

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 July 2009 (30.07.2009)

PCT

(10) International Publication Number
WO 2009/094593 A1

(51) International Patent Classification:
A01N 43/04 (2006.01)

(21) International Application Number:
PCT/US2009/031910

(22) International Filing Date: 23 January 2009 (23.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/023,712 25 January 2008 (25.01.2008) US

(71) Applicant and

(72) Inventor: **FOKER, John, E.** [US/US]; 112 Black Bass Road, River Falls, WI 54022 (US).

(74) Agent: **HUSTON, Marilyn, M.**; Wong, Cabello, Lutsch, Rutherford & Bruculeri, LLP, 20333 SH 249, Ste. 600, Houston, TX 77070 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

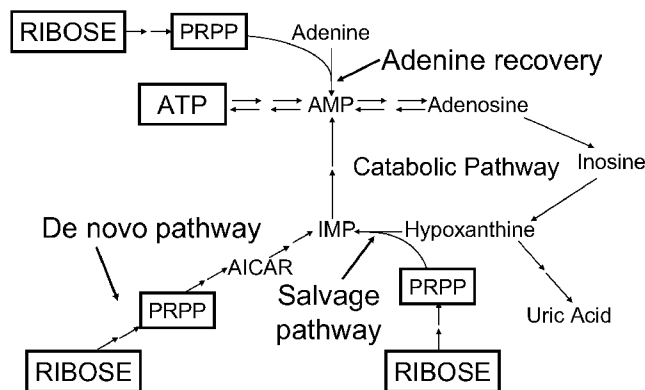
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

(54) Title: METHODS AND COMPOSITIONS FOR INHIBITING PROGRESSION TO CHRONIC CARDIAC FAILURE

Figure 1

Adenine nucleotide metabolism



(57) Abstract: The present invention provides methods and formulations for preventing or ameliorating progression to chronic heart failure subsequent to cardiac stress, including as a consequence of myocardial infarction (MI), coronary artery disease, hypertension, cardiomyopathy, myocarditis, valvular regurgitation, severe lung disease, and/or severe anemia of chronic disease, by administration of one or more rate-limiting precursors to the synthesis of ATP. In one embodiment the ATP precursor is a pentose selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose.

WO 2009/094593 A1

METHODS AND COMPOSITIONS FOR INHIBITING PROGRESSION TO CHRONIC CARDIAC FAILURE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority based on United States Provisional Application No. 61/023712, filed Jan. 25, 2008, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates generally to compositions and methods for reducing progression to heart failure as a consequence of cardiac stress.

BACKGROUND OF THE INVENTION

[0003] Without limiting the scope of the invention, its background is described in connection with the existing understanding of heart failure. The myocardium, when stressed from a variety of causes including myocardial infarction (MI), coronary artery disease, hypertension, cardiomyopathy, myocarditis, valvular regurgitation, severe lung disease, and severe anemia of chronic disease, may develop increasing dysfunction and go on to apoptosis of cardiocytes and a detrimental remodeling of the myocardium. This progression ultimately results in the clinical entity of chronic heart failure (CHF), also known as chronic cardiac failure (CCF) or chronic congestive heart failure. The present invention is focused on an important distinction between the inciting cardiac lesion, whether myocardial infarction, valve disease etc., and the remote, often normal, myocardium. It is this remote myocardium that suffers compensatory stress and which descends into failure. Also of importance to the present invention is a recognition that the dysfunction which may affect the normal or remote myocardium is often progressive in nature. Although this progression has been well documented and recognized, what controls it is unknown

[0004] According to national surveys, an estimated 4.8 million Americans have congestive heart failure, divided equally between men and women. Of these, almost 1.4 million are under 60 years of age. Prevalence of CHF is increasing substantially with an estimated 400,000 new cases each year according to National Heart, Lung, and Blood Institute (NHLBI) statistics. As CHF is the end stage of cardiac disease, half of the patients diagnosed with CHF

will be dead within 5 years. Increasing prevalence, hospitalizations, and deaths have made CHF a major chronic problem in the United States and the most common cause of hospitalization.

[0005] CHF treatments are currently limited to alleviating symptoms of existing heart failure including through significant life style changes, medications such as diuretics and ACE inhibitors which can have significant side effects, and surgery. All current treatments for heart disease which do not treat the inciting lesions themselves (i.e., coronary artery stents, valve replacements, etc.) are secondary in nature. Some medications, for example, will produce dilation of the vessels in the body and, therefore, reduce the resistance to blood flow which the heart must overcome. This does not treat the cardiomyocytes directly but it does reduce the work the heart must do, providing secondary benefit. No measures currently exist, however, that directly prevent or even ameliorate root causes of the progression to CHF.

[0006] From the foregoing it is apparent there is a need in the art for compositions and methods for preventing or significantly slowing the progressive damage to the myocardium which results in CHF. The invention described provides a novel method and compositions which significantly reduce the progression to CHF in individuals at risk for development.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention is directed to preventing or ameliorating progression to chronic heart failure subsequent to cardiac stress by administration of one or more rate-limiting precursors to the synthesis of ATP. In one embodiment the ATP precursor is selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose. In one embodiment the pentose is selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose.

[0008] In one embodiment the cardiac stress results from myocardial infarction (MI), coronary artery disease, hypertension, cardiomyopathy, myocarditis, valvular regurgitation, severe lung disease, and/or severe anemia of chronic disease.

[0009] In one embodiment of the invention, progression of normal, or nearly normal, myocardium to chronically damaged and failing heart tissue is prevented or limited by administration of one or more rate-limiting precursors to the synthesis of ATP in such a way that the precursors are continuously available for a prolonged period in order to prevent return to the continuing progression of injury, subsequent remodeling and CHF. In one embodiment, the prolonged period where rate-limiting precursors to the synthesis of ATP are continuously

available by parenteral administration and preferably by continuous intravenous infusion for at least a period of acute hospitalization. In such embodiments, the prolonged period is at least 3 days, followed by oral administration for at least 3 weeks. In other embodiments the intravenous treatment is extended to 7 to 14 days or longer depending on the status of the individual and their individual response to therapy. In such embodiments, the patient, if discharged but still considered to have some degree of dysfunction, the patient is discharged with an I.V. line in place, which is connected to a source of rate-limiting precursors to the synthesis of ATP. The period of oral administration begins at least upon cessation of parenteral treatment and continues for 3 weeks or more. Treatment by oral administration is preferably continued for 3 to 6 months, depending on preservation of LV function.

[0010] In one embodiment of the invention, rate-limiting precursors to the synthesis of ATP are provided either by bolus injection or by i.v. administration as soon as an acute myocardial stress is strongly suspected and warrants insertion of a venous line in the patient. This acute treatment may be begun in an ambulance or in the emergency room and continued for the aforementioned prolonged period. Thus, in one embodiment of the invention, an emergency or crash-cart kit is provided including a premixed formulation of one or more rate-limiting precursors to the synthesis of ATP. In one particular embodiment the kit contains a volume of solution sufficient to provide a "loading dose" equivalent to about 1 ml/kg of a 5% solution of a pentose moiety, preferably ribose, over 1-2 hours. Following the loading solution administration, a continuous infusion is begun of a pentose solution equivalent to about 0.2 to about 0.4 ml/kg/hr of a 5% solution thereafter for as long as an intravenous line is in place during hospitalization.

[0011] In one embodiment the one or more rate-limiting precursors to the synthesis of ATP are made continuously available by parenteral infusion. In one embodiment, a parenteral infusion set is provided including the rate-limiting precursors to the synthesis of ATP as well as instructions for delivery. In one embodiment, a continuous infusion pump is provided for long term administration of the rate-limiting precursors to the synthesis of ATP. Following infusion, one or more rate-limiting precursors to the synthesis of ATP are delivered by oral administration.

[0012] In another embodiment, the one or more rate-limiting precursors to the synthesis of ATP are given initially intravenously to insure continuous high levels and overcome any

difficulty to eating caused by the inciting cardiac event (e.g. MI) and later given orally when hospitalization is no longer necessary.

[0013] Also provided herein are parenteral solutions including one or more rate-limiting precursors to synthesis of ATP for use in preventing myocardial stress from progressing to chronic heart failure (CHF) and which are adapted to be administered continuously for at least a period of hospitalization to a patient at risk for development of CHF. In one aspect the rate-limiting precursor to synthesis of ATP is selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose moiety. The pentose moiety is selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose. In one aspect, the parenteral solution is formulated for delivery at a dosage equivalent to about 0.2 to about 0.4 ml/kg/hr of a 5% solution of a pentose. In certain embodiments, the parenteral solution further comprises a glucose solution.

[0014] A parenteral loading dose solution for use in preventing myocardial stress from progressing to chronic heart failure (CHF), wherein parenteral loading dose solution comprises a pentose formulated for delivery of an amount of pentose equivalent to about 1 ml/kg of a 5% solution given over about 1 - 2 hours.

[0015] In one embodiment of the invention, progression of damage in tissues bordering an area of infarction in a myocardial infarction patient are reduced and at least a portion of the at risk border zone is allowed to recover, thereby reducing the ultimate size of the infarction, by administering a composition including an effective amount of one or more rate-limiting precursors to the synthesis of ATP. The ATP precursor is selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose moiety.

[0016] In one embodiment of the invention, an effective amount of one or more rate-limiting precursors to the synthesis of ATP is provided to prevent functional consequences resulting from stress on the relatively normal remaining portions of the ventricle following a MI. In one embodiment, the functional consequence is mitral valve regurgitation. In one embodiment the relatively normal remaining portions of the ventricle are the papillary muscles. In one embodiment an effective amount of one or more rate-limiting precursors to the synthesis of ATP are administered to reduce the occurrence of arrhythmias which arise in the stressed normal remaining tissue following a MI.

[0017] For a more complete understanding of the present invention, including features and advantages, reference is now made to the detailed description of the invention along with the accompanying figures:

BRIEF DESCRIPTION THE DRAWINGS

[0018] Figure 1 illustrates the role of ribose in adenine nucleotide metabolism. The irreversible breakdown (catabolism) of AMP to small compounds that are washed out of the cell is shown centrally. The three pathways of resynthesis of AMP are shown leading to it. The most important seems to be the de novo pathway, but all three require ribose as the essential compound.

[0019] Figure 2 represents the progression to CCF resulting from an earlier infarct. This carton depicts the LAD artery ligation procedure with the resulting infarction (death) and surrounding border zone areas. With time, as LV function decreases, the LV begins to dilate and progresses to CHF.

[0020] Figure 3 represents M-Mode echocardiographic images of a rat heart at baseline and after CHF has begun to develop. These echocardiograms, which represent a slice of a LV, show the wall thinning and the dilation of the cavity (the dark, wide band centrally) as the ventricle begins to fail (control animal without ribose infusion).

[0021] Figure 4 depicts the effects of ribose on LV systolic diameter in a rat model of CHF. The 2-D echo-derived LV dimensions at the end of systole (contraction) are shown for ribose-treated and control animals. This revealed that during the 2 weeks of ribose infusion, there was little reduction in contractility. During the next 2 weeks, however, some decrease in function occurred which supports the benefit of longer-term therapy.

[0022] Figure 5 depicts the effects of ribose on LV ejection fraction in a rat model of CHF. The ejection fractions (EFs) of the two groups are plotted and reveal the clear benefit of the longer-term therapy.

[0023] Figure 6 depicts the effects of ribose on EDV, ESV, SV and EF in a rat model of CHF. Representative 2-D images of a LV during systole and diastole are presented. By modeling calculations, the volumes both at full relaxation and contraction as well as the EF can be determined. The significant LV dilation with reduced function in the untreated animal is apparent.

DETAILED DESCRIPTION OF THE INVENTION

[0024] While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts which can be employed in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not limit the scope of the invention.

[0025] ABBREVIATIONS: The following abbreviations are used throughout this application:

ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
CHF	chronic heart failure
EDV	end-diastolic volume (maximal filling)
EF	ejection fraction
ESV	end-systolic volume (maximal ejection)
G6PDH	glucose-6-phosphate dehydrogenase
LAD	left anterior descending
LV	left ventricular
MI	myocardial infarction
PRPP	5-phosphoribosyl-1-pyrophosphate
RM	remote myocardium
SV	stroke volume

[0026] To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as “a”, “an” and “the” are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not limit the invention, except as outlined in the claims.

[0027] As used herein the term “parenteral infusion” means other by a gastrointestinal route of administration. Examples include by subcutaneous, intramuscular and intravenous.

[0028] For purposes of the present invention, “rate-limiting precursors to the synthesis of ATP” include adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, as well as pentose moieties. For purposes of the present invention, the term “pentose moiety” means a monosaccharide, including but not limited to, ribose, D-ribose, ribulose, xylitol, xylulose, and any 5-carbon precursor of ribose.

[0029] Ribose is a 5-carbon sugar that is the foundation for several vital functional classes of molecules use ribose (or deoxyribose) as the foundation for active groups to form informational (RNA and DNA), messenger (cAMP and cGMP), certain vitamins, cofactors, the NAP, NADP, NADPH acceptor molecules, and the energy transporting nucleotides (ATP and ADP). The importance of these compounds to the cell can not be overstated. Thus, ribose is the vital structural backbone of critical cellular compounds formed by adding the active moieties (either purines or pyrimidines and the phosphate groups) to it or to its more active form 5-phosphoribosyl-1-pyrophosphate (PRPP) as depicted in **Figure 1**. Therefore, the production of these vital cellular constituents requires an adequate supply of these components including ribose, purines and pyrimidines and phosphate moieties. Among these, ribose, is the rate-limiting component.

[0030] Ribose provides the foundation for the synthesis of these fundamental cellular compounds. Because these compounds are in relatively constant supply in cells and are not consumed (turnover is slow), the need for ribose is relatively predictable and not marked by sudden large surges in synthetic requirements. It is not surprising, therefore, that the synthetic rate of these important compounds is relatively low and can not increase very much. Analysis of the nucleotide synthetic rate, moreover, has shown that ribose is the rate-limiting precursor. Ribose is produced from the commonly present 6-carbon sugar glucose by the coupled enzyme which includes G6PDH and accomplishes the decarboxylation. Because of the normally limited need for ribose and the heavy use of glucose in glycolysis and energy production, the cell severely limits the diversion to ribose by this rate-controlling step.

[0031] For the heart, however, the situation is more complex. Nucleotide synthesis has much smaller bursts of activity and significant deficiency states related to this synthesis are unlikely to occur. The myocardium is particularly vulnerable to the loss of ATP by stress and the subsequent breakdown of the resulting AMP to its component parts, producing in effect a deficiency in ribose.

[0032] In times of stress to the heart, the concentrations of ATP will fall when its production from ADP (and AMP) does not meet demand, as would be expected. Of much more significance, and unexpected when it was discovered, is the further response of myocardial energy metabolism to this situation, principally the irreversible breakdown of AMP. Recovery from stress then requires a resynthesis of a greatly increased amount of AMP (which can be charged to ATP) but this is normally a very slow process. The resulting AMP was found not to accumulate to any degree and, instead, is broken down to small components which are washed out of the heart, insuring that the ATP levels will not easily recover.

[0033] As noted above, the availability of ribose-5-P and the form, PRPP, is what limits AMP synthesis. The phosphate groups are typically in abundance and, although the purine base, adenine in excess has been used experimentally in the recovery from global ischemia, at best, it seems to have a minor effect. Ribose is the rate-limiting compound but, unfortunately, even under severe stress, the myocardial cell has only a limited capacity to increase ribose-5-P synthesis and G6PDH activity. As a result, the relatively slow synthesis of ribose-5-P and, therefore, of AMP, makes the recovery of ATP levels a slow process, requiring days to recover fully after a moderate insult.

[0034] Because heart disease itself is a chronic condition, it typically imposes a relatively continuous stress, and a slow fall in ATP may result with little opportunity to recover. Because recovery requires the slow synthesis of AMP, in a practical sense, a significant deficiency of ribose is produced. In these settings, the present inventor recognized that the synthesis of AMP is most limited by the availability of ribose and, that continued efforts to generate AMP would result in a significant deficiency of ribose. The present inventor further proposed that this ribose deficiency not only limits recovery but is a significant cause of progression to CHF. Thus, in these settings, a hypothesis was tested that providing adequate supplies of ribose would be effective in preventing, or at least slowing, a progression into CHF. The confirmation of this hypothesis disclosed herein provides a mechanism to prevent the development of CHF, which is clearly a much more effective strategy than trying to ameliorate the resulting condition.

[0035] As detailed herein, by far the most important direct purpose of pentose sugar administration will be to increase the synthetic rate of AMP, which will, in turn, be fully charged to ATP by the oxidation of the various fuels (sugars, fatty acids and amino acids) in the cell. By far the most significant consequence then of administration of a pentose sugar

such as ribose, a simple 5-carbon sugar, is to raise cellular energy (ATP) levels. The mechanism by which the ATP levels are increased is only through the enhanced synthesis of AMP. Once AMP is synthesized, the energy produced by cell metabolism is easily transferred to AMP and ADP, resulting in the fully charged ATP.

[0036] Ribose is used by the cell only for the synthesis of the vital molecules previously listed and as a result, the cell will not significantly consume or oxidize ribose as they do other sugars such as glucose. Ribose is not broken down to provide energy to convert ADP to ATP. The biochemical pathways of adenine nucleotide metabolism via ribose and ATP are depicted in Figure 1.

[0037] Chronic heart failure (CHF) has become epidemic in numbers in the US and other industrialized countries. Many different insults to the heart (infarcts, diseased valves, cardiomyopathies, etc.) can lead to CHF, the most common being coronary artery disease which produces severe ischemia and infarction of the areas previously supplied by the occluded vessels. Despite the many different forms of the inciting heart disease, the failing heart has many similarities. A hypothesis is that the early subcellular consequences of these various lesions on the myocardium are similar as is the pathway to and the progression of failure. As noted, the remote myocardium which fails may be essentially normal, apart from the inciting cardiac event. The failing heart has been extensively studied to elucidate the subcellular changes which occur nevertheless, it is not known what sets in motion the pathway to failure. It is agreed, however, that CHF is often a progressive disease even if no new heart lesions occur. On this basis, the present inventor proposed that a common pathway is activated and that the trigger persists.

[0038] The present inventor undertook to discriminate between two possible general mechanisms for beginning the path to failure, expecting this understanding would suggest one or more effective methods of therapy. The first one being that an excessive stress placed on the remaining normal ventricle gradually breaks down the contractile apparatus. Indeed, some authorities on CHF believe this is the primary mechanism and that the stress on the remaining myocardium begins a progressive breakdown of the contractile apparatus of the myocardial cells leading to CHF.

[0039] An alternative hypothesis, advanced and tested by the present inventor as disclosed herein, provides that stress placed on the heart, or portions thereof, result in a greater energy demand on the normal tissue than can be supplied. By the biochemical response of the

myocardium, as discussed earlier, the ATP levels gradually fall and this in turn leads to the decreased functioning of the myocardium. The next part of this theory states that it is the concentration or level of ATP that is of particular importance to the various functions which occur in the myocardium. There is evidence for this proposal, including among others that the uptake of calcium by the sarcoplasmic reticulum, which governs diastolic function, is directly affected by ATP levels.

[0040] Under normal conditions, ATP levels are remarkably stable despite the heart using more energy per weight than any other organ. The energy needed requires the turnover from ADP to ATP and back (energy production and utilization) to occur 10,000 times/day for each molecule. Under sufficient stress, however, the energy production can not keep up with demand and the ATP levels fall and, momentarily AMP levels rise. If the duration of stress is short, the AMP can be recharged and ATP levels will recover. With heart disease, however, the stress persists and the enzymes which break down AMP are activated and reduce it to small components which are washed out of the cell. The pathophysiologic explanation disclosed herein is that the stress of heart disease leads first to an irreversible breakdown of AMP which requires new synthesis of AMP to maintain adequate ATP levels. Because this stress will predictably continue, recovery will not occur and a further slide in ATP levels may result if the rate-limiting component, ribose, is not provided.

[0041] Based on an understanding of the underlying pathogenesis disclosed herein, the treatment provided by this invention, therefore, will have to be for a relatively prolonged period and will in most cases exceed the period of an acute injurious episode such as immediately following a myocardial infarction and, optimally, the treatment will be continued until the remote myocardium can compensate for the stress or until the stress is removed..

[0042] For example, in the example described herein, ribose was given for two weeks, during which time the remaining (remote) normal myocardium was under stress. The border zone adjacent to the infarct was also put in jeopardy of going on to infarction. The continued infusion of ribose was done to prevent the ATP levels in the normal myocardium from falling to levels which would significantly decrease function. In addition, the ribose infusion was given to prevent the border zone from going on to infarction and, moreover, to allow a portion to recover.

[0043] Consequently, the present therapy is specifically directed to the energy metabolism of the remaining functional tissue. By preventing the fall in energy levels which will

otherwise occur, the treatment limits or prevents the dysfunction which will result and by minimizing the increasing cycle of severity, significantly reduces the longer term consequence of prolonged cardiac stress, which is chronic heart failure. Of course, a similar benefit will be found in tissue which is not normal but maintains a degree of function and its progression to failure can be slowed. Finally, the improved energy levels and function of the remote myocardium will also favorably affect the recovery of at least part of the neighboring border zone.

[0044] In one embodiment, treatment is initiated in patients who have just had an MI or developed other heart lesions and diseases. Because this invention demonstrates that the primary event controlling the pathway to failure is a fall myocardial energy levels rather than the usual explanation that this begins with an initial and progressive breakdown of the cellular contractile apparatus, this treatment is applicable to a variety of heart lesions expected to produce CHF. Because of the importance of heart disease and the common progression to CHF, this represents a significant advance. Treatment with a pentose, such as for example ribose, provides a direct treatment of the sub-cellular myocardial changes that lead to heart failure. In one embodiment of the invention, pentose is administered as an additive to other treatments. There is no known down-side to raising myocardial (and other cells) energy levels.

[0045] In one embodiment of the invention, pentose is administered chronically in a patient having a condition that presents a known risk of progression to CHF. As chronically administered, the pentose: 1) will directly correct and prevent the central problem of reduced energy stores, 2) is additive to existing therapies, 3) is only positive in effect, i.e. increases synthesis of AMP and related molecules, 4) does not inhibit other biochemical or physiological events, and, very importantly, 5) has virtually no risk.

[0046] Many investigators have attempted to show that specific precursors will block the fall in ATP levels or will augment ATP recovery in severe and acute situations, such as ischemia and very unfavorable situations such as the creation of a significant cardiac lesion, such as valve disruption, when one expected consequence would be a fall in ATP levels. Adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside and ribose are some of the ATP precursors that have been studied to acutely increase ATP synthesis. Most studies were of short duration, and directed to amelioration of the acute injury. The one exception was the longer term oral clinical study, cited below, which assessed only a few secondary

function parameters. The significant studies were only directed at improving an acute cardiac problem and not to reducing or preventing the severe consequences of CHF. Consequently, in these acute studies, only partial ATP recovery was found, and none accomplished complete return of ATP levels once severe depression had been induced. Moreover, none were directed to preventing the progression to failure that includes dysfunction of the remaining myocardium, which leads to the ominous wall thinning and ventricular dilation that are the clinical hallmarks of CHF and which indicate cell death (apoptosis) and replacement fibrosis (remodeling) as the condition becomes chronic. It is these changes, however, both physiological and subcellular, which define CHF which we seek to prevent or, at least, greatly ameliorate.

[0047] For example Seifart et al. (*Basic Res. Cardiol.* 75 (1980) 57) studied isolated, electrically-driven guinea pig atria in which adenine and ribose were found to “inhibit the loss of cardiac adenine and pyridine nucleotides during anoxia.” In this study the isolated atria were stabilized for an hour then subjected to nitrogen to cause 2 hours of anoxia (blood flow but no oxygen), not ischemia (no blood flow and no oxygen). The addition of adenine and ribose after one hour of anoxia reduced the further fall in ATP levels during the next hour of anoxia. No investigation was made of the ability of adenine and ribose to restore fallen ATP levels.

[0048] H. G. Zimmer (*Science* 220 (1983) 81) reported a study in which ATP levels were shown to be maintained for 24 hours in rats treated with ribose after being given a toxic dose of isoproterenol and subjected to constriction of the abdominal aorta. The combined stresses of catecholamine stimulation and increased blood pressure on the heart resulted in lowered myocardial ATP levels in controls. This study focused on acute stresses and Zimmer concluded that “the reductions in ATP and total adenine nucleotides were prevented” by this treatment. The ability of ribose to prevent any consequences after 24 hours or to enhance recovery after an ATP fall had occurred were not tested.

[0049] In a later study, Zimmer (*Basic Res. Cardiol.* 84 (1989) 332) reported that continuous i.v. administration of ribose beginning prior to coronary artery ligation and continuing for up to 48 hours in a rodent MI model was able to reduce the fall of ATP in the nonischemic myocardium determined at the first (24 hr) time point. For the next 3 days, ATP recovery in both ribose-treated and control rats increased at the same rate. It should be noted that the ribose dosage was extremely large (a 70kg man would receive 336 gms daily

intravenously). Among the function parameters studied (under general anesthesia and with a tracheostomy in place), only the post-MI rise in LV end-diastolic pressure was reduced (helped) by the ribose infusion. Zimmer believed that pretreatment was necessary to achieve the benefit, however, in the commonly occurring MI in humans, treatment can only occur after the event. He further speculated that the basic mechanism of the LVEDP dysfunction resulted from changes in the contractile apparatus or “the stretch of myocardial fibers.” This is one of the two general possibilities, although the evidence presented in this application strongly indicates a fall in ATP levels is the primary event.

[0050] The present inventor previously discovered that administration of ribose was able to reduce the period of recovery from an acute ischemic episode. Only the recovery from a complete global insult such as occurs during heart surgery was studied. There was no normal tissue in these hearts to study and the longer-term consequences were not considered. *See* Foker U.S. Patent Nos. 4,605,644 and 4,719,201.

[0051] Finally in a prospective, double-blind, randomized, crossover design study, the effect of oral D-ribose supplementation on cardiac hemodynamics and quality of life was studied in 15 patients with chronic coronary artery disease and CHF. In patients with existing CHF, 3 weeks of oral D-ribose resulted in an improvement in some of the echo markers used to assess LV filling. The left atrial contribution to left ventricular filling was improved (40 ± 11 vs. $45 \pm 9\%$, $P = 0.02$) and a smaller left atrial dimension (54 ± 20 vs. 47 ± 18 ml, $P = 0.02$) and a shortened E wave deceleration (235 ± 64 vs. 196 ± 42 , $P = 0.002$) were seen by echocardiography. Further, D-ribose also led to an improvement of the patient’s quality of life by questionnaire (417 ± 118 vs. 467 ± 128 , $P \leq 0.01$). In summary, this study showed that the administration of ribose to patients who already had CHF could produce small but, statistically significant, improvements in certain echo markers of diastolic function and in the responses to a quality of life questionnaire. The study provided neither information nor speculation on the possibility of reducing or preventing the events which start and continue the pathway to CHF.

[0052] The ability of a nucleotide precursor to prevent the progression to CHF has not heretofore been shown. Progression to heart failure is a long-term problem that takes over 4 weeks to develop in rats and months to years in humans. The present inventor has now shown that ribose can prevent progression to heart failure in a rat model that is analogous to the development of heart failure in humans.

[0053] The following examples are included for the sake of completeness of disclosure and to illustrate the methods of making the compositions and composites of the present invention as well as to present certain characteristics of the compositions. In no way are these examples intended to limit the scope or teaching of this disclosure.

EXAMPLE 1:

[0054] Although believed to be applicable to several different precipitating causes of CHF, the present inventor initially chose a myocardial infarction model because it would allow the effects of the infarct on the normal remaining myocardium to be studied without confounding factors, particularly the presence of disease in the tissues studied. The experiment involved long-term infusion of ribose into rats having had a coronary artery ligated to produce a MI.

[0055] An important consequence of an MI is that the uninvolved, often normal, remote myocardium (RM) must assume the entire workload of the ventricle. This additional strain on the RM has been shown to lead to apoptosis and remodeling and the dilation of the LV that is characteristic of CHF. The subcellular events which control and set in motion, the progression to CHF were heretofore unknown. The present inventor hypothesized that the progression begins when the remaining normal myocardium (RM) must assume the entire cardiac load, in effect a large increase for the RM, producing an unfavorable myocardial energy supply/demand ratio which leads to depressed myocardial energy levels. Moreover, because of the continuous nature of the stress imposed, there is essentially no opportunity to recover. As a result, the continued breakdown of AMP with further erosion of ATP levels occurs. Studies to understand this progression in a myocardial infarction (MI) model were undertaken. The hypothesis that a fall in RM energy levels, including myocardial ATP, leads to decreased function was tested by infusing ribose in a rat MI model. A rat myocardial infarction model involving (left anterior descending (LAD) artery ligation) was utilized. In this model the RM must produce the entire cardiac output and left ventricular (LV) dysfunction develops as depicted in **Figure 2** and in the results depicted in **Figures 3-6**.

[0056] On a molecular level, stress results in an energy supply that is less than the demand. Consequently, ATP levels fall and catabolic pathways are activated resulting in increased breakdown of the ATP precursor AMP and the washout of the resulting components. From acute stress models of recovery (i.e. global ischemia) ATP recovery takes days after the insult. ATP recovery proceeds by the synthesis of AMP and conversion to ATP. The first phase, the synthesis of AMP, is by far, the slowest and is limited by the conversion of glucose-6P (by the

coupled G6PDH enzyme) to ribose-5P. Administration of ribose bypasses the G6PDH step and speeds ATP recovery by at least 10 fold.

[0057] Methods: Male Lewis rats (250 – 300 g, n = 12) were evaluated by initial baseline 2D guided M-mode echocardiographic analysis using an HP SONOS 1550 system. The echocardiography included short axis views and EF by cubed formula, analyzing the variables of LVdd, LVsd, RM wall thickness, EF and SF. Each animal had an osmotic mini-pump (Durect, Inc.) implanted. Animals underwent ligation of the left anterior descending coronary artery by to produce an anterior wall MI at 1-2 days after pump placement and received continuous venous infusion of 0.9% NaCl solution (at 30 μ l/kg/hr) with or without 2.5% D-ribose (N=6 for each group) via the implanted osmotic mini-pump for 14 days. Echocardiographic analysis was performed 2 and 4 weeks post-MI to assess changes in function by ejection indices (ventricular contractility, ejection and shortening fractions), chamber dimensions, and wall thickness. **Figure 3** depicts the M-mode echocardiographic appearance of a rat heart in which post MI CHF has developed.

[0058] Results: Important and clinically relevant indices of function were chosen. **Figure 4** depicts the results of long-term ribose treatment on LV systolic diameter after an MI. **Figure 5** depicts the results of long-term ribose treatment on LV ejection fraction after an MI. **Figure 6** depicts the results of ribose treatment on EDV, ESV, SV and EF by 2D long Axis volume tracing. The results showed that ribose treatment better preserved contractility (EF, SF) and increased wall thickness compared to the untreated animals. Very importantly, ventricular dilation, the hallmark of CHF was significantly reduced. These data show (1) the RM shows a significant decrease in function four weeks following an MI, and (2) ribose infusion prevents, to a significant degree, the dysfunction. The benefit of ribose suggests the increased workload on the RM produces an unfavorable energy supply/demand ratio which results in lower myocardial energy levels.

[0059] It was determined that in a global ischemia and reperfusion model that ribose infusion will greatly enhance return of myocardial ATP levels and function. Because ribose is the rate-limiting precursor to adenine nucleotide synthesis and is not itself a fuel source, increased AMP synthesis was concluded to be the reason for the enhanced recovery.

[0060] By all indices, as summarized in Table 1 below, the function of the RM was better maintained with ribose treatment following an anterior MI.

Table 1

Echo Indices	Treatment	Pre-MI	2 wks post MI	4 wks post MI
LV diastolic diameter (cm)	Ribose	0.64 ± 0.04	0.72 ± 0.08	0.76 ± 0.07*
	Control	0.68 ± 0.03	0.79 ± 0.11	0.94 ± 0.07
LV systolic diameter (cm)	Ribose	0.39 ± 0.06	0.47 ± 0.22*	0.64 ± 0.09*
	Control	0.40 ± 0.03	0.73 ± 0.10	0.95 ± 0.07
Septal diastolic thickness (cm)	Ribose	0.13 ± 0.02		0.12 ± 0.02
	Control	0.12 ± 0.01		0.10 ± 0.01
Posterior wall diastolic thickness (cm)	Ribose	0.13 ± 0.02	0.18 ± 0.12	0.13 ± 0.03*
	Control	0.13 ± 0.03	0.10 ± 0.01	0.10 ± 0.01
Ejection fraction (EF) %	Ribose	76.4 ± 5.9	50.5 ± 5.9*	49.1 ± 9.4*
	Control	76.3 ± 2.3	23.5 ± 12.6	31.2 ± 4.8
Shortening fraction (SF) %	Ribose	38.6 ± 5.3	19.8 ± 4.4	19.9 ± 6.1*
	Control	38.9 ± 2.1	8.7 ± 5.3	10.7 ± 1.1

* P < 0.05 vs. control.

[0061] These data show that raising myocardial energy levels clearly improves function and, on the basis of known pathophysiology, is therefore expected to delay chronic changes, including apoptosis, in MI induced CHF conditions. Importantly, when administered for a prolonged period after the MI, ribose treatment reduces the progressive dilation and wall-thinning, characteristic of CHF, which untreated animals undergo. Critical systolic function (contractility) was also better preserved by long term ribose treatment. With improved ejection fraction (EF) and increased cardiac output, perfusion of the RM will be better maintained as will much of the border zone. The slide into failure would be expected to be reduced or even prevented.

[0062] In addition, reduced dilation of the LV was achieved with long term treatment. Because dilation is the hallmark of the progression to heart failure, the ability to reduce dilation is an important finding. In a similar vein, the LV wall thickness was much better preserved by long term ribose administration. The effect continued for the 2 weeks of i.v. ribose treatment, while a lesser effect was shown to have persisted by 4 weeks after the MI. On this basis, in one embodiment of the invention, pentose therapy includes continued intravenous therapy to produce high levels during the time of recovery from the acute event

(e.g. an MI) and when oral intake may be very limited, followed by oral pentose for as long as needed. In one embodiment of the invention an intravenous therapy is provided including administration of a solution of approximately 5% ribose and approximately 5% glucose (the glucose is added to preserve blood glucose levels during this period of limited oral intake).

[0063] In one embodiment, a “loading dose” is provided equivalent in dosage to approximately 1 ml/kg for a 5% ribose solution is given over 1-2 hours, followed by a dosage equivalent to about 0.2 to about 0.4 ml/kg/hr of a 5% ribose solution thereafter. In a preferred embodiment the ribose solution is supplemented with glucose, such as for example 5% glucose, to preserve blood glucose levels. Upon discharge, the patient would be converted to oral dosage of about 10-20 grams of ribose, typically in divided doses. The amount of ribose is given above and it is anticipated that other pentoses would be given at the same rate or slightly greater to compensate for the inefficiencies in the conversion to ribose.

[0064] As with other medications, the amount, route and duration will be adjusted by several factors. The first consideration in the duration of intravenous therapy would be the length of hospitalization and this has steadily declined over the past few decades. Currently, for an uncomplicated MI, the patient might be discharged in 3-5 days. Although i.v. ribose may be more beneficial, if the patient has responded well and LV dysfunction is minimal, switching to an oral dose would be considered. On the other hand, if significant LV dysfunction still exists, the more effective, but more cumbersome, home i.v. ribose infusion might be chosen. The duration of oral pentose would also depend on LV function on follow-up echocardiograms. In some embodiments the oral pentose is continued for about 3 – 6 weeks initially with consideration to continue treatment for 3 - 6 months or even longer depending on status of ventricular function.

[0065] The patient is evaluated non-invasively to determine the efficacy of treatment and its duration. For example, the patient may be examined by echocardiogram frequently initially and later at weekly intervals following the MI. The echocardiogram will be used to provide evidence that the detrimental changes that signal CHF development (LV dilation and wall-thinning) have first stabilized then improved as well as to demonstrate systolic (e.g. EF, SF, LESV) and diastolic (e.g. LEDV, mitral and left atrial indices) functions have returned essentially to pre-MI levels. If these parameters show deterioration, particularly if there is no evidence for a new MI, then a period of more intensive therapy, including i.v. ribose, may be again undertaken.

[0066] All publications, patents and patent applications cited herein are hereby incorporated by reference as if set forth in their entirety herein. While this invention has been described with reference to illustrative embodiments, this description is not intended to be construed in a limiting sense. Various modifications and combinations of illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to the description. It is therefore intended that the appended claims encompass such modifications and enhancements.

We claim:

1. A method of preventing myocardial stress from progressing to chronic heart failure, comprising providing a prolonged and continuous administration of a composition including one or more rate-limiting precursors to synthesis of ATP, wherein the prolonged and continuous administration is sufficient to normalize a level of ATP in the stressed myocardium.
2. The method of claim 1 wherein the rate-limiting precursor to the synthesis of ATP is selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose moiety.
3. The method of claim 2, wherein the pentose moiety is selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose.
4. The method of any one of claims 1 – 3, wherein the myocardial stress is a result of one or more of: myocardial infarction (MI), coronary artery disease, hypertension, cardiomyopathy, myocarditis, valvular regurgitation, severe lung disease, and severe anemia of chronic disease.
5. The method of claim 1, wherein prolonged and continuous administration is initiated by parenteral administration for an initial period of about 3 to about 14 days followed by oral administration for at least 3 weeks.
6. The method of claim 1, wherein the rate-limiting precursor to synthesis of ATP is a ribose or D-ribose and the prolonged and continuous administration is initiated by an acute loading dose equivalent to approximately 1 ml/kg of a 5% solution given over about 1 - 2 hours, followed by a subacute dose having a dosage equivalent of approximately 0.2 to about 0.4 ml/kg/hr of a 5% solution given at least 3 days thereafter.
7. The method of claim 5, wherein the oral administration is at a daily dose of 10 – 20 gms of ribose, including by divided doses.

8. A method of preventing or limiting progression of normal, or nearly normal, myocardium to chronically damaged heart tissue comprising:
- identifying a condition placing a patient at risk for development of CHF;
 - immediately initiating continuous intravenous administration of a composition including one or more rate-limiting precursors to synthesis of ATP;
 - continuing the intravenous administration for a duration of hospitalization;
 - continuing administration of the one or more rate-limiting precursors to the synthesis of ATP by oral dosage following the intravenous administration;
 - assessing LV function periodically during the administration of the one or more rate-limiting precursors to the synthesis of ATP; and resuming intravenous administration of the one or more rate-limiting precursors to the synthesis of ATP if LV function declines.
9. The method of claim 8 wherein the rate-limiting precursors to synthesis of ATP are selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose moiety.
10. The method of claim 9, wherein the pentose moiety is selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose.
11. The method of claim 8, wherein the condition placing the patient at risk for development of CHF is one or more of: myocardial infarction (MI), coronary artery disease, hypertension, cardiomyopathy, myocarditis, valvular regurgitation, severe lung disease, and severe anemia of chronic disease.
12. A parenteral solution comprising one or more rate-limiting precursors to synthesis of ATP for use in preventing myocardial stress from progressing to chronic heart failure (CHF) and which is adapted to be administered continuously for at least a period of hospitalization to a patient at risk for development of CHF.
13. The parenteral solution of claim 12, wherein the rate-limiting precursor to synthesis of ATP is selected from one or more of adenosine, adenine, inosine, 5-amino-4-imidazolcarboxamide riboside, and a pentose moiety.
14. The parenteral solution of claim 13, wherein the pentose moiety is selected from one or more of ribose, D-ribose, ribulose, xylitol, xylulose, and a 5-carbon precursor of ribose.

15. The parenteral solution of claim 14, wherein the pentose moiety is formulated for delivery at a dosage equivalent to about 0.2 to about 0.4 ml/kg/hr of a 5% solution.
16. The parenteral solution according to any one of claims 12 through 15 that further comprises a glucose solution.
17. A parenteral loading dose solution for use in preventing myocardial stress from progressing to chronic heart failure (CHF), wherein parenteral loading dose solution comprises a pentose formulated for delivery of an amount of pentose equivalent to about 1 ml/kg of a 5% solution given over about 1 - 2 hours.
18. The parenteral loading dose solution of claim 16, wherein the pentose is a ribose.
19. A crash kit comprising the parenteral loading dose solution of either any one of claims 12 through 18.

Figure 1

Adenine nucleotide metabolism

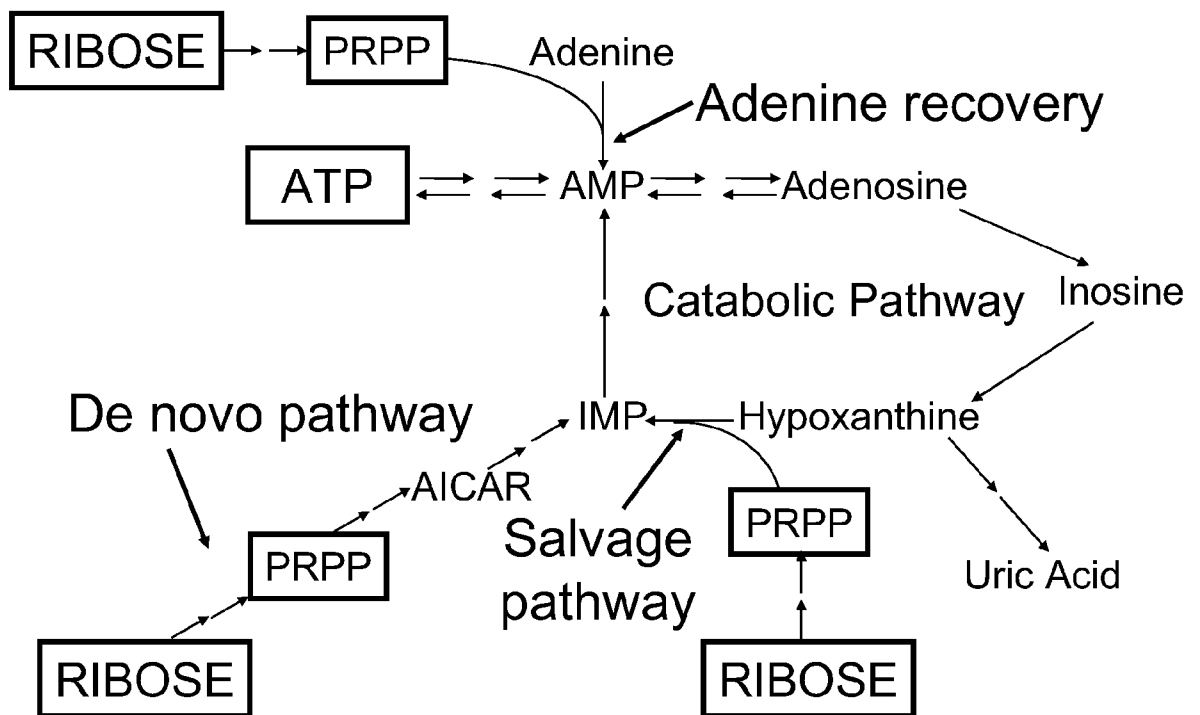


Figure 2

Ventricular cross section
(LAD ligation model)

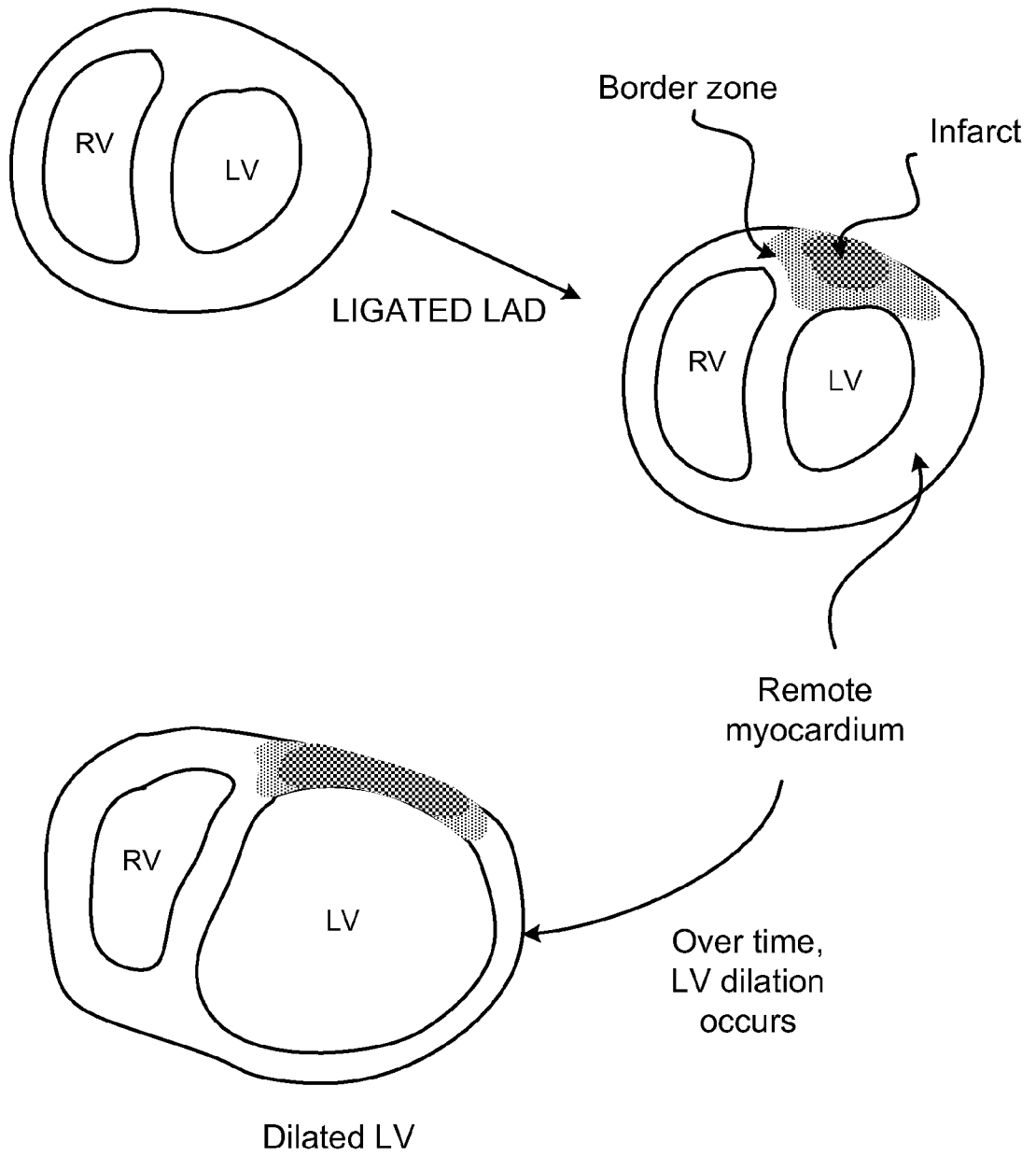
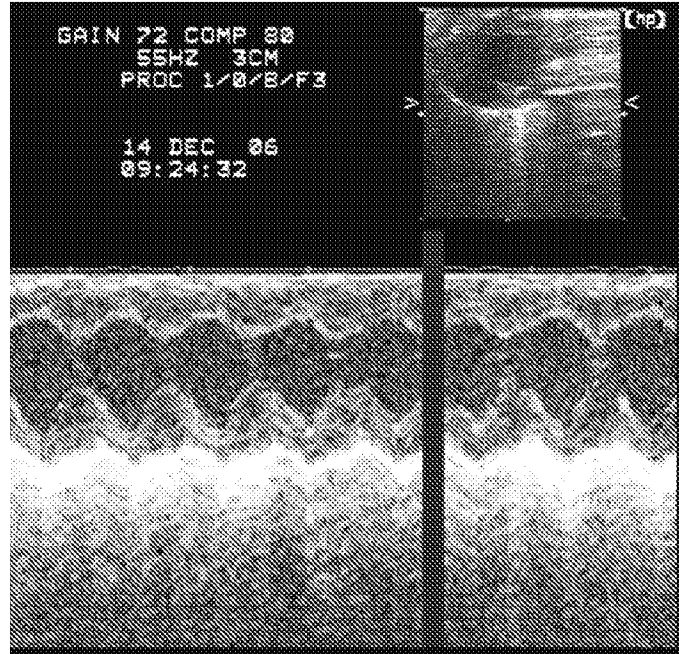


Figure 3

M-Mode Echocardiography

A. Baseline before MI



B. Untreated – 4 weeks after MI

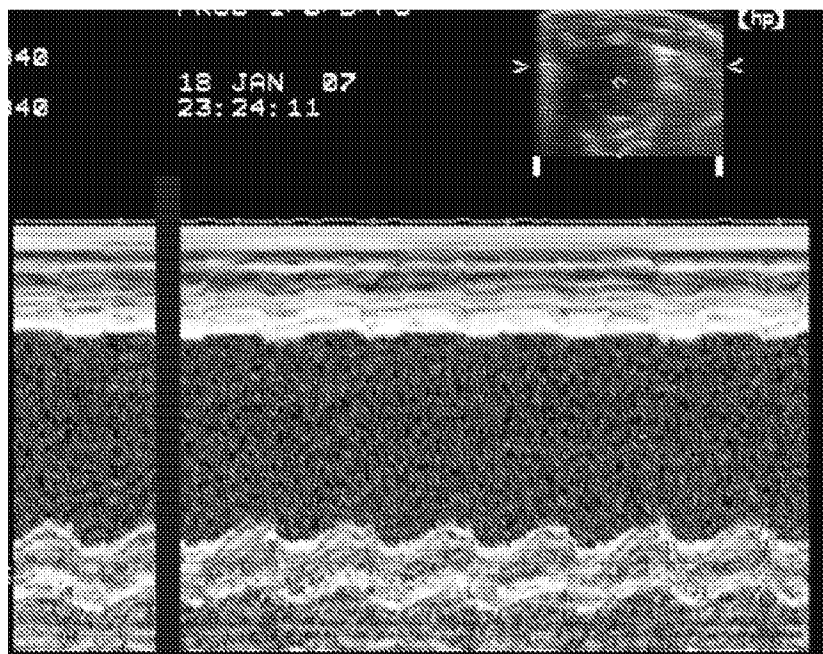


Figure 4

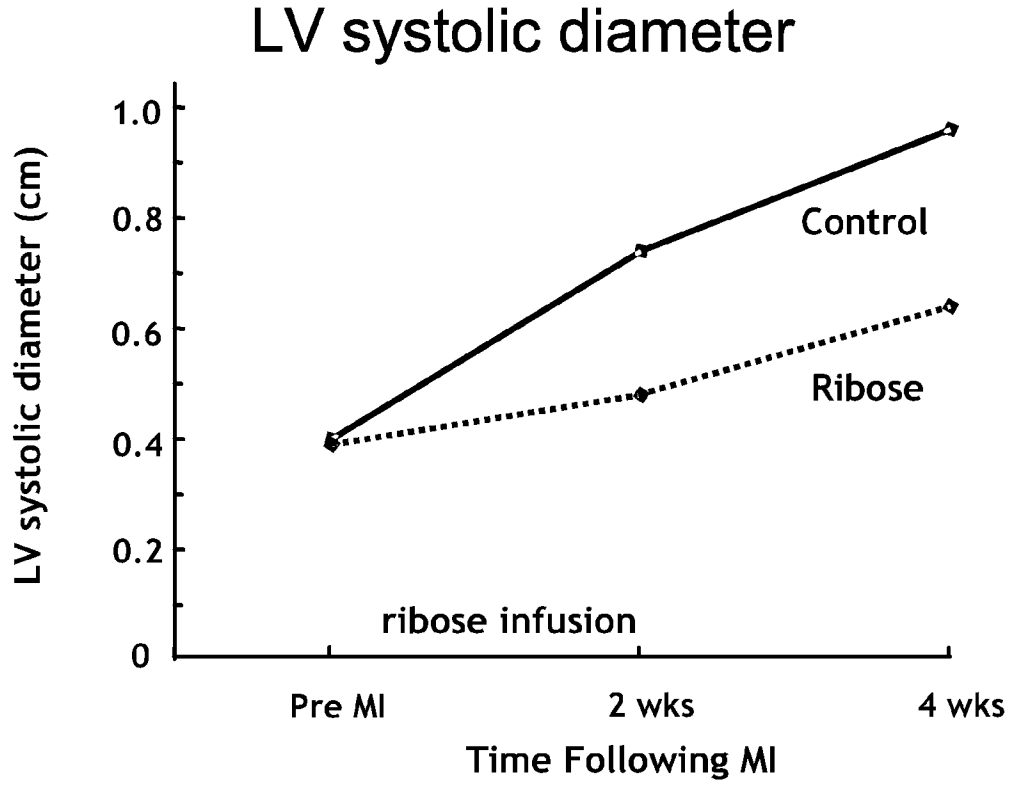


Figure 5

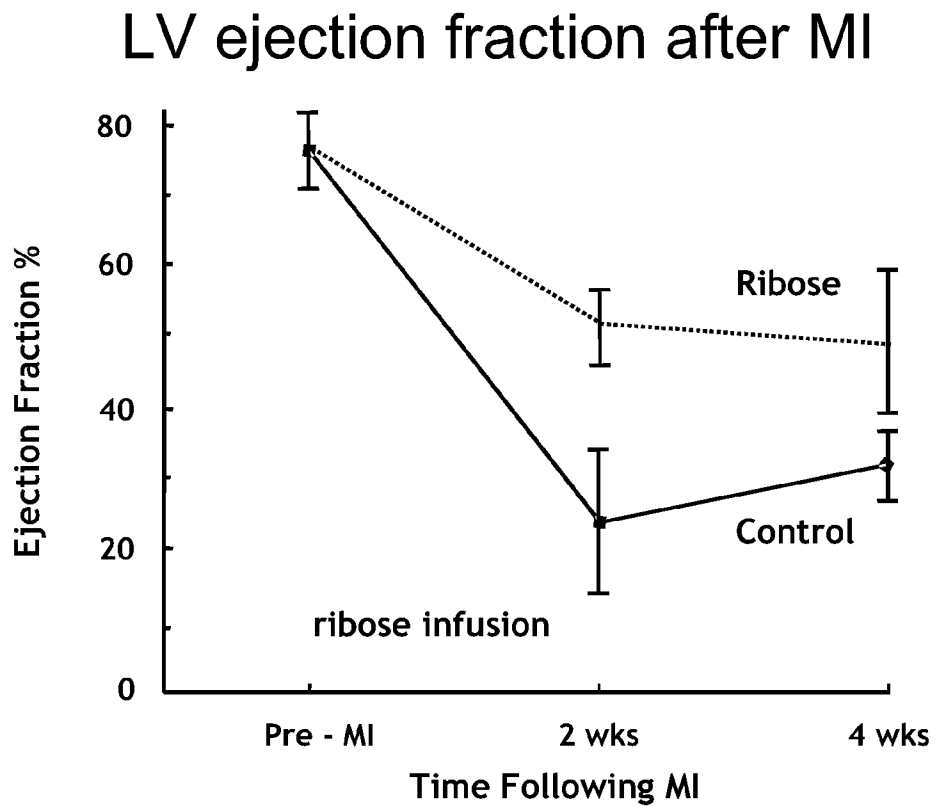
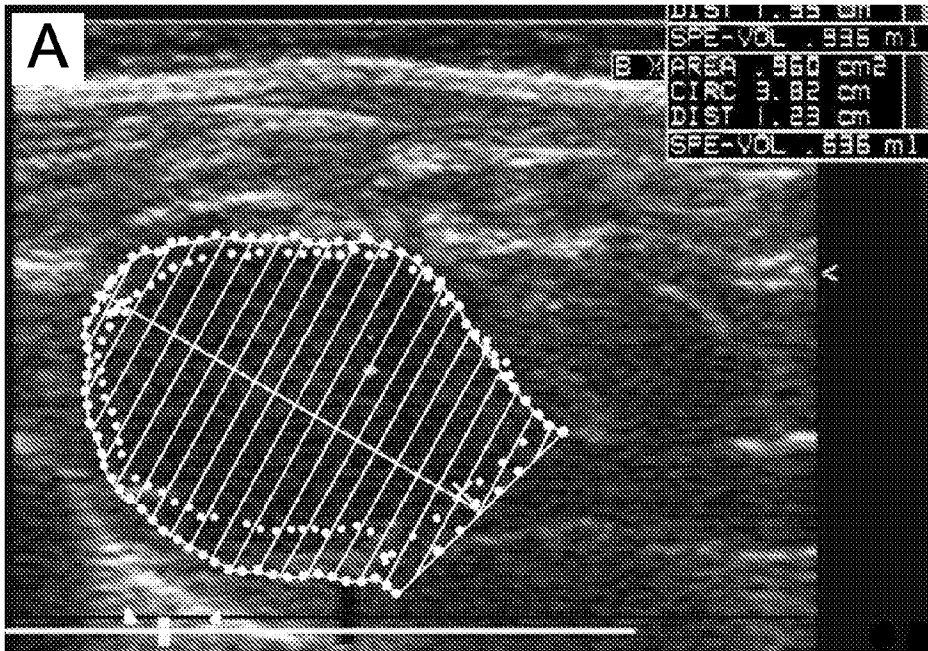
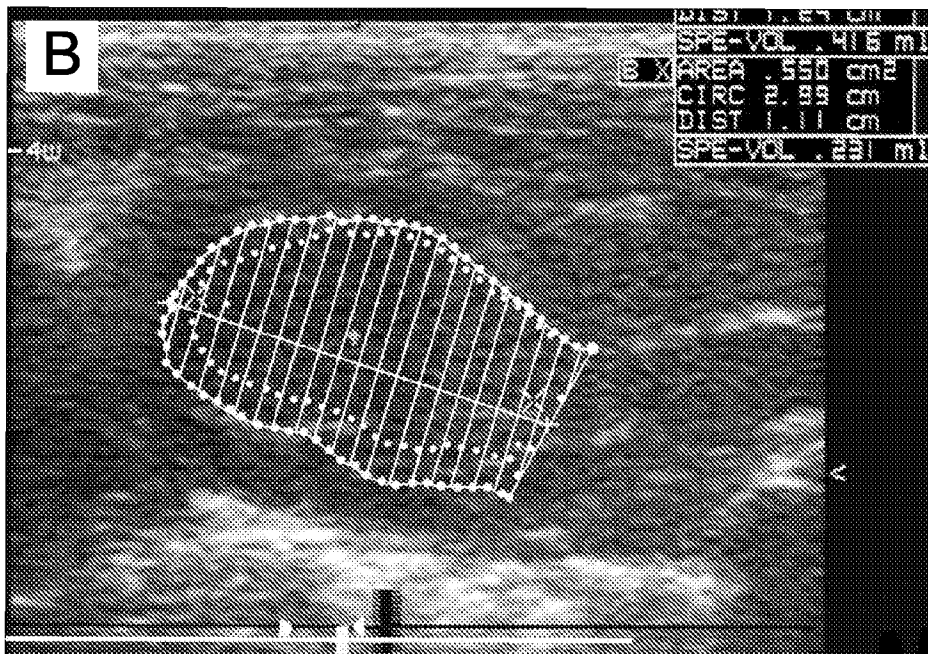


Figure 6



Control

EDV 0.94 ml
 ESV 0.64 ml
 SV 0.30 ml
 EF 32.1 %



Ribose

EDV 0.42 ml
 ESV 0.23 ml
 SV 0.19 ml
 EF 44.5 %

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/31910

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/04 (2009.01) USPC - 514/23 According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) USPC: 514/23</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 435/105, 435/139 (see search terms below)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST: US Patents full-text; US PGPubs full-text; EPO Abstracts; and JPO Abstracts; Google Terms: heart failure, cardiac stress, sythesis of ATP (adenosine triphosphate), adenosine, adenine, inosine, riboside, pentose (ribose, ribulose, xylitol, xylulose), rate-limiting, parenteral infusion (gastrointestinal, intravenous),</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X --- Y</td> <td>US 6,218,366 B1 (ST. CYR et al.) 17 April 2001 (17.04.2001) col 3-7; col 12, ln 61 to col 14, ln 48</td> <td>1-7 and 12-18 ----- 8-11</td> </tr> <tr> <td>Y</td> <td>US 6,339,716 B1 (SAWADA et al.) 15 Jan. 2002 (15.01.2002) col 2-5</td> <td>8-11</td> </tr> <tr> <td>A</td> <td>US 4,605,644 A (FOKER) 12 Aug. 1986 (12.08.1986) entire document</td> <td>1-18</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X --- Y	US 6,218,366 B1 (ST. CYR et al.) 17 April 2001 (17.04.2001) col 3-7; col 12, ln 61 to col 14, ln 48	1-7 and 12-18 ----- 8-11	Y	US 6,339,716 B1 (SAWADA et al.) 15 Jan. 2002 (15.01.2002) col 2-5	8-11	A	US 4,605,644 A (FOKER) 12 Aug. 1986 (12.08.1986) entire document	1-18
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
X --- Y	US 6,218,366 B1 (ST. CYR et al.) 17 April 2001 (17.04.2001) col 3-7; col 12, ln 61 to col 14, ln 48	1-7 and 12-18 ----- 8-11												
Y	US 6,339,716 B1 (SAWADA et al.) 15 Jan. 2002 (15.01.2002) col 2-5	8-11												
A	US 4,605,644 A (FOKER) 12 Aug. 1986 (12.08.1986) entire document	1-18												
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>														
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed			
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family													
"P" document published prior to the international filing date but later than the priority date claimed														
<p>Date of the actual completion of the international search 13 Mar. 2009 (13.03.2009)</p>		<p>Date of filing of the international search report 23 MAR 2009</p>												
<p>Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201</p>		<p>Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>												

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/31910

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 19
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.