A1 Adenosine Receptor Upregulation Accompanies Decreasing Myocardial Adenosine Levels in Mice With Left Ventricular Dysfunction

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Background—It is well known that adenosine levels are increased during ischemia and protect the heart during ischemia/reperfusion. However, less is known about the role of adenosine–adenosine receptor (AR) pathways in hearts with left ventricular dilation and dysfunction. Therefore, we assessed adenosine levels and selective AR expression in transgenic mice with left ventricular systolic dysfunction secondary to overexpression of tumor necrosis factor-α (TNF 1.6).

Methods and Results—Cardiac adenosine levels were reduced by 70% at 3 and 6 weeks of age in TNF 1.6 mice. This change was accompanied by a 4-fold increase in the levels of A1-AR and a 50% reduction in the levels of A2A-AR. That the increase in A1-AR density was of physiological significance was shown by the fact that chronotropic responsiveness to the A1-AR selective agonist 2-chloro-N6-cyclopentanyladenosine was enhanced in the TNF 1.6 mice. Similar changes in adenosine levels were found in 2 other models of heart failure, mice overexpressing calsequestrin and mice after chronic pressure overload, suggesting that the changes in adenosine-AR signaling were secondary to myocardial dysfunction rather than to TNF overexpression.

Conclusions—Cardiac dysfunction secondary to the overexpression of TNF is associated with marked alterations in myocardial levels of adenosine and ARs. Modulation of the myocardial adenosine system and its signaling pathways may be a novel therapeutic target in patients with heart failure. (Circulation. 2007;115:2307-2315.)

Key Words: adenosine ■ heart failure ■ mice, transgenic ■ receptors

The ubiquitous purine nucleoside adenosine regulates a variety of cardiovascular functions, including growth and differentiation, angiogenesis, coronary blood flow, cardiac conduction and heart rate, substrate metabolism, and sensitivity to adrenergic stimulation.1,2 These effects are modulated by the quantity of myocardial adenosine and by the number of functional adenosine receptors (ARs) expressed on the cell surface. Four known G protein–coupled AR subtypes (A1, A2A, A2B, and A3) have been identified and are expressed in a tissue-specific manner.2 Although controversial, a substantial body of evidence supports the finding that myocardial levels of adenosine increase during ischemia and that increased levels of adenosine play a role in protecting the heart during and after an ischemic insult.3–6 Indeed, genetic deletion of A1-AR limits the ability of mouse myocardium to withstand injury during ischemia/reperfusion,7 whereas A1-AR overexpression confers enhanced tolerance.8

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Far less is known about the role of adenosine in the failing heart. Adenosine levels have been reported to be elevated in patients with heart failure.9 In addition, subjects with heart failure who harbor a nonsense mutation in the AMP deaminase gene, resulting in high levels of muscle adenosine, have a markedly improved survival compared with patients having the wild-type (WT) genotype.10 In contrast, recent studies have reported that high levels of overexpression of A2A-AR or A3-AR in the heart can have untoward effects.11–13 Indeed, overexpression of high levels of A2A-AR results in the development of a dilated cardiomyopathy. However, information is not available on changes in adenosine signaling in the failing heart. Therefore, the present study was undertaken to evaluate the myocardial adenosine system in a well-studied model of heart failure, transgenic mice with left ventricular systolic dysfunction.
dysfunction secondary to overexpression of tumor necrosis factor-α (TNFα).14–16

Methods

Animal Model

Experiments were carried out in TNFα mice with cardiac-restricted overexpression of TNFα (TNF 1.6).14–16 Nontransgenic mouse litters served as controls, and unless otherwise noted, all mice were male. The TNF 1.6 mice were engineered on an FVB background. Studies also were performed in 2 additional murine heart failure models: mice overexpressing calsequestrin17,18 in a DBA/2 background and C57BL/6 mice that underwent long-term aortic banding. We also studied TNF 1.6 mice that were crossed with mice in which either the TNFα receptor 1 (TNFR1) or receptor 2 (TNFR2) had been ablated as previously described.19 All protocols were approved by the Institutional Animal Care and Use Committee of Thomas Jefferson University.

Chemicals

The nonselective AR agonists 2-chloroadenosine (CADO) and N6-2-phenylisopropyl-adenosine, the A1-AR–selective agonist 2-chloro-N6-cyclopenyladenosine (CPA), and the A2aAR–selective agonist 2-p-(2-carboxyethyl)phenethylamino-5′-N-ethylcarboxaminoadenosine hydrochloride (CGS21680) were purchased from Sigma-Aldrich Co (St Louis, Mo). Radiolabeled [3H]DPCPX was purchased from Aldrich Co (St Louis, Mo). Radiolabeled [3H]DPCPX was purchased from Aldrich Co (St Louis, Mo).

Echocardiography

Echocardiographic studies were performed with an ultrasonicographic system (Acuson Sequoia C256; Seimens Medical Solutions, Malvern, Pa) as previously described14,15 after anesthesia with 2.5% Avertin (10 mL/g body weight IP, Sigma-Aldrich Co, St Louis, Mo). A 1:1000 dilution: anti–A1-AR (Affinity BioReagents, Golden, Colo), anti–A2a-AR (Alpha Diagnostics, Owings Mills, Md), anti–ectonucleotide pyrophosphatase/phosphodiesterase 2 (Ennp2, Cayman Chemical, Ann Arbor, Mich), anti–xanthine oxidase (XO, Laboratory-Vision, Freemont, Calif) and anti-GADPH (Fitzgerald Industries International, Inc., Concord, Mass).

Immunohistochemistry

The immunostaining with anti–A1-AR antibody was performed on the Dako Autostainer (Dako, Glostrup, Denmark) by MDR Global Systems (Windber, Pa). Briefly, frozen sections of LV myocardium were cut at 5 to 7 μm and placed on positively charged slides. The slides were allowed to dry at room temperature and then fixed in acetone. A peroxide procedure was used to block endogenous peroxidase. The primary antibody was applied to the slides and then detected by a non–avidin-biotin polymer peroxidase detection system. Diaminobenzidine/hydrogen peroxide was used for color visualization. Once staining was completed, all the slides were counterstained with hematoxylin.

Surgical Procedure for Aortic Banding

Six-week-old male C57BL/6 mice were anesthetized with 2.5% Avertin (10 μL/g body weight IP) and placed in the supine position. Mice were ventilated with a tidal volume of 0.15 mL and a respiratory rate of 120 breaths per minute. After a 0.5- to 1.0-cm-long vertical skin incision was made at the level of the suprasternal notch, a 2- to 3-mm longitudinal incision was made in the proximal portion of the sternum to allow visualization of the aortic arch under low-power magnification. An aortic band was created by placing a ligature (7-0 nylon suture) securely between the origin of the right innominate and left common carotid arteries with a 28-gauge needle as the suture was secured around the needle, it was quickly removed. The skin was closed, and mice were allowed to recover on a warming pad until they were fully awake. The sham procedure was identical except that the aorta was not ligated. Ten weeks after banding, echocardiography was performed on the mice, and hearts were harvested.

Affymetrix Microarray Hybridization and Data Analyses

Affymetrix (Santa Clara, Calif) microarray analyses were performed using a standard protocol as described previously.20 In brief, total RNA was extracted from the biventricular tissues, and 10 μg total RNA was used to synthesize double-stranded cDNA with a SuperScript kit (Invitrogen, Carlsbad, Calif), incorporating a T7 oligo(dT)24 promoter primer. Biotin-labeled cRNAs were then generated from the cDNA and hybridized to Affymetrix murine U74Av2.
microarrays. RNA isolated from individual mice was hybridized on individual chips, and each experimental grouping consisted of 3 chips. Data were analyzed with the Affymetrix GeneChip Operating Software and Affymetrix Data Mining Tool 2.0. Genes were considered significant if probability values were <0.05 for both statistical tests; signal intensity was >100. The analyses detailed here comply with minimal information about a microarray experiment guidelines established by the Microarray Gene Expression Data Society (www.mged.org), and the expression data for all samples described in the present study can be obtained from Gene Expression Omnibus website (http://www.ncbi.nlm.nih.gov/geo/). The Gene Ontology Mining Tool (Affymetrix website) was used to define gene groups according to their function.

Enzyme-Linked Immunosorbent Assay

The protein levels were assessed with kits for mouse TNFα (Quantikine, R&D Systems, Minneapolis, Minn) according to manufacturer’s instructions as previously described.23 Results were expressed as picograms of target proteins per gram of tissue protein.

Cardiac ATP, ADP, and AMP Measurements

AMP, ADP, and ATP were measured by ion-pairing high-performance liquid chromatography separation as described previously.24 In brief, under isoflurane anesthesia and with ventilation, beating hearts were exposed by opening the mouse chest cavity. Exposed hearts were then clamped with liquid nitrogen–cooled aluminum blocks (Wollenberger clamp25,26) to smash into a thin layer. The frozen hearts were preserved in −80°C and transported in dry ice.

Frozen samples (20 to 30 mg) were pulverized in a porcelain mortar and pestle under liquid N₂. The frozen powder was homogenized in a glass grinding tube containing 600 mL of 1.2 mol/L perchloric (4°C). The slurry was neutralized with 1 mol/L K₂HPO₄, pH 12, and centrifuged. The supernatant was centrifuged at 14,000 rpm for 5 minutes, and the resulting supernatant was centrifuged for a second time. The resulting supernatant was filtered. Ad2P5, an adenosine kinase inhibitor, was added, and the solution was filtered. The tissues were then homogenized with a power homogenizer.

Cardiac Adenosine Measurements

Adenosine was measured on a Thermofinnigan LCQ Duo mass spectrometer equipped with electrospray ionization as described.27 The tissues were then homogenized with a power homogenizer. The homogenate was centrifuged at 14,000 rpm for 5 minutes, and the supernatant was centrifuged for a second time. The resulting supernatant was loaded onto centrifugal filter devices (Biomax-30, Millipore, Billerica, Mass) and filtered to remove proteins. Aliquots were used for analysis.

Adenosine was measured on a Thermofinnigan LCQ Duo mass spectrometer equipped with electrospray ionization.27 Extracted supernatants were resolved on a C18 column with water methanol containing 7.5 mmol/L N,N-dimethylhexylamine (ion pair agent) at a flow rate of 0.5 mL/min. The filtrate was diluted 1:100 in water, and the supernatant was centrifuged. The supernatant was filtered. Adenosine was measured on a Thermofinnigan LCQ Duo mass spectrometer equipped with electrospray ionization.27 Adenosine and adenine 9-D-arabinofuranoside (internal standard), were used for analysis.

Statistical Analysis

Analysis was performed with SPSS for Windows (version 11.5, SPSS Inc, Chicago, Ill) and detailed in the figure legends. The results are presented as mean±SEM. In vivo cardiac responsiveness (the slope) between the experimental value before drug administration and the experimental value at 10 minutes after administration was compared with an ANOVA general linear model with repeated measures. Positive correlation between adenosine levels and fractional shortening was obtained through linear regression. All other data used nonparametric methods to protect against violation of ANOVA assumptions and 2-tailed probability value calculation. Differences were considered statistically significant at P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Adenosine Levels in TNF 1.6 Mice

Baseline echocardiographic and hemodynamic data for TNF 1.6 mice are given in Table 1. As reported previously, these mice demonstrated LV dilation, marked diminution in heart rate and fractional shortening, and significant increases in LV end-diastolic pressure and ventricular weight. As seen in the chromatograph, these changes in cardiac morphology and function were associated with a substantial decrease in myocardial adenosine levels in 6-week-old TNF 1.6 mice compared with gender-matched nontransgenic controls (Fig-
We also observed a significant decrease in adenosine levels in young TNF 1.6 mice (3 weeks of age) before the onset of profound morphological and hemodynamic changes and in 22-week-old mice with end-stage disease (Figure 1B). We compared the traditional Wollenberger clamp method with our modified rapid pinch-excision method. Both methods worked equally well in preserving adenosine (data not shown).

**Regulation of A1-AR and A2A-AR**

The change in myocardial adenosine levels was associated with subtype selective alterations in the expression of ARs. As seen in Figure 2A, A1-AR expression was enhanced 4.9-fold in TNF 1.6 myocardium. In contrast, A2A-AR was decreased by 40% in the same samples (Figure 2A). The changes in protein levels for A1-AR were largely independent of steady-state levels of the A1-AR mRNA (WT versus TNF 1.6, 100±23% versus 70±32%; n=5). Consistent with analysis of receptor levels by Western blotting, A1-AR binding was significantly higher in the TNF 1.6 myocardium than in age- and gender-matched controls (Figure 2B). It is not unexpected that the Western blotting would give higher values than radioligand binding because Western blotting assesses the total amount of protein in a tissue, whereas radioligand binding detects only receptors that are in the correct conformation and are present on the membrane surface. Thus, receptors that are “downregulated” would not be identified by radioligand binding assays. More important, both methods demonstrated the same finding, ie, an increase in the amount of A1-AR. Finally, when A1-AR levels were measured in 12-week-old male TNF 1.6 mice that had been crossed with TNFR1 knockout mice, A1-AR levels were not changed compared with age-matched WT controls (Figure 2C). Ablation of TNFR1 but not TNFR2 blocks cardiotoxic effects in TNF 1.6 mice.

To identify the cell types that expressed A1-AR protein, we stained WT and TNF 1.6 myocardium with an anti–A1-AR antibody. As shown in Figure 2D, in WT and TNF 1.6 mouse hearts, A1-AR was expressed throughout the myocardium but was more abundant in the TNF 1.6 hearts. An important point is that all cell types, including cardiac myocytes, had enhanced A1-AR staining in TNF 1.6 hearts. The specificity for binding was shown by the fact that binding could be inhibited by competition with a selective peptide (Figure 2D).

**A1-AR–Specific Functional Response**

To determine whether the changes in A1-AR levels had functional significance in TNF 1.6 mice, we determined the chronotropic response to the selective A1-AR agonist CPA. In WT mice, CPA effectively decreased heart rate. However, as seen in Figure 3A, CPA produced a far more robust decrease in heart rate in TNF 1.6 mice compared with age- and gender-matched WT controls. However, CPA increased arterial pressure and cardiac contractility only slightly (Figure 3B). In contrast, infusion of the nonselective adenosine

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A, High-pressure liquid chromatography/mass spectrometry analysis for adenosine level in the ventricles of TNF 1.6 and age-matched WT mice. B, Average adenosine levels in 3-, 6-, and 22-week-old WT and TNF 1.6 mice. Values are mean±SEM (n=3 to 6) and were analyzed with the nonparametric method. *P<0.05 vs WT.
agonist CADO or the A2A-AR–selective agonist CGS21680 had similar effects in TNF 1.6 and WT mice.

Myocardial Adenosine Levels in Models of LV Dysfunction
To insure that the changes in adenosine levels in mice with heart failure secondary to TNFα overexpression were reflective of changes in LV function and not simply a phenomenon associated with constitutive overexpression of TNFα, we evaluated adenosine levels in other models of heart failure and maladaptive cardiac remodeling: mice with LV dysfunction secondary to overexpression of CSQ and mice with cardiac dysfunction secondary to surgically induced chronic pressure overload. As seen in Figure 4A, mice overexpressing CSQ and mice with surgically induced cardiac pressure overload both demonstrated significant decreases in myocardial adenosine levels compared with the appropriate WT or sham-operated (for aortic constriction model) controls. In addition, an inverse linear relationship existed between LV performance as measured by fractional shortening and adenosine levels across the 3 heart failure models (Figure 4B). In contrast to TNF 1.6 mice, cardiac TNFα expression in both CSQ and banded mice was almost undetectable despite significant decreases in LV function (Figure 4C). Although controversial, adenosine production in disease is thought to occur through the metabolism of ATP.28 However, as seen in Table 2, we did not see a change in ATP levels in TNF1.6 mice compared with controls.

Expression Profiling of TNF 1.6 Mice
To identify changes in enzymes that might contribute to the production of either adenosine or adenosine precursors, we performed gene profiling using an Affymatrix platform. Of the 5962 genes screened in mRNA isolated from the hearts of 6-week-old TNF 1.6 and WT control mice, we identified 2 ATP synthase components with an expression that was significantly decreased in the TNF 1.6 mice: ATP synthase, H1001-transporting, mitochondrial FO complex, subunit F (Atp5j) and ATP synthase, H1001-transporting, mitochondrial F1 complex, subunit O (Atp5o) (data not shown). These results were confirmed by real-time PCR quantification (Figure 5A). In contrast, mRNA levels of Enpp2 were substantially increased in the myocardium. Enpp2, also known as autotoxin, is an integral membrane enzyme that degrades extracellular ATP, ADP, AMP, and cAMP to adenosine. Real-time PCR on mRNA isolated from the same gender- and age-matched mice confirmed the findings from the Affymatrix displays (Figure 5B). Finally, we determined the expression of the 2 major enzymes involved in adenosine catabolism: purine nucleoside phosphorylase and xanthine dehydrogenase/XO. Real-time PCR data showed that both enzymes were significantly enhanced in TNF 1.6 myocardium compared with WT controls (Figure 5C). To the best of our knowledge, this is the first evidence of purine nucleoside phosphorylase upregulation in the failing heart, although XO has been shown to be upregulated in cases of TNFα overexpression. Upregulation of ENPP2 and XO proteins in TNF1.6 myocardium was confirmed by immunoblotting with specific anti-Enpp2 and anti-XO antibodies (Figure 5D).

Discussion
The present study demonstrates for the first time that myocardial levels of adenosine are markedly decreased in mice with diminished LV performance. The decrease in myocardial adenosine levels was seen both early and late in the development of cardiac dilation and was accompanied by a robust increase in the levels of the A1-AR and a small significant decrease in the
and increased its functional coupling with adenylyl cyclase accompanied by an increase in the function of the A2A-AR.

The finding of a differential effect on A1- and A2A-AR signaling in this animal model is consistent with earlier data demonstrating that adenosine has disparate and, in fact, opposite effects of A1-AR agonists on heart rate and hemodynamics may cause the transient augmentation of dP/dt.37,38 Because TNF 1.6 responded to A1-AR agonists differently than WT mice, the effects of A1-AR agonists on heart rate and hemodynamics may be dependent on the mode of administration, experimental system, and physiological state of the myocardium. It should be noted that Liao et al39 showed that A1-AR agonists delivered regularly via minipump attenuated cardiac hypertrophy and prevented heart failure in mice with LV pressure overload but had no effect on heart rate.

In addition, the administration of CADO did not differentiate heart rate response between WT and TNF 1.6 mice. CADO, an adenosine analogue, activates all 4 cardiac adenosine receptor subtypes, each of which affects physiological outcomes by interacting with either stimulatory or inhibitory G proteins. Therefore, the physiological effect of any adenosine agonist is due in large part to the stoichiometric balance between receptor number and receptor affinity. Thus, in the presence of a “balanced” agonist, the overall effect on heart rate (or on contractility) may be negligible. The finding that the TNFα mice demonstrated a decrease in heart rate at baseline was consistent with an earlier study that demonstrated a decrease in heart rate in mice overexpressing TNFα.40

The results of the present study are disparate from measurements in patients with heart failure secondary to LV systolic dysfunction.9,41 However, the adenosine cellular reuptake inhibitor dipyridamole failed to effect an increase in plasma adenosine levels in patients with heart failure,42 suggesting that despite higher levels of adenosine in the peripheral circulation, the number of A2A-ARs. These changes in receptor density were seen by immunoblotting, radioligand binding, and immunohistochemical staining of cardiac myocytes but were not associated with a change in the steady-state levels of the mRNA encoding the A1-AR, suggesting that the change in receptor density was modified posttranslationally. A decrease in adenosine levels also was seen in mice with cardiac dysfunction secondary to overexpression of CSQ and to ascending aortic banding, suggesting that a decrease in adenosine levels might be attributable to activation of a non–TNFα-mediated pathway.

The increase in A1-AR density appears to follow the loss of adenosine in the failing mouse heart as a potential compensatory mechanism. To increase adenosine responsiveness, the interplay between specific ARs is complex. A1-AR–selective agonists desensitize A1-ARs through uncoupling, downregulation, and phosphorylation10 in a time- and dose-dependent fashion,31 whereas A2A-AR antagonists increased the density of the A1-AR and increased its functional coupling with adenyl cyclase inhibition.32 Less is known about the regulation of the A2A-AR. However, studies suggest that although selective A2A-AR agonists can effect a desensitization of the A2A-AR, they do not cause a change in receptor number.33 Furthermore, the loss of A2A-AR function in the presence of adenosine analogues is accompanied by an increase in the function of the A1-AR, effects that are reversed in the presence of an adenosine receptor antagonist.33 The finding of a differential effect on A1- and A2A-AR signaling in this animal model is consistent with earlier data demonstrating that adenosine has disparate and, in fact, opposite effects on the expression of these 2 receptor subtypes.34 Therefore, the selective changes in AR subtypes in the presence of a marked decrease in myocardial adenosine suggest that the change in adenosine levels in the TNF 1.6 mice is a specific biological response.

That the change in the level of the A1-AR receptor was of number and receptor affinity. Thus, in the presence of a "balanced" agonist, the overall effect on heart rate (or on contractility) may be negligible. The finding that the TNFα mice demonstrated a decrease in heart rate at baseline was consistent with an earlier study that demonstrated a decrease in heart rate in mice overexpressing TNFα.40

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human failing heart may not have an adenosine reserve. These disparities between human and murine hearts also may be explained by the use of concomitant medications in heart failure patients or by the significant species differences that have been well described in the pharmacology of adenosine and ARs.2

The finding that adenosine levels decrease in a murine model of heart failure also differs markedly from changes in myocardial adenosine levels seen in murine and rodent models of ischemic heart disease. In ischemia, a rapid and immediate increase takes place in cardiac adenosine concentrations43–45 that serves as an intrinsic protective mechanism. In contrast, the role of adenosine in murine heart failure is far less clear. Consistent with the present results, Meyer et al46 showed that adenosine production was initially increased during the compensated phase of pressure-overloaded rat heart; however, myocardial adenosine production decreased during cardiac decompensation. In contrast, activation of A1-AR attenuated the development of cardiac hypertrophy and heart failure in mice with aortic banding.39 However, overexpression of A1-AR diminished Ca2+ transport into the sarcoplasmic reticulum,47 increased the heart-to-body-weight ratio, and decreased the response to catecholamines without influencing intrinsic myocardial contractility in C57Bl6 mice48 but caused marked cardiac dilatation and dysfunction in friend virus B-type mice.12 Thus, it is unclear whether the marked decrease in myocardial adenosine levels found in the TNF 1.6 mice is cardioprotective or maladaptive.

To understand the regulatory pathways that might alter adenosine production in the TNF 1.6 mice, we performed gene profiling using the Affymatrix platform. These studies identified a marked increase in the expression of the Enpp2 gene, a gene that encodes an integral membrane enzyme class that degrade 5’ phosphates of nucleotides. However, the physiological role of increased Enpp2 is unclear because the levels of ATP in the hearts of the TNF 1.6 mice were unchanged. In contrast, we also found that both major enzymes involved in adenosine catabo-
lism, purine nucleoside phosphorylase and XO, were upregulated in TNF 1.6 mice (Figure 5C). These findings are consistent with the changes in XO activity in other animal models of heart failure, and hydroxyl radicals, known stimulants of XO activity, are significantly elevated in TNF 1.6 mice. However, the relative contribution of each of these enzyme pathways to the decreased adenine levels in TNF 1.6 mice remains to be defined because they depend on the substrate concentration, enzyme kinetics, and abundance of each nucleotide in the failing heart.

In summary, our data suggest that altered adenine and A1-AR signaling contribute to the pathobiology of the heart muscle in several mouse models with ventricular dysfunction, including TNFα overexpression, CSQ overexpression, and surgically induced pressure overload. One limitation of the present study is that we have not demonstrated the role that adenosine plays in the development of heart failure. Therefore, additional experimental approaches, including transgenic and knockout models and clinical studies, are required to better understand the role of adenosine and ARs. However, the adenosinergic pathway may provide a novel therapeutic target for the treatment of patients with heart failure.

Acknowledgments

We are grateful to Huamei He, MD, PhD, and James A. Balschi, PhD (Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School), for measuring adenine nucleotides in our samples.

Sources of Funding

This work was supported by National Institutes of Health grant RO1 DK68575 (Dr Jackson), Pennsylvania Research Formulary Fund (Dr Feldman), Pennsylvania Research Formulary Fund (Dr Chan), and American Heart Association grant SDG F64702 (Dr Chan).

Disclosures

None.

References

Adenosine plays a critical role in the heart. Through interactions with specific receptor subtypes, adenosine can elicit a variety of physiological effects. For example, a large body of work has shown conclusively that myocardial levels of adenosine increase during even brief periods of ischemia and mediate the phenomenon of ischemia preconditioning. Far less is known about the role of adenosine in the failing heart. Several small studies suggest that circulating levels of adenosine are elevated in patients with heart failure; however, the effects of left ventricular dysfunction on myocardial levels of adenosine are unknown. Furthermore, recent studies in transgenic mice suggest that overexpression of the A1-adenosine receptor in mice results in adverse but reversible changes in cardiac morphology and function. Circulation. 2006;114:2240–2250.

CLINICAL PERSPECTIVE
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Circulation. 2007;115:2307-2315; originally published online April 16, 2007;
doi: 10.1161/CIRCULATIONAHA.107.694596
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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