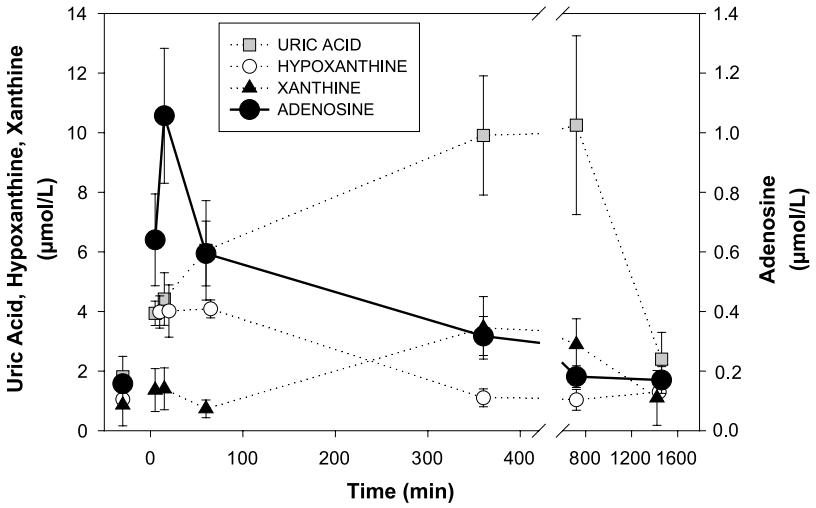

FIGURE 1 Blood concentrations of adenosine and other purine metabolites in rats following administration of Ado metabolism inhibitors and nucleotide precursors.

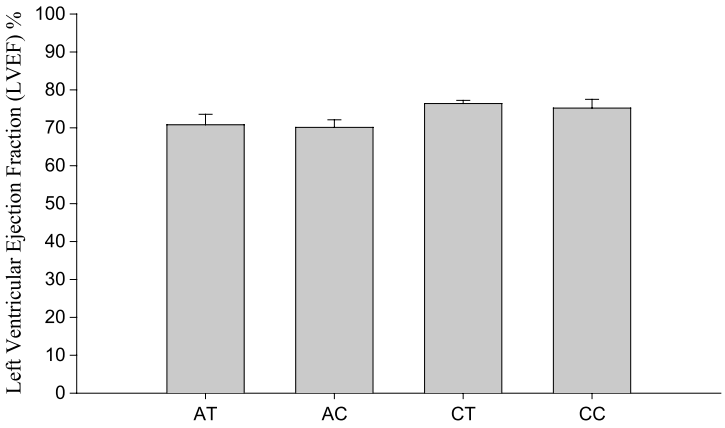

FIGURE 2 Cardiac function in experimental groups at the beginning of the experiment. No difference was observed.

returned to normal after 12 h. The concentration of hypoxanthine and uric acid increased shortly after the injection and xanthine concentration increased at the later stage. All purines concentrations returned to their normal levels after 24 h. In the second study, there were no differences in the cardiac function at the beginning of the experiment between all 4 groups (Figure 2). However, following 2 weeks of adriamycin administration and 4 weeks of treatment, heart failure developed in the AC group, which was prevented in AT group. Cardiac function was not changed in CC or CT groups (Figure 3).

We found that Ado metabolism inhibitor together with the nucleotide precursors increased endogenous Ado production. This increased in Ado

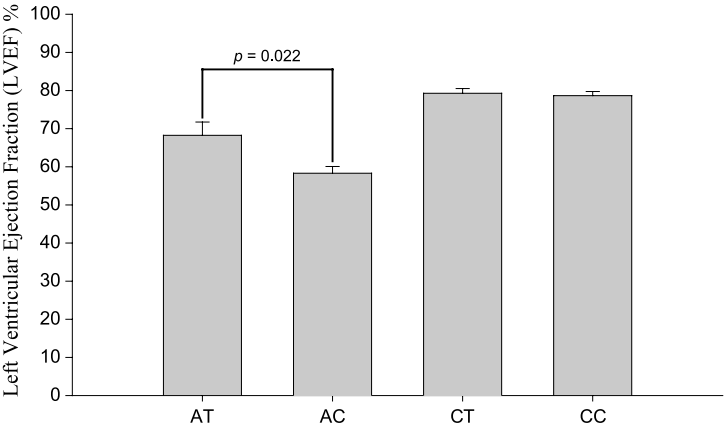

FIGURE 3 Cardiac function following 2 weeks of adriamycin administration and 4 weeks of treatment with Ado metabolism inhibitors and nucleotide substrates. Heart failure development was prevented in AT group ($p = 0.022$).

production partially protected from adriamycin-induced heart failure. We conclude that the regulation of Ado production by inhibition of Ado metabolism and provision of nucleotide substrates might be a variable therapeutic strategy, beneficial not only during ischemia/reperfusion injury or allograft rejection as we have shown before,[7] but also to prevent heart failure.

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