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(54) Title: METHODS OF CARDIOPROTECTION USING DICHLOROACETATE IN COMBINATION WITH AN INOTROPE

(57) Abstract: The present invention provides for the treatment for maintaining or improving cardiac function after a cardiac function disturbing event by the use of a cardioprotective amount of dichloroacetate (DCA) and an inotropic drug. The invention also provides for pharmaceutical compositions comprising the combination of DCA and inotropic drug, pharmaceutically acceptable carriers and optionally other therapeutic agents. Also provided are the dosage protocols for the DCA and inotropic drug combination.



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METHODS OF CARDIOPROTECTION USING DICHLOROACETATE IN
COMBINATION WITH AN INOTROPE

CROSS-REFERENCE TO RELATED APPLICATIONS

This claims benefit of priority to United States
5 Serial No. 11/013,666, filed December 15, 2004, and
United States Serial No. 11,229,101, filed September 16,
2005.

BACKGROUND AND INTRODUCTION TO THE INVENTION

There is a need for methods of protecting the heart
10 from injury, which may occur due to ischemic incidents
and during reperfusion following ischemia, and
maintaining cardiac function at a predetermined level
thereafter.

Clinically, ischemia-reperfusion may occur in the
15 setting of cardiac surgery. In order to perform many
surgical procedures it is necessary to interrupt coronary
blood flow resulting in ischemia to the heart. This
ischemia not only limits the time available for the
surgical procedure, it can also result in contractile
20 dysfunction upon restoration of coronary flow. This is
not only a problem in the adult patient undergoing
coronary artery bypass surgery ("CABG") or other surgical
procedures, it is also a significant clinical problem
during surgical heart procedures to correct congenital
25 heart defects in neonates.

Current therapies aimed at improving contractile
function following cardiac surgery in adult, pediatric
and neonatal patients often involve the use of inotropes

(e.g., calcium, dopamine, epinephrine, ephedrine, phenylephrine, dobutamine) in an attempt to increase contractile function. Although inotropic agents such as dobutamine have been reported to increase myocardial stroke volume and work, they also have been reported to increase myocardial oxygen consumption, and therefore may not enhance mechanical efficiency (1). In fact, the potential for inotropes to increase oxygen consumption to a greater extent than contractile function has been termed an oxygen wasting effect (2, 3). Inotropic drugs are also reportedly associated with increases in intracellular calcium concentration and heart rate, which may also be potentially harmful, especially in hearts with impaired energy balance (4).

15 SUMMARY OF THE INVENTION

The present invention is directed to methods of maintaining and improving cardiac function during and following an ischemic event and during reperfusion by administration of dichloroacetate ("DCA") in combination with an inotropic drug. According to one aspect the methods of the present invention improve cardiac functional recovery and metabolism after an ischemic event, such as surgical heart procedures (including cardiopulmonary bypass and congenital lesions) in patients, as well as cardiovascular disorders such as hemorrhagic shock, stroke, hypoxia and trauma.

According to an aspect of the present invention, combination therapy of DCA with an inotropic drug will enable administration of a lower dose of inotropic drug
30 needed to maintain contractile function post-surgery.

One aspect of the present invention is directed to a method of decreasing the amount of inotropic drug needed to maintain a predetermined level of cardiac function in a patient which comprises administering to said patient a
5 cardioprotective amount of dichloroacetate (DCA). According to this aspect, DCA may be administered as a bolus of at least about 50 mg/kg. According to one embodiment, DCA is administered in a bolus of at least about 100 mg/kg. According to one embodiment,
10 administration of the DCA bolus is followed by a continuous infusion of about 12.5 mg/kg/hour DCA for at least about 24 hours. According to another embodiment, the DCA bolus is followed by a continuous infusion beginning about 1/4 hour to within 1/4 hour and is
15 continued for a period of at least about 9 to 11 hours. According to other embodiments, infusion may begin immediately after administration of the bolus, at effectively 0 hours. According to another embodiment, the DCA bolus is followed within about 1/4 hour to 1/2
20 hour by an infusion of about 25 mg/kg/hour DCA for a period of at least about an hour, followed by an infusion of 12.5 mg/kg/hour DCA for a period of at least about 8 to 10 hours.

According to another embodiment, the DCA bolus is
25 followed within about 1/4 hour to about 1/2 hour by an infusion of about 12.5 mg/kg/hour DCA for a period of at least about 24 hours.

According to another embodiment, the DCA bolus is followed within about 1/4 hour to 1/2 hour by an infusion
30 of about 25 mg/kg/hour DCA for a period of about 1 to 12

hours, followed by continuous infusion of 12.5 mg/kg/hour DCA for the remainder infusion period at least about 24 hours. In one aspect of this embodiment, the DCA bolus is followed within about 1/4 hour to about 1/2 hour by an
5 infusion of about 25 mg/kg/hour DCA for a period of about 1 hour, followed by continuous infusion of 12.5 mg/kg/hour DCA for a period of about 23 hours. According to another aspect of this embodiment, the DCA bolus is followed within about 1/4 hour to about 1/2 hour by an
10 infusion of about 25 mg/kg/hour DCA for a period of about 4 to 6 hours, followed by continuous infusion of at least 12.5 mg/kg/hour DCA for a period of about 18 to 20 hours. According to yet another aspect of this embodiment, the DCA bolus is followed within about 1/4 hour to about 1/2
15 hour by an infusion of about 25 mg/kg/hour DCA for a period of about 12 hours, followed by continuous infusion of at least 12.5 mg/kg/hour DCA for a period of about 12 hours.

According to another aspect of the present
20 invention, provided is a method of maintaining cardiac function at a predetermined level in a patient after cardiac surgery and decreasing said patient's need for inotropes which comprises administering to said patient a cardioprotective amount of DCA in a bolus of at least 100
25 mg/kg followed within about 1/4 hour to 1/2 hour by continuous infusion of at least about 12.5 mg/kg/hour for at least about 9 to 11 hours. According to another embodiment, the continuous infusion of DCA is at least about 25 mg/kg/hour for about one hour and at least about
30 12.5 mg/kg/hour for about 8 to 10 hours.

According to another embodiment, the DCA bolus is followed within about 1/4 hour to 1/2 hour by an infusion of about 25 mg/kg/hour DCA for a period of at least about an hour, followed by an infusion of 12.5 mg/kg/hour DCA
5 for a period of at least about 8 to 10 hours.

According to another embodiment, the DCA bolus is followed within about 1/4 hour to 1/2 hour by an infusion of about 12.5 mg/kg/hour DCA for a period of at least about 24 hours.

10 According to another embodiment, the DCA bolus is followed within about 1/4 hour to 1/2 hour by an continuous infusion of about 25 mg/kg/hour DCA for a period of about 1 to 12 hours followed by continuous infusion of 12.5 mg/kg/hour DCA for the remainder
15 infusion period at least about 24 hours. In one aspect of this embodiment, the DCA bolus is followed within about 1/4 hour by an infusion of about 25 mg/kg/hour DCA for a period of about 1 hour, followed by continuous infusion of 12.5 mg/kg/hour DCA for a period of about 22 hours.
20 According to another aspect of this embodiment, the DCA bolus is followed within about 1/4 hour to 1/2 hour by an infusion of about 25 mg/kg/hour DCA for a period of about 4 to 6 hours, followed by continuous infusion of at least 12.5 mg/kg/hour DCA for a period of about 18 to 20 hours.
25 According to another aspect of this embodiment, the DCA bolus is followed within about 1/4 hour to about 1/2 hour by an infusion of about 25 mg/kg/hour DCA for a period of about 12 hours, followed by continuous infusion of at least 12.5 mg/kg/hour DCA for a second period of about 12
30 hours. In an alternate aspect, the present invention

provides an improved method of maintaining cardiac function at a predetermined level in a patient in need of treatment while decreasing inotropic drug requirements, wherein the improvement comprises administering DCA
5 within 15 minutes of administering said inotropic drug.

In another aspect, the present invention is directed to a method of decreasing the inotrope score in a patient who has undergone cardiac surgery which comprises administering a cardioprotective amount of DCA.

10 Please note that while the present invention is not limited to a particular dose level of DCA, doses and dosing protocols are suitable for use according to the methods of the present invention include the following. According to one aspect, DCA is administered continuously
15 and a plasma level of at least about 1mM is maintained in the patient for at least about 24 hours. According to one embodiment, a plasma level of at least about 1mM, alternatively from about 1mM to about 2mM is maintained. The plasma level is maintained for at least about 1 hour,
20 alternatively at least about 24 hours. According to an aspect of this embodiment, DCA is administered as a bolus before beginning the continuous administration of DCA. Suitable bolus doses are at least about 50 mg/kg, alternatively at least about 100 mg/kg. Suitable dose
25 ranges for the bolus include at least about 50 mg/kg, alternatively from about 50 mg/kg to about 100 mg/kg or more. Suitable dose ranges for DCA infusion include at least about 12.5 mg/kg/hour, alternatively at least about 25 mg/kg/hour. The DCA infusion may be maintained for a
30 prolonged period of time, suitably for at least about 10

hours, alternatively DCA infusion takes place for about 24 hours or more.

According to one aspect, the present invention provides DCA and inotropic drug to be administered in combination with each other, as in a single solution comprising DCA and inotrope. This combination method of administration allows decreasing the inotrope score in a patient who has undergone cardiac surgery wherein DCA is administered in a cardioprotective amount. In a further aspect of the invention, the method entails the administration of a bolus of DCA as described herein followed by administration of the combination intravenously, such as by intravenous infusion.

According to another aspect of the invention, provided is a pharmaceutical combination comprising a cardioprotective amount of DCA and an inotropic drug, the inotropic drug may be present at a therapeutically effective concentration to provide a lower dose of inotropic drug than the dose of inotropic drug that would be therapeutically effective in the absence of DCA.

According to one aspect, the present invention is directed to a method of maintaining or improving cardiac function during or following a cardiac function disturbing event or a cardiac metabolism disturbing event in a patient which comprises administering to said patient a cardioprotective amount of DCA and an inotropic drug. In an alternate aspect, the present invention is directed to methods of maintaining cardiac function at a predetermined level in a patient during or following a cardiac function or cardiac metabolism disturbing event

and decreasing the patient's need for inotropic drugs which comprises administering to said patient a cardioprotective amount of DCA.

In another aspect, the present invention is directed
5 to methods of treating an ischemic, hypoxic or metabolic event or an event which results in cardiac dysfunction in a patient which comprises administering said patient a cardioprotective amount of DCA and an inotropic drug.

According to a further aspect of the methods of the
10 present invention, the inotropic drug is administered with arginine or an agent which increases arginine levels or stimulates arginine release.

One aspect of the present invention are methods of improving or maintaining cardiac function during or
15 following a cardiac function disturbing event in a patient by administration of a cardioprotective amount of DCA, a cardioprotective amount of an inotropic drug, and anti-arrythmia drugs.

Another aspect of the invention are methods of
20 treating patients with ventricular fibrillation (VF) or hemodynamically unstable stable tachycardia and may require an anti-arrythmia drug(s) for treatment of hypotension. Examples of such anti-arrythmia drugs include but are not limited to amiodarone (coradone),
25 desethylamiodarone, and ion channel blocker agents including RSD 1235.

According to a further aspect of the methods of the present invention, cardiac function may be improved or maintained during a cardiac function disturbing event or

shortly following the event, prior to surgery, or during surgery, or following surgery in a patient by administration of a cardioprotective amount of DCA, a cardioprotective amount of an inotropic drug in combination with other agents selected from the group consisting of beta blockers, alpha adrenergic blockers, calcium channel blockers, dual action blocker (carvedilol), nitroglycerin, ACE Inhibitors, Angiotensin receptor blockers, Angiotensin II Antagonists, GPIIb/IIIa inhibitors, diuretics (loop or thiazide), calcium sensitizers, phosphodiesterase inhibitors, digoxin, Nersiritide, vasodilators, neurohormonal agents (vasopressors, aldosterone receptor antagonists, endothelin receptor blockers, endopeptidase inhibitors, ET-1 antagonists, nitric oxide enhancing therapies (L-Arginine), natriuretic peptides (BNP), erythropoietin analogues, statins, matrix metalloproteinase inhibitors, advanced glycosylated end-product antagonists, insulin, potassium, glucose, GIK, vitamin B6 isomers, a xanthine oxidase inhibitors, thrombin inhibitors, enoxaparin sodium, heparin, aspirin, anticoagulants, biguanides, sulfonylureas.

According to another aspect of the invention, methods of improving or maintaining cardiac function may include administering other agents which improve myocardial tissue perfusion and coronary flow in infarct patients treated with a fibrinolytic drugs. Such agents include agents selected from acetylsalicylic acid, an analgesic agent, an antipyretic agent, an anti-inflammatory agent and a GP IIb/IIIa inhibitor. By way of example only, aspirin is an example of an

analgesic agent, an antipyretic agent, and an anti-inflammatory agent. An example of a GP IIb/IIIa inhibitor is Clopidogrel.

According to one aspect of the invention, an
5 ischemic event is a stroke and may be treated by co-administering a tissue plasminogen activator (tPA) or a direct thrombin inhibitor in combination with a cardioprotective amount of DCA and an inotropic drug.

According to another aspect of the invention, the
10 cardiac function disturbing event is infarct or stroke in patients with or without diabetes, and may be treated by administering another agent selected from insulin, glucose and potassium.

According to another aspect of the invention, the
15 cardiac function disturbing event is decompensated heart failure and may be treated by administering an inotropic drug, B-type natriuretic peptide (BNP), for example Natrecor.

According to another aspect of the invention, the
20 cardiac function disturbing event or cardiac metabolism disturbing event is heart failure in a patient requiring an organ transplant, such as a heart transplant, a lung transplant or a renal transplant and may be treated by administering a vasodilator drug, prostaglandin E1,
25 adrenaline/noradrenaline, glucocorticoid or corticosteroid. Examples of prostaglandin E1 are selected from the group consisting of misoprostol, and a combination of azathioprine, prednisolone and cyclosporin A. Examples of vasodilator include but are not limited

to prostaglandins, for example PGE1, and further compromising administering N-acetylcysteine (NAC: Apothecon).

According to another aspect of the invention, the
5 cardiac function disturbing or cardiac metabolism disturbing event is caused by hemorrhagic shock, hypoxia or trauma and may be treated by methods according to the present invention.

According to another aspect of the invention, the
10 cardiac function disturbing event is or cardiac metabolism disturbing event is due to cardiomyopathy, for example diabetic myopathy and may be treated by methods according to the present invention.

According to another aspect of the invention, the
15 cardiac function disturbing event is due to HIV infection.

According to another aspect, the cardiac function disturbing event or cardiac metabolism disturbing event is due to malaria and may be treated by methods according
20 to the present invention.

According to another aspect, the cardiac function disturbing event or cardiac metabolism disturbing event is due to an acute coronary syndrome (ACS), including but not limited to post-AMI, post Percutaneous Transluminal
25 Coronary Angioplasty (PTCA) or angina.

According to another aspect, the cardiac function disturbing event or cardiac metabolism disturbing event

is shock, for example shock is secondary to hemorrhage, hypoxia, trauma or sepsis.

According to another aspect, the cardiac function disturbing event or cardiac metabolism disturbing event
5 is associated with diabetes.

According to another aspect, the cardiac function disturbing event or cardiac metabolism disturbing event is associated with the hypothalamic sensing of glucose and said administering may improve glucose homeostasis in
10 diabetes, or aging or obesity. Administering another agent selected from insulin, glucose and potassium, biguanide, sulfonylurea, hormonal and nutritional supplement or nutraceutical, maintains or improves cardiac function.

15 Another aspect of the present invention are methods of maintaining cardiac function at a predetermined level in a patient during or following a cardiac function disturbing event or a cardiac metabolism disturbing event and decreasing said patient's dose needed to give a
20 cardioprotective amount of an inotropic drug which comprises administering to said patient a cardioprotective amount of DCA.

In another aspect, DCA and inotropic drug are administered in combination.

25 In yet another aspect, DCA is administered within about 15 minutes of administering an inotropic drug.

In another aspect of the present invention inotropic drugs are selected from the group consisting of

dobutamine, epinephrine, dopamine, norepinephrine, phentolamine, digoxin, amrinone, milrinone, isoprotenerol and enoximone.

Another aspect of the present invention are methods
5 wherein DCA is administered to a patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 25 mg/kg/hour for at least about 10 hours.

Another aspect of the invention are methods wherein
10 the infusion of DCA is for at least about 24 hours.

Another aspect of the invention are methods wherein an inotropic drug is selected from the group consisting of a beta-adrenergic receptor agonist, a phosphodiesterase 3 ("PDE3") inhibitor, an agent which increases cyclic AMP
15 levels, a sodium hydrogen (Na^+, H^+) exchange inhibitor, and a sodium calcium ($\text{Na}^+/\text{Ca}^{2+}$) exchange blocker.

Another aspect of the invention are methods wherein an inotropic drug is a $\text{Na}^+/\text{Ca}^{2+}$ exchange blocker.

Another aspect of the invention are methods wherein
20 said inotropic drug is a non-adrenergic vasopressor.

Another aspect of the invention are methods wherein the inotropic drug is vasopressin.

Another aspect of the invention are methods wherein an inotropic drug is an alpha-2-adrenergic agonist.

25 Another aspect of the invention are methods wherein an inotropic drug is moxonidine or clonidine.

Another aspect of the invention are methods wherein an inotropic drug is an endothelin 1 (ET-1) antagonist.

Another aspect of the invention are methods wherein said ET 1 antagonist is bosetan or tezosentan.

5 Another aspect of the invention are methods wherein an inotropic drug is an ion channel blocker.

Another aspect of the invention are methods wherein an ion channel blocker is an Na⁺ pump inhibitor or an Na⁺,H⁺ exchange inhibitor or a K⁺ inhibitor, or a multiple
10 acting ion channel blocker (RSD 1235).

Another aspect of the invention are methods wherein an inotropic drug is a calcium-sensitizing agent.

Another aspect of the invention are methods wherein an inotropic drug is levosimendan.

15 Another aspect of the invention are methods wherein an inotropic drug is a calcium channel blocker.

Another aspect of the invention are methods wherein an inotropic drug is diltiazem or nifedipine or amlodipine or filopidine.

20 Another aspect of the invention are methods wherein an inotropic drug is an angiotensin converting enzyme ("ACE") inhibitor or a dual acting angiotensin inhibitor (Duo ACE)

Another aspect of the invention are methods wherein
25 an inotropic drug is quinaprilat or enalapril or

benazepril or lisinopril or captopril, or ramapril or
trandolapril.

Another aspect of the invention are methods wherein
an inotropic drug is a PDE3 inhibitor and methods further
5 comprising administering a beta-adrenegic receptor
agonist with said inotropic drug.

Another aspect of the invention are methods wherein
an inotropic drug is an agent which increases cyclic AMP
levels.

10 Another aspect of the invention are methods wherein
an inotropic drug is an Na^+, K^+ -ATPase inhibitor or a
cardiac glycoside, for example, but not limited to
vandate, 2-methoxy-3,8,9-dihydroxy coumestan or digoxin.

Another aspect of the invention are methods further
15 comprising administering an agent which increases
arginine levels in combination with DCA and said
inotropic drug.

Another aspect of the present invention are methods
of treating an ischemic, hypoxic or metabolic event or an
20 event resulting in cardiac dysfunction in a patient which
comprises administering to said patient a
cardioprotective amount of dichloroacetate ("DCA") and a
cardioprotective amount of an inotropic drug.

According to one embodiment, the methods of treating
25 follow an event is due to a cardiac surgical procedure,
percutaneous intervention, acute myocardial infarction or
an acute coronary syndrome.

According to another embodiment, the methods of treating follow an event due to an acute coronary syndrome and are selected from cardiogenic shock, hemorrhagic shock and trauma.

5 According to another embodiment, the methods of treating follow an event resulting from sepsis, HIV or malaria.

According to another embodiment, the methods of treating follow cancer chemotherapy, and the therapy
10 compromises administering a drug selected from an alkalizing agent selected from busulphan, carmustine, chlorambucil, cyclophosphamid, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphelan, mesna, streptozocin, and thiotepa; and an antimetabolite
15 selected from cytarabine, cladribine, fluoouracel, gemcitabine, and methotrexate.

According to another embodiment, the methods of treating follow an event which is due to or results from
20 angina, hypertension, pulmonary hypertension, diabetic cardiomyopathy, cardiomyopathy, congestive heart failure or diabetes, or when the event results in cognitive impairment.

In an alternative embodiment of the method, the cardioprotective amount of DCA comprises a bolus of at
25 least about 50 mg/kg followed by infusion of at least about 12.5 mg/kg/hour.

In another embodiment of the method, the cardioprotective amount of DCA comprises a bolus of at

least about 100 mg/kg followed by infusion of at least about 25 mg/kg/hour.

In another embodiment of the method, the cardioprotective amount of DCA is infused for at least
5 about 10 hours.

In another embodiment of the method, the cardioprotective amount of DCA is infused for at least about 24 hours.

Another aspect of the present invention are
10 pharmaceutical compositions comprising a cardioprotective amount of DCA and an inotropic drug selected from the group consisting of a beta-adrenergic receptor agonist, a PDE3 inhibitor, an agent which increases cAMP levels; a
Na⁺, H⁺ exchange inhibitor; a Na⁺, Ca²⁺ exchange blocker; a
15 non-adrenergic vasopressor; an alpha-2-adrenergic agonist; an ET-1 antagonist; an ion channel blocker(s); a calcium sensitizing agent; a calcium channel blocker; an ACE inhibitor; a Na⁺, K⁺-ATPase inhibitor; a Na⁺, K⁺ exchange inhibitor; a cardiac glycoside; a naturetic
20 peptide (BNP); a prostaglandin E1; a GPIIb/IIIa inhibitor; acetylsalicylic acid; an analgesic, antipyretic, and anti-inflammatory agent; an anti-arrhythmia agent; glucose; insulin; and potassium; a tissue plasminogen activator; and a sympathomimetic, and
25 a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to another aspect of the invention comprise inotropic drugs which are Na⁺/Ca²⁺ exchange blockers, for example but not

limited to non-adrenegic vasopressors, for example but not limited to vasopressin.

Pharmaceutical compositions according another aspect of the invention comprise an inotropic drug which is an
5 alpha-2-adrenegic agonist, for example but not limited to, moxonidine or clonidine.

Pharmaceutical compositions according to another aspect of the invention comprise an inotropic drug which is an endothelin 1 (ET-1) antagonist, for example but not
10 limited to bosetan or tezosentan.

Pharmaceutical compositions according to another aspect of the invention comprise an inotropic drug which are ion channel blockers selected from the group consisting of an Na⁺ pump inhibitor, an Na⁺,H⁺ exchange
15 inhibitor, a K⁺ channel blocker, or a multiple acting ion channel blocker (RSD 1235)

Pharmaceutical compositions according to another aspect of the invention comprise an inotropic drug which is a calcium-sensitizing agent, for example, but not
20 limited to levosimendan.

Pharmaceutical compositions according to another aspect of the invention comprise an inotropic drug which is a calcium channel blocker, for example, but not limited to diltiazem or nifedipine or amlodipine.

25 Pharmaceutical compositions according another aspect of the invention further comprise an angiotensin converting enzyme ("ACE") inhibitor or a duo acting antiotensin inhibitor (Duo ACE).

Pharmaceutical compositions according to another embodiment of the invention comprises quinaprilat

Pharmaceutical compositions according to another aspect of the invention comprise an inotropic drug, a
5 PDE3 inhibitor, for example Saterinone and which further comprises a beta-adrenegic receptor agonist.

Pharmaceutical compositions according to another embodiment of the invention comprise an inotropic drug which is an agent which increases cyclic AMP levels.

10 Pharmaceutical compositions according to another embodiment of the invention comprise an inotropic drug which is an Na^+, K^+ -ATPase inhibitor or a cardiac glycoside, for example, but not limited to, vandate, 2-methoxy-3,8,9-dihydroxy coumestan or digoxin.

15 Another aspect of the present invention are pharmaceutical compositions further comprising administering an agent which increases arginine levels in combination with DCA and said inotropic drug.

20 Another aspect of the present invention are kits comprising pharmaceutical compositions and kits further comprising a label or packaging insert containing instructions for use, in vitro, in vivo or ex vivo and components of said kit.

25 Additionally, the present invention provides pharmaceutical compositions suitable for use in to the methods of the present invention. Thus, provided are pharmaceutical compositions comprising a cardioprotective amount of DCA and an inotropic drug. Suitable inotropic

drugs include, but are not limited to, agents selected from the group consisting of a beta-adrenergic receptor agonist, a PDE3 inhibitor, an agent which increases cAMP levels; a Na^+ , H^+ exchange inhibitor; a Na^+ , Ca^{2+} exchange
5 blocker; a non-adrenergic vasopressor, an alpha-2-adrenergic agonist, an ET-1 antagonist; an ion channel blocker; an ACE inhibitor; a Na^+ K^+ -ATPase inhibitor, a Na^+ , K^+ exchange inhibitor; a cardiac glycoside; a sympathomimetic and other agents having a positive
10 inotropic effect which are known to those of skill in the art.

According to one embodiment, the composition may further comprise a beta-adrenergic receptor agonist. According to an alternate embodiment, the composition may
15 further comprise an agent which increases arginine levels.

Also included within the present invention are kits which comprise a pharmaceutical composition as described herein. The kit may also comprise a label or packaging
20 insert containing instructions for use.

Definitions:

"Inotrope" or "inotropic drug" refers to a member of a class of pharmaceutical agents that have a positive inotropic effect, including agents which increase the
25 contractility of cardiac muscle, have a strengthening effect on the heart, or increase cardiac output. These agents include cardiac glycosides, sympathomimetics, beta-adrenergic receptor agonists, phosphodiesterase 3 (PDE3) inhibitors, calcium-sensitizers; sodium, calcium
30 (Na^+ / Ca^{2+}) exchange blockers; sodium potassium (Na^+ / K^+)

exchange inhibitors; $\text{Na}^{(+)}$, $\text{K}^{(+)}$ -ATPase inhibitors; sodium hydrogen (Na^+ , H^+) exchange inhibitors; alpha-2-adrenergic agonists; non-adrenergic vasopressors; endothelin 1 (ET-1) antagonists; angiotensin converting enzyme (ACE) inhibitors; agents which increase cyclic adenosine monophosphate (cAMP) levels; agents which increase L-arginine levels or release of L-arginine, and other agents having a positive inotropic effect as noted in the "Detailed Description of the Invention" or known to those of skill in the art. Inotropes or inotropic drugs conventionally used to maintain cardiac function and contractility include dobutamine, epinephrine, dopamine, norepinephrine, phenylephrine, phentolamine, digoxin, amrinone, and other agents known to those in the art and include, without limitation, the inotrope or inotropic drugs mentioned in the "Detailed Description of the Invention" as well as others known to those of skill in the art. Indications where inotropes or inotropic drugs may be used to treat patients include after myocardial infarct, during and after cardiac surgical procedures, in shock or in congestive heart failure.

The term "positive inotropic effect" refers to an agent having a positive effect on the force of muscular contractions of cardiac tissue and includes agents that increase the contractility of cardiac muscle, that have a strengthening effect on the heart or that can increase cardiac output.

The term "cardiac event" refers to an event in a patient where cardiac function changes from what had been the patient's baseline function. Cardiac events include

events which disturb cardiac function and events which disturb cardiac metabolism. Examples of cardiac events include, but are not limited to, ischemic events, hypoxic events, acute myocardial infarction, acute heart failure, congestive heart failure, cardiomyopathy, diabetic cardiomyopathy, acute coronary syndrome, angina, post-percutaneous transluminal coronary angioplasty, shock, hemorrhagic shock, trauma, sepsis, cardiac surgical procedures (including CAGB), HIV, malaria, cancer chemotherapy, hypertension, pulmonary hypertension, and other conditions known to those of skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a chart noting the pre-op and post-op cardiac medications used for the patients in the study described in Example A.

Figure 2 depicts a graph of pyruvate dehydrogenase activity (PDH) after administration of a 50 mg/kg bolus of DCA or placebo. See Example A.

Figure 3 depicts a graph of plasma levels of acetate following infusion of placebo or 50 mg/kg DCA via cardiac bypass pump in the study of Example A.

Figure 4 depicts a graph for the inotrope score for patients treated with DCA (50 mg/kg bolus) versus placebo and the relative decrease in 1 hour inotrope score of DCA treated patients compared to placebo. See Example B.

Figure 5 depicts a graph of decrease in ICU time for patients treated with DCA (50 mg/kg bolus) as compared to placebo. See Example B.

Figure 6 depicts a graph of the decrease in ventilator time for patients treated with DCA (50 mg/kg bolus) versus placebo. See Example B.

Figure 7A depicts a summary of patients in the study of Example C treated pre-op or post-op with inotropes.

Figure 7B depicts a list of hemodynamic drugs routinely administered pre-op or post-op to cardiac surgery patients such as the patients of the studies described in Examples B and C.

Figure 8 depicts a graph of the effects on inotrope score of administration of a 50 mg/kg bolus of DCA followed by a 25 mg/kg/hour infusion versus placebo in post-heart surgery patients. See Example C.

Figure 9 depicts a graph of the effects on inotrope score of DCA administration as a 100 mg/kg bolus and 12.5 mg/kg/hour infusion versus placebo post-surgery in pediatric patients. See Example C.

Figure 10 depicts a graph of effects on reducing ICU time of DCA administration as a 50 mg/kg bolus and 25 mg/kg/hour infusion post-surgery in patients as compared to placebo. See Example C.

Figure 11 depicts a graph of the effects on reducing ICU time for patients with DCA treatment as 100 mg/kg bolus and 12.5 mg/kg/hour infusion post-surgery as compared with placebo. See Example C.

Figure 12 depicts a graph of the effects on reducing ventilator time for patients with DCA administration as a 50 mg/kg bolus and 25 mg/kg/hour infusion post-surgery as compared with placebo. See Example C.

5 Figure 13 depicts a graph of the effects on ventilator time for patients with DCA treatment as a 100 mg/kg bolus and 12.5 mg/kg/hour infusion post-surgery as compared to placebo. See Example C.

10 DETAILED DESCRIPTION OF THE INVENTION

As noted, in one aspect, the present invention provides methods of maintaining or improving cardiac function following a cardiac function disturbing event or a cardiac metabolism disturbing event by administering a cardioprotective amount of DCA and an inotropic drug.

15 Such cardiac function disturbing events and/or cardiac metabolism disturbing events include an ischemic event (such as acute myocardial infarction), acute heart failure, an event caused by hemorrhagic shock, hypoxia or trauma; cardiomyopathy (including diabetic

20 cardiomyopathy); an event due to an HIV infection; an event due to malaria; acute coronary syndrome (including events which are post-AMI, post PTCA or angina); shock (including events where shock is secondary to hemorrhage,

25 hypoxia, trauma or sepsis); and events associated with diabetes; events following or resulting from cancer chemotherapy and other events resulting from disturbances in cardiac function or cardiac metabolism.

The present invention provides methods of maintaining cardiac function at a predetermined level during or following a cardiac function disturbing event or a cardiac metabolism disturbing event and of decreasing the patient's need for inotropic drugs by administering a cardioprotective amount of DCA. Suitably, DCA and an inotropic drug are administered in combination. According one embodiment, DCA is administered within about 15 minutes of administering the inotropic drug. Suitable inotropic drugs include dosutamine, epinephrine, dopamine, morepinephine, phentolamine, digoxin, amrinone, milrone, enoximore, as well as other inotropic drugs described herein or known to those of skill in the art.

Suitable dosing protocols for these methods include administering DCA in a bolus of at least about 50 mg/kg, or advantageously about 100 mg/kg or more. The DCA bolus is followed by continuous infusion of DCA of at least about 12.5 mg/kg/hour, or advantageously at least about 25 mg/kg/hour, for at least an hour. Suitably DCA is infused for at least about 10 hours or alternatively for at least about 24 hours or more.

Accordingly to one aspect of these methods, the inotropic drug is selected from the group consisting of a beta-adrenergic receptor agonist, a phosphodiesterase 3 (PDE3) inhibitor, an agent which increases cyclic AMP levels; a sodium, hydrogen (Na^+ , H^+) exchange inhibitor; and a sodium, calcium (Na^+ , Ca^{2+}) exchange blocker. Where the inotropic drug is a PDE3 inhibitor, the methods may further comprise administering a beta-adrenergic receptor

agonist. According to alternate aspects, the inotropic drug may be either a non-adrenergic agonist, an endothelin 1(ET-1) antagonist, an ion channel blocker, a calcium-sensitizer, a calcium channel blocker, an
5 angiotensin converting enzyme (ACE) inhibitor, a PDE3 inhibitor (optimally administered with a beta-adrenergic receptor agonist), an agent which increases cyclic AMP levels; an Na⁺, K⁺-ATPase inhibitor, a cardiac glycoside or other agent having a positive inotropic effect.

10 The present invention provides methods of treating an ischemic, hypoxic or metabolic event or an event resulting in cardiac dysfunction by administering a cardioprotective amount of DCA and an inotropic drug. Such an event may be due to a surgical procedure,
15 percutaneous intervention, acute myocardial infarction or an acute coronary syndrome (ACS). Acute coronary syndromes include cardiogenic shock, hemorrhagic shock and trauma. Alternatively, such an event may result from, sepsis, HIV or malaria. The event to be treated
20 may follow cancer chemotherapy. Such event may be due to or result from, angina, hypertension, pulmonary hypertension, diabetic cardiomyopathy, cardiomyopathy, congestive heart failure or diabetes. The event to be treated may result in cognitive impairment. According to
25 one embodiment, the dosing protocol for DCA comprises administering a bolus of DCA, followed by continuous infusion of DCA for a period of time. DCA may be administered in a bolus of at least about 50 mg/kg, and suitably in a bolus of about 100 mg/kg or more. DCA may
30 be infused at a rate at least about 12.5 mg/kg/hour, and suitably at least about 25 mg/kg/hour. DCA may be

infused for an extended period of time, for example for at least about 1 hour, alternatively about 10 hours or more or about 24 hours or more.

Pharmaceutical compositions suitable for use
5 accordingly to the present invention include a cardioprotective amount of DCA and an inotropic drug. The composition suitably comprises an amount of inotropic drug effective to maintain or improve cardiac function when in combination with the cardioprotective amount of
10 DCA. Suitable inotropic drugs for use in the pharmaceutical compositions include those described herein as well as other inotropic drugs or agents having a positive inotropic effect when administered to a patient which are known in the art.

15 Cardiac Metabolism

Under normal aerobic conditions, oxidation of fatty acids is the predominant source of energy (ATP) production in the heart, with a lesser contribution being derived from lactate and glucose. However, during
20 ischemia (such as occurs during cardiac surgery), when the supply of oxygen becomes limiting, anaerobic glycolysis assumes a more important role, and fatty acid and carbohydrate oxidation decrease (5, 6). During reperfusion following ischemia, ATP production,
25 tricarboxylic acid (TCA) cycle activity and oxygen consumption rapidly recover. Fatty acid oxidation also quickly recovers providing over 90% of the overall ATP production (7, 8). The reason for this increase in fatty acid oxidation is reportedly due both to ischemic-induced
30 alterations in the control of myocardial fatty acid

oxidation (9, 10), as well as an increase in circulating fatty acid levels (11, 12). The use of inotropes with adrenergic agonist properties can also contribute to these high plasma levels of fatty acids. This excessive
5 use of fatty acids by the heart following ischemia can have adverse effects on both cardiac function and cardiac efficiency.

The availability of different energy substrates and the type of energy substrate used by the heart can have
10 profound effects on cardiac functional recovery during and following an ischemic episode. Specifically, high rates of fatty acid oxidation may contribute to a marked decrease in cardiac efficiency secondary to inhibition of glucose oxidation (5, 6, 7). However, if glucose
15 oxidation is stimulated during reperfusion, a significant increase in cardiac efficiency results, with a parallel improvement in cardiac function (11). This is partly due to a decreased requirement of oxygen to produce equivalent amounts of ATP (7, 13). Stimulating glucose
20 oxidation also decreases the production of protons in the heart, therefore decreasing the amount of ATP necessary to maintain ionic homeostasis in the heart.

In fetal life, glycolysis and lactate oxidation are the major sources of ATP production. However, following
25 birth there is a rapid maturation of fatty acid oxidation, which rapidly becomes the predominant source of ATP production in the newborn heart (13, 19, 20). Under aerobic conditions, glucose oxidation rates are lower in neonatal hearts compared with adult hearts (21,
30 22). Simultaneous measurement of both glycolysis and

glucose oxidation in neonatal hearts has demonstrated that glycolytic rates are much greater than rates of glucose oxidation, suggesting low flux through pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidation (21). Therefore, when the newborn heart is subjected to ischemia-reperfusion injury during open heart surgery, the increase in fatty acid oxidation may be particularly detrimental, since the glucose oxidation pathway in these hearts has not completely matured.

Studies in immature rabbit hearts have shown that addition of pyruvate, a substance that stimulates PDH activity, significantly increases aortic flow, cardiac work, and developed pressure (23). Based on these studies, we believe that a metabolic therapy, which stimulates glucose oxidation at the expense of fatty acid oxidation, would enhance cardiac recovery following ischemia.

Cardioprotective Effects of Dichloroacetate on the Heart

We have found dichloroacetate (DCA) to be particularly effective at stimulating glucose oxidation in the heart. DCA has been reported to stimulate pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidation in the heart (14, 15). This stimulation appears to occur via DCA inhibition of PDH kinase, which normally phosphorylates and inhibits PDH. In experimental studies on isolated rat hearts, we showed that DCA dramatically improves functional recovery and cardiac efficiency during reperfusion of hearts following a severe episode of ischemia (9, 16, 17). This beneficial effect of DCA is due to a dramatic stimulation of glucose oxidation and a switch in energy substrate use

by the heart from fatty acid oxidation towards glucose metabolism (15, 7). DCA also dramatically decreases proton production in the reperfused ischemic heart, which is a major reason for the DCA-induced improvement in
5 cardiac efficiency during reperfusion (16).

Since DCA has demonstrated such dramatic effects in our studies on cardioprotective effects on the ischemic heart, it may be of clinical use in maintaining and improving cardiac function (including contractility) in
10 the setting of cardiac surgery both for the adult and pediatric patient. Plasma levels of fatty acids have been observed to increase significantly during reperfusion following cardiac surgery. This increase is observed to be highest in pediatric patients, including
15 patients as young as three weeks of age (10). Elevations in free fatty acids may result in an increase in myocardial oxygen consumption, which may potentiate ischemic injury (11).

Inotropes are frequently administered to patients to
20 improve contractile function of the heart following cardiac surgery. However, some effects of inotropes may not be desirable. For example, epinephrine, an inotropic agent, has been reported to increase the uncoupling between glycolysis and glucose oxidation resulting in a
25 significant increase in proton production from glucose metabolism (24). This potentially may accelerate acidosis during the reperfusion period, at a time when the heart is trying to clear a preexisting proton load produced during ischemia, and would be another
30 undesirable effect of inotrope use (8, 1).

While not wanting to be bound to a particular theory, we believe that by stimulating glucose oxidation, administration of DCA lessens the need for inotropes (or dose of inotrope) and other hemodynamic drugs used post-operatively. We have shown that DCA is cardioprotective in adults, pediatric patients, and neonates undergoing open heart cardiac surgical procedures. The present examples describe studies that determine that DCA when used in combination with inotropes lessens the dose of inotrope needed.

In one aspect, the present invention is directed to the use of dichloroacetate (DCA) to improve cardiac functional recovery and metabolism after open heart surgical procedures (cardiopulmonary bypass and congenital lesions) in patients and to decrease the need for administering of inotropes and if inotropes are administered, decrease the dose of inotrope needed to maintain cardiac function (including contractility) at a desired predetermined level. Administration of DCA lessens the need for inotropes and other hemodynamic agents. As a result, combination therapy with DCA will allow for a lowering of the amount and doses of inotropes used.

We believe that pediatric patients receive even greater benefits from DCA during cardiac surgery because, as previously noted, they have the highest fatty acid levels during and after cardiac surgery accompanied by the lowest rates of glucose oxidation. In a study of 40 pediatric patients (age 0.03-15.1 years) requiring open heart surgery (see Example B), DCA was given as a bolus

dose of 50 mg/kg into the aortic root just prior to the release of the cross clamp. One-hour Inotrope Score was significantly lower in the DCA group compared to placebo (which indicated better cardiac function). ICU days and ventilator hours were also lower in the DCA group. This study demonstrated that DCA, when used in combination with inotropes, will lessen the requirements for inotropes in the immediate post-surgery period.

Use of DCA as a Cardioprotective Agent and to Decrease the Need for Inotropes or Inotropic Drugs

The studies described in Example A demonstrate that DCA administration increases PDH activity in the human heart and improves carbohydrate oxidation.

In Example A, studies in 18 adult Coronary Artery Bypass Graft (CABG) patients demonstrated that giving DCA as a bolus was effective in producing the desired metabolic effects of DCA. Cardiac PDH enzyme activity following surgery was increased significantly following administration of DCA. As well, DCA also significantly decreased plasma lactate levels.

In the studies described in Examples B and C we observed that DCA administered as a bolus dose post-surgery to pediatric patients undergoing cardiac surgery significantly lowered the dose of inotropes required to sustain contractile function and decreased the time spent in the Intensive Care Unit (ICU).

When DCA was administered using a bolus and infusion protocol to maintain therapeutic levels of DCA over a 24 hour period during reperfusion for surgical heart

procedures, the therapeutic benefits of DCA were sustained in the presence of other clinically recommended hemodynamic drugs, the requirements for inotropes were decreased, and the patients' time spent on the ventilator and in the ICU was significantly decreased.

In Example B, where DCA was administered as a bolus dosing protocol, the clinical benefit of DCA was demonstrated in a study which consisted of a 40 pediatric patients study for surgical heart procedures. Data from this trial revealed that patients treated with DCA had a significantly reduced Inotrope Score, had reduced time in ICU and had reduced time on the ventilator as compared to patients treated with placebo. The results observed after administration of DCA as a bolus of 50 mg/kg in the study described in Example B encouraged us to proceed with the DCA protocol used for the study described in Example C.

A dose range for DCA of about 1mM has been shown to be effective in increasing PDH levels and improving myocardial function in isolated perfused hearts. (This dose range was also supported by data from the study described in Example A using a bolus administration of 50m/kg DCA.) The bolus and infusion administration in the study described in Example C provided the therapeutic benefits of DCA at a DCA therapeutic level in blood plasma of 1mM (7, 9, 16, 17) during the critical 24 hour period post-surgery. Using a bolus and infusion protocol, data from the study described in Example C (which consisted of 51 pediatric patients) revealed that such treatment resulted in a reduced need for inotropic drugs. (As noted in Example C, the final results were based on

47 patients, 51 patients less 4 infusion pump failure cases).

In the study described in Example C, the DCA protocols used two different dosing administrations in the presence of clinical recommended therapeutic levels of hemodynamic drugs: Group A was originally given a bolus of 50 mg/kg and an infusion of 25 mg/kg/hr; and Group B was given a bolus of 100 mg/kg and an infusion of 12.5 mg/kg/hr. (The cardiac surgeon in the study described in Example C had good results and therefore used less inotropes to maintain cardiac index in all patients.)

In the study described in Example C, the DCA therapeutic range level of the DCA patients in both Groups A and B, showed benefits at DCA therapeutic plasma levels 0.229mM to 2.22mM at the 1 to 6 hour interval, and from 1.74mM to as high as 3.9mM at the 24 hour interval (Table I). There were 11 DCA patients in each of Groups A and B, and noted below in Table I as n= the number of DCA patients where the DCA blood plasma levels measured at each interval.

Table I

Average DCA Plasma Levels (Example C)

	mM at 1 hr	mM at 6 hr	mM at 12 hr	mM at 24 hr
<u>Group A</u>	.460	1.134	1.771	2.724
50 mg/kg bolus and 25 mg/kg/hr	(n=11)	(n=10)	(n=9)	(n=11)

infusion				
<u>Group B</u>	1.131	.894	1.427	2.231
100 mg/kg bolus and 12.5 mg/kg/hr infusion	(n=11)	(n=11)	(n=11)	(n=10)

The DCA therapeutic optimum means for the different intervals from the study described in Example C were based on the DCA patient outcomes with the greatest degree of clinical benefits (cardiac index, ICU and ventilator time) as compared to placebo. These DCA plasma range outcomes were from both the *simple* open heart surgery and *complex* open heart surgery patients - at the 1 hour interval from Group B, and at the 12 and the 24 hour intervals from Group A. The optimum DCA therapeutic dose level average means are as summarized below in Table II.

Table II

Average Optimum Mean of DCA Plasma Levels (Example C)

Group A and Group B *n=* data from DCA patients numbers with Greatest Degree of Clinical Benefits

	MM at 1 hr	mM at 6 hr	mM at 12 hr	mM at 24 hr
<u>Group A</u>	1.0	0.916	1.523	2.288
50 mg/kg bolus and 25 mg/kg/hr infusion		(m=5)	(m=5)	(m=6)

Group B	1.012	1.0	1.0	1.0
100 mg/kg bolus and 12.5 mg/kg/hr infusion	(n=7)			

The known DCA therapeutic dose level mean of 1mM was observed in Group B at the 1 to 6 hour interval (with a DCA plasma level range of .229mM to 2.22mM) A different optimum DCA therapeutic dose level at 2.29mM means was observed from Group A at the 24 hour period (with a DCA plasma level range of 1.73mM to 3.91mM).

The resulting data in the Group A protocol of a bolus of 50 mg/kg and an infusion of 25 mg/kg/hour post-surgical heart procedure for 23 patients reduced the time in ICU (Figure 10) post-surgical procedure by 60 hours (a 41 % decrease) as compared to placebo. The reduction of Inotrope Scores (Figure 8) was by 1 hour at a 50% decrease, and by 12 hours at a 45% decrease and by 24 hours at a 38% decrease as compared to placebo. Ventilator time (Figure 12) was reduced by 46 hours (a 47% decrease) as compared to placebo.

The resulting data in the Group B protocol of a bolus of 100 mg/kg and an infusion of 12.5 mg/kg/hour, post-surgical heart procedure for 24 patients, reduced the time in ICU (Figure 11), post surgical procedure over the 24 hour period by 50 hours (a 40% decrease) as compared to placebo. The reduction of Inotrope Scores (Figure 9) averaged by 1 hour at a 57% decrease, and by 12 hours at a 49% decrease, and by 24 hours at a 45%

decrease as compared to placebo. Ventilator Time (Figure 13) was reduced by 19 hours (a 23 % decrease) as compared to placebo.

The merit of reducing inotropic drugs with the bolus and infusion administration of DCA is supported by the data from the 1 hour period through the 24 hour period post surgical heart procedures from the study described in Example C.

The data measurement outcomes from *in vitro* modeling testing (17) indicate that the administration of DCA at a constant therapeutic level of 1mM maintains its benefits in the presence of clinically high levels of hemodynamic drugs. Administering a constant optimum therapeutic mean level (based on the optimum outcome) of DCA observed in the presence of clinically acceptable lower levels of hemodynamic drugs will provide significant cardioprotective benefits and decrease deleterious effects which may occur with use of such hemodynamic agents. In the studies described in the Examples, we found optimum mean levels for DCA plasma ranges at specific intervals were as to include: 1mM (.229mM to 2.22mM DCA plasma range) during the 1 to 6 hour period, 1.52mM (.38mM to 3.07mM plasma range) at the 12 hour interval, and 2.29mM (1.73mM to 3.91mM DCA plasma range) at the 24 hour interval.

Taken together, improving cardioprotective benefits, and improved cardiac function were maintained by using DCA at a constant therapeutic level of about 1mM in the presence of clinically recommended dose levels of hemodynamic drugs over a 24 hour period. In the presence

of clinically high levels of hemodynamic drugs, by using our DCA protocol to maintain a constant therapeutic range of 1mM at the 1 to 6 hour period, 1.5mM at the 12 hour interval, and 2.29mM at the 24 hour interval, improving
5 cardioprotective benefits, and improved cardiac function are also maintained.

Events Treated with DCA and Inotropic Drug Therapy

Cardiac events to be treated with the methods of the present invention include cardiac function disturbing and
10 cardiac metabolism disturbing events which may have a number of causes. These events include ischemic, hypoxic and/or metabolic events or events which result in dysfunction in acute disease indications including cardiac surgical procedures such as CABG, CPB and
15 valvular surgeries, percutaneous interventions ("PCI"), acute myocardial infarction ("AMI") and Acute Coronary Syndromes ("ACS") such as cardiogenic shock, hemorrhagic shock and trauma. Certain of these events may be due to pathologic conditions which result in cardiac
20 dysfunction.

Other such events include ischemic, hypoxic or metabolic events or events resulting in cardiac dysfunction in a patient having sepsis, HIV or malaria.

Additional such events include ischemic, hypoxic or
25 metabolic events or events resulting from cardiac dysfunction occurring following cancer chemotherapy. Other events suitable for treatment include ischemic, hypoxic or metabolic events or cardiac dysfunction resulting in cognitive impairment.

Additional events for treatment according to the compositions and methods of the present invention include ischemic, hypoxic or metabolic events or events resulting in cardiac dysfunction in acute or chronic disease
5 indications which include, but are not limited to, unstable or stable angina, hypertension, pulmonary hypertension, diabetic cardiomyopathy, cardiomyopathy, congestive heart failure or diabetes.

Administration and Dosing of DCA

10 While it is not intended that the present invention be limited by the particular delivery means, one delivery means is an intravenous means, such as that achieved by introduction through an intravenous drip. Other means includes (but is not limited to) delivery with a
15 catheter. Another means involves direct injection into the aorta, for example, with a catheter. Still other routes of administration include subcutaneous, sublingual and oral routes to achieve a decrease in the amount of inotrope needed to maintain a predetermined level of
20 cardiac function.

The particular dosage of DCA is also not intended to be limiting. A variety of temporal protocols is contemplated. Delivery in a bolus as well as continuous delivery is contemplated. In one embodiment, DCA (such
25 as sodium dichloroacetate) is given in a bolus of at least 100 mg/kg of an approximately 100 mg/ml solution (1.0 cc/kg bolus) and, immediately thereafter, dichloroacetate is given as an infusion at approximately 12.5 mg/kg/hr for greater than about 10 hours and, more

preferably, is given as an infusion for about 24 hours or more.

According to an alternate embodiment, DCA is given in a bolus of at least about 100 mg/kg and, immediately thereafter DCA is given as an infusion at about 25 mg/kg/hour for greater than about 10 hours and, suitably, about 24 hours or more.

According to one aspect of the present invention, DCA is administered to a patient under conditions such that said subject has a blood (e.g., serum or plasma) concentration of DCA of greater than approximately 200µM, alternatively greater than 500µM, and even greater than 1mM, for a period of time longer than 1 hour, alternatively longer than 6 hours, and even 24 hours or longer. In one embodiment, DCA is delivered as a bolus, followed by continuous administration.

Higher dosages than those noted above may be used. We have not observed DCA to have significant side-effects, although it has been reported that some patients on chronic dosing experience mild drowsiness.

Inotropic Drugs

A number of pharmaceutical agents have been reported as inotropic drugs and have been reported as having exhibited positive inotropic activity when administered to a patient. These inotropic drugs have been reported to have a positive inotropic effect. Such positive inotropic effects have been reported as resulting from one or more of a number of different mechanisms of action. Classes of pharmaceutical agents reported to

exhibit a positive inotropic effect include sodium calcium ($\text{Na}^+/\text{Ca}^{2+}$) exchange blockers, phosphodiesterase 3 ("PDE3") inhibiting drugs, calcium-sensitizers, agents which increase cyclic AMP (cAMP) levels, agents which
5 increase intracellular Na^+ , ion channel blockers (including Na^+ or H^+ exchange inhibitors and Na^+ pump inhibitors), sodium potassium (Na^+ , K^+) exchange inhibitors, alpha-2-adrenergic agonists, endothelin 1 (ET-1) antagonists (or endothelin 1 (ET-1) receptor
10 agonists), calcium channel blockers, angiotensin converting enzyme ("ACE") inhibitors; $\text{Na}^{(+)}$, $\text{K}^{(+)}$ -ATPase inhibitors; cardiac glycosides; sympathomimetics; beta-adrenergic receptor agonists; non-adrenergic vasopressors; and other vasoconstrictor agents.

15 Examples of ACE inhibitors include quinoprilat.

 Examples of alpha-2-adrenergic agonists include clonidine and moxonidine.

 Examples of beta-adrenergic receptor agonist inotropic agents include isoproterenol, dopexamine and
20 dobutamine.

 Examples of calcium channel blocking agents include diltiazem, nifedipine and other such agents.

 Examples of calcium-sensitizers include levosimendan.

25 Examples of Endothelin 1 (ET-1) antagonists include bosentan and tezosentan.

 Examples of Na^+ , H^+ exchange inhibitors include cariporide.

Examples of Na⁺, K⁺ ATPase inhibitors include vanadate and 2-methoxy-3,8,9-trihydroxy coumestan.

Examples of non-adrenergic vasopressors include vasopressin.

5 Examples of sodium pump inhibitors include ouabain.

Examples of PDE3 inhibitors include amrinone, milrinone and enoximone.

The listing of classes of pharmaceutical agents having positive inotropic activity is intended as
10 exemplary in nature and other classes of such agents known to those of skill in the art are intended to be included as inotropic drugs. Similarly, with respect to particular agents given as examples of the classes noted above, they are intended as examples only and are not
15 intended as to be an exhaustive listing of suitable agents of a particular class.

Pharmaceutical Compositions and Kits

The invention further provides pharmaceutical compositions comprising a cardioprotective amount of DCA
20 and an inotropic drug or their pharmaceutically acceptable salts, esters or prodrugs. Also contemplated to be within the scope of the present invention are pharmaceutical compositions further comprising a beta-adrenergic receptor agonist. According to an
25 alternate aspect, the pharmaceutical compositions of the present invention further comprise an agent which increases arginine levels.

Pharmaceutical compositions or formulations include compositions and formulations conventionally used in the pharmaceutical arts and may comprise carriers and excipients compatible with oral, intravenous, intramuscular, intraarterial, intracranial, and/or intracavity administration. Suitable pharmaceutical compositions and/or formulations may further compose colloidal dispersion systems, or lipid formulations (e.g., cationic or anionic lipids), micelles, microbeads, etc.

As noted, pharmaceutical compositions of the present invention may comprise pharmaceutically acceptable and physiologically acceptable carriers, diluents or excipients. Examples of suitable carriers, diluents and excipients include solvents (aqueous or non-aqueous), solutions, emulsions, dispersion media, coatings, isotonic and absorption promoting or delaying agents, compatible with pharmaceutical administration, and other commonly used carriers known in the art.

Pharmaceutical compositions may also include carriers to protect the composition against rapid degradation or elimination from the body, and, thus may comprise a controlled release formulation, including implants and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed.

Pharmaceutical compositions can be formulated to be compatible with a particular route of administration. For oral administration, a composition can be incorporated

with excipients and used in the form of tablets, pills or capsules, e.g., gelatin capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included in oral formulations. The tablets, pills, capsules, etc., can contain any of the following ingredients, or similar compounds: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; or a flavoring or sweetening agent.

Pharmaceutical compositions for parenteral, intradermal, or subcutaneous administration can include a sterile diluent, such as water, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose.

Pharmaceutical compositions for injection include sterile aqueous solutions (where water-soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate

buffered saline (PBS). Antibacterial and antifungal agents include, for example, parabens, chlorobutanol, phenol, ascorbic acid and thimerosal. Isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride may be included in the composition. Including an agent which delays absorption, for example, aluminum monostearate and gelatin can prolong absorption of injectable compositions.

The pharmaceutical formulations can be packaged in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier or excipient.

The compositions can be administered by any route compatible with a desired outcome. Thus, routes of administration include oral (e.g., ingestion or inhalation), sublingual, intraperitoneal, intradermal, subcutaneous, intravenous, intraarterial, intracavity, intracranial, and parenteral. The compositions can also be administered using implants and microencapsulated delivery systems.

Compositions, including pharmaceutical formulations can further include particles or a polymeric substance, such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide

copolymers, or ethylenevinylacetate copolymers.
Cyclopropanecarboxylic acid, cyclopropanecarboxylic acid
and derivatives and modified forms thereof can be
entrapped in microcapsules, for example, by the use of
5 hydroxymethylcellulose or gelatin-microcapsules, or poly
(methylmethacrolate) microcapsules, respectively, or in a
colloid drug delivery system.

The invention provides kits containing a
cardioprotective amount of DCA and an inotropic drug,
10 including pharmaceutical formulations, packaged into a
suitable set. A kit typically includes a label or
packaging insert including instructions for use, *in*
vitro, *in vivo*, or *ex vivo*, of the components therein.

The term "packaging material" refers to a physical
15 structure housing the components of the kit, such as DCA
and inotropic drug and, if present, pharmaceutically
acceptable carrier. The packaging material can maintain
the components sterilely, and can be made of material
commonly used for such purposes (e.g., paper, corrugated
20 fiber, glass, plastic, foil, ampules, etc.). The label
or packaging insert can include appropriate written
instructions, for example, practicing a method of the
invention.

Kits of the invention therefore can additionally
25 include instructions for using the kit components in a
method of the invention. Instructions can include
instructions for practicing any of the methods of the
invention described herein. Thus, for example, a kit can
include DCA and inotropic drug in a pharmaceutical
30 formulation in a container, pack, or dispenser together

with instructions for administration to a human subject. Instructions may additionally include indications of a satisfactory clinical endpoint or any adverse symptoms that may occur, or any additional information required by
5 the Food and Drug Administration for use in humans.

A kit may include instructions for administering DCA and inotropic drug in the treatment of an ischemic, hypoxic or metabolic event or an event resulting in cardiac dysfunction *in vitro*, *ex vivo* or *in vivo*. In
10 other embodiments, a kit includes instructions for treating a disorder associated with deficient or inefficient glucose utilization. In one aspect, the instructions comprise instructions for treating a subject having or at risk of having ischemic/reperfusion injury,
15 post myocardial infarction, angina, heart failure, a cardiomyopathy, peripheral vascular disease, diabetes, or lactic acidosis. In another aspect, the instructions comprise instructions for treating a subject having or at risk of having heart surgery (e.g., open heart surgery,
20 bypass surgery, heart transplant and angioplasty).

The instructions may be on "printed matter," e.g., on paper or cardboard within the kit, or on a label affixed to the kit or packaging material, or attached to a vial or tube containing a component of the kit.
25 Instructions may additionally be included on a computer readable medium, such as a disk (floppy diskette or hard disk), optical CD such as CD- or DVD-ROM/RAM, magnetic tape, electrical storage media such as RAM and ROM and hybrids of these such as magnetic/optical storage media.

Kits can additionally include a buffering agent, a preservative, or a stabilizing agent. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single
5 package.

To assist in understanding, the present invention will now be further illustrated by the following Examples. These Examples as they relate to the present invention should not, of course, be construed as
10 specifically limiting the invention and such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and hereinafter claimed.

15 **EXAMPLES**

Methods Used in the Studies Described in Examples A to C

The studies described in Examples A to C describe three different clinical studies of the effect of DCA when administered to patients during and/or following
20 cardiac surgery.

The study described in Example A involved adult patients in which the effects of DCA on cardiac metabolism were studied. DCA was administered to patients undergoing elective cardiac bypass grafting
25 surgery (CABG). This study was performed in the presence of clinically recommended dosages of hemodynamic drugs in coronary artery bypass grafts.

The study described in Example B involved the administration of a single bolus dose of DCA to pediatric patients undergoing cardiac surgery to correct congenital heart lesions. This protocol, performed in the presence
5 of clinically recommended hemodynamic drugs, determined that the dose and amount of these agents could be decreased with DCA use.

The study described in Example C involved the use of a bolus and infusion protocol to administer DCA over a 24
10 hour period to pediatric patients undergoing cardiac surgery to correct congenital heart lesions. This protocol was also performed in the presence of clinically recommended hemodynamic drugs, and determined that the dose and amount of these agents could be decreased with
15 DCA use.

EXAMPLE A

Description of Study Protocol

DCA or saline was administered to 18 patients undergoing elective cardiac bypass grafting surgery
20 (CABG) in a double blinded randomized manner DCA (50 mg/kg in 100 ml of saline) or placebo was injected into the aortic root, immediately prior to removing aortic cross clamp. Based on the pharmacokinetics of DCA, we anticipated that this would produce a plasma
25 concentration of approximately 1 mM. The study consisted of 8 DCA-treated patients and 10 placebo-treated patients.

1. Intervention

a. "Usual" Therapy

All procedures and drugs normally given for CABG patients were given routinely. A list of medications
5 provided for these patients shown in Figure 1.

b. "Intervention" Therapy

The intervention involved DCA (50 mg/kg) or placebo injected into the aortic root immediately prior to removing aortic cross clamp. The coded solution was made
10 such that a dose of 1ml/kg provides the appropriate dose of DCA or placebo. Based on the pharmacokinetics of DCA, this was expected to result in a plasma level of DCA in the therapeutic range of (1mM). All blood samples were analyzed by HPLC for DCA concentration.

15 2. Sample Processing

Plasma samples were processed for DCA levels using a high performance liquid chromatography (HPLC) technique that separated the DCA from other plasma constituents. In brief, 20 μ l of plasma sample was injected into a
20 Beckman Gold HPLC containing a IonoBpher 5A column (250x4.6mm LxID) and a AX Guard Column. The mobile phase of the column consisted of 10-3 M pyromellitate buffer (pH = 4.0). The flow rate of the HPLC was set at 3.0 ml/min and the DCA eluted from the column was detected by
25 comparing DCA elution times to acetate, monochloroacetate, and trichloroacetate standards. Heart ventricular biopsy samples were taken at 0, and 20 minutes, and at 1 hour, following release of the cross clamp and reperfusion of the heart muscle, and
30 immediately frozen in liquid N₂. Blood samples were also

taken at various intervals during the reperfusion period between 0 to 24 hours post-surgery.

PDH activity was measured in ventricular biopsies using a radioisotope procedure which determines the production of ^{14}C -citrate formed from ^{14}C -oxaloacetate and acetyl CoA derived from PDH (8). Blood levels of lactate, fatty acids and glucose were measured using standard enzymatic assays.

3. Statistical Analysis

Comparisons of demographics between groups were done using unpaired t-tests (continuous variables) and Chi-square tests (discrete variables). Comparison of cardiac index between groups was done using a nonparametric unpaired test. Statistical significance is defined as $p < 0.05$. Data handling and statistical analysis was performed by the Epicore Center at the University of Alberta.

Results of Study

In this study in 18 adult cardiovascular surgery patients, DCA was administered as a bolus dose of 50 mg/kg to 8 adult patients in the presence of other clinically recommended doses of hemodynamic drugs (Figure 1). DCA was administered immediately prior to restoration of coronary blood flow following the cardiac procedure. In patients treated with DCA, compared to placebo, there was a significant increase in PDH activity in heart muscle biopsies taken in the early reperfusion period (Figure 2). DCA also significantly decreased lactate levels (Figure 3), indicating that DCA increases

carbohydrate oxidation during reperfusion. There was a single mortality in the placebo group and no mortalities the DCA group.

Plasma levels of DCA were also measured in patients at 1 hour following administration of DCA. Plasma levels of DCA were approximately 1 mM, a concentration we have shown to be efficacious in stimulating glucose oxidation in experimental animal studies (9, 16).

10

Table III

Plasma Levels of Dichloroacetate Following Infusion of 50 mg/kg Na ⁺ Dichloroacetate via Cardiopulmonary Bypass Pump
Plasma Dichloroacetate Levels (mM) (n=8)
0.948 ± 0.061

Combined, the data in this study of adult patients demonstrated that our dosing protocol: 1) resulted in a therapeutic level of DCA in the critical early period of reperfusion post cardiac surgery, and 2) this dose of DCA

increased cardiac PDH activity and lowers circulating plasma lactate levels.

EXAMPLE B

Description of Study Protocol

5 This study was a randomized, placebo-controlled, double blinded, single surgeon, study of the use of DCA in 40 high-risk pediatric patients requiring heart surgery to connect complex congenital heart lesions.

1. Study Population

10 In this trial, 40 children were recruited to participate in a single surgeon study, of which 18 received DCA and 22 received placebo. The 1995 power calculations were based on separation of the CPB-1 trial of n = 40 patients.

15 2. Inclusion Criteria

- a. Age less than 1 year.
- b. Consent from parent or guardian.
- c. Requirement for open-heart surgery to correct complex congenital heart lesions (e.g., such as Tetralogy of Fallot).
- 20 d. Agreement of the surgeon, anesthetist and cardiologist.
- e. Significant non cardiac complications precluding study protocol implementation.

25 3. Exclusion Criteria

- a. Lack of parental consent.

- b. Refusal for entry from surgeon or anesthesiologist or cardiologist

4. Randomization, Data Collection, and Blinding Procedures

5 Computerized randomization of study medications were performed by the Epicore Centre at the University of Alberta. The patients and all study personnel were blinded throughout the study. Unblinding was set into the procedures only if, in the opinion of the patient's physician or study personnel, information concerning the
10 identity of the study drug was essential for the patients' safety reasons.

5. Intervention

a. "Usual" Therapy

15 All procedures and drugs normally given for infants undergoing cardiopulmonary bypass were given routinely. A list of medications provided is shown in Figure 7B.

b. "Intervention" Therapy

The intervention involved DCA (50 mg/kg) or placebo
20 injected into the aortic root immediately prior to removing aortic cross clamp. The coded solution was made such that a dose of 1ml/kg provides the appropriate dose of DCA or placebo. Based on the pharmacokinetics of DCA, this was expected to result in plasma levels of DCA in
25 the therapeutic range of (1mM). All blood samples were analyzed by HPLC for DCA concentration.

6. Sample Collections

Arterial blood samples were obtained from patients at the following times:

- 5 a. Immediately after the insertion of
arterial line in operating room, *i.e.*, the
beginning of surgery.
- b. Thirty minutes after the bolus of DCA was
given, whether or not cardiopulmonary
bypass had been discontinued.
- 10 c. One hour after discontinuing
cardiopulmonary bypass.
- d. Six hours after discontinuing
cardiopulmonary bypass.
- e. Twelve hours after discontinuing
15 cardiopulmonary bypass.
- f. Twenty four hours after discontinuing
cardiopulmonary bypass.

7. Sample Processing

Blood samples were collected from indwelling
20 arterial lines into citrate-containing tubes (0.5 ml
blood samples). The samples were spun in the microfuge,
the plasma separated, and frozen immediately for later
analysis. All plasma samples were stored at -80 degrees
centigrade, until further processing. Plasma glucose and
25 lactate were determined using a Sigma glucose kit and a
spectrophotometric assay involving lactate dehydrogenase
respectively. Plasma fatty acid levels were measured
using an ELISA system and WAKO free fatty acid kit.

8. Inotrope Drug Score

In both the operating room at the end of cardiopulmonary bypass and in the intensive care unit, parenteral drugs were scored on an hourly basis with 1 point allotted for each level for each bolus or infusion given within the previous hour for the first 24 hours post-operatively. Thus, at the end of 24 hours high scores indicated poorer cardiac function.

9. Validation of Index

In this study, we anticipated a 30% decrease in Inotrope Score at the 1 hour interval.

10. Ascertainment of Response Variables

a. Data Collection

The drug score chart in the operating room was filled out by the anesthetist. In the pediatric intensive care unit, the research coordinator was responsible for completing drug score charts, corroborated by nursing staff, ICU staff and physicians. Fatty acids, glucose, DCA, and lactate levels were determined with technicians blinded as to treatment category.

b. Data Monitoring and Safety issues

Careful attention was paid to safety precautions in this study. A data monitoring committee had the authority to terminate the study should have serious adverse side effects occurred. In previous pilot studies, no adverse effects of DCA were noted.

c. Data Analysis

DCA was deemed beneficial if Inotrope Score was significantly lower in the intervention patients than in placebo patients.

11. Statistical Analysis

Comparison of demographics between groups was done using unpaired t-tests (continuous variables) and Chi-square tests (discrete variables). Comparison of Cardiac functional Index between groups was done using a nonparametric unpaired test. Statistical significance is defined as $p < 0.05$. Data handling and statistical analysis was performed by the Epicore Center.

Results of Study

DCA administration significantly reduced the need for inotropic drugs during the critical first 1 hour period following surgery (Figure 4). Data from this bolus administration of DCA to pediatric patients (40) also demonstrates that post surgical DCA administration reduces ICU time (Figure 5) and ventilator time (Figure 6). In this protocol which had 40 pediatric patients, 18 pediatric patients received a DCA bolus of 50 mg/kg. Echocardiography in the DCA patients (35% versus 26%) demonstrated better shortening fraction as compared to placebo patients.

EXAMPLE C

Description of Study Protocol

This study was a randomized, placebo-controlled, double blinded, single surgeon, study of the use of DCA in 51 high-risk pediatric patients requiring heart surgery to correct complex congenital heart lesions.

5 1. Study Population

In this trial, 53 infants were recruited to participate in a study, of which 51 patients met inclusion criteria after parental consent. Two dosing groups resulted from the study team changing the dosing protocol after the data from the initial 10 patients were
10 analyzed. The data from patients number 1 to number 10 was analyzed for DCA therapeutic blood levels and therapeutic effect. A recommendation by the research team was made to increase the bolus dose of DCA and to
15 decrease the infusion dose of DCA to maintain a DCA dose range of 1mM for 24 hours. The intent was to administer the new protocol at patient number 20. The 1997 Epicore power calculations were based on separation of the study groups patients into group A of n = 20 patients and Group
20 B of n = 31 patients

Half of each group received different dosages of DCA and the other half received placebo in a double blinded, randomized fashion. Candidates for entry into the study were recruited from weekly surgical lists and from
25 notification by the cardiac surgeon.

2. Inclusion criteria

- a) Age less than 1 year.
- b) Consent from parent or guardian.

c) Requirement for open-heart surgery to correct complex congenital heart lesions (e.g., tetralogy of Fallot).

5 d) Agreement of the surgeon, anesthetist, and cardiologist.

3. Exclusion Criteria

a) Lack of parental consent.

b) Refusal for entry from surgeon or anesthetist or cardiologist.

10 c) Significant non cardiac complications precluding study protocol implementation.

4. Randomization, Data Collection, and Blinding procedures

Computerized randomization of study medications were
15 performed by the Epicore Centre. The patients and all study personnel were blinded throughout the study. Unblinding was set into the procedures only if, in the opinion of the patient's physician or study personnel, information concerning the identity of the study drug was
20 essential for the patients' safety reasons.

5. Intervention

a) "Usual" therapy

All procedures and drugs normally given for infants undergoing cardiopulmonary bypass were given routinely. A
25 list of medications provided in shown in Figures 7A and 7B.

b) "Intervention" therapy

The interventions in the two groups of this study were as follows:

5 (i) Group A

DCA (50 mg/kg) or placebo was injected into the aortic root immediately prior to removing aortic cross clamp. The coded solutions were made such that a dose of 1 ml/kg provided either a DCA therapeutic level of 1mM
10 plasma concentration of DCA, or a placebo solution. Immediately thereafter, an infusion of DCA at 25 mg/kg/hr or placebo in the same volume was initiated and run for 24 hours. Based on the pharmacokinetics of DCA, this was expected to maintain plasma levels of DCA in the
15 therapeutic range of (0.2-1mM). However, the plasma concentrations of DCA were below 1mM after the first hour interval, and that the 24 hour plasma concentrations were elevated above 1mM DCA levels at the 24 hour interval, a decision was made to modify the dosing protocol. This
20 change in dosing protocol was approved by the Ethics Committee, but not implemented until patient number 24. All blood samples were analyzed by HPLC for DCA concentration.

(ii) Group B

25 DCA (100mg/kg) or placebo was injected into the aortic root immediately prior to removing aortic cross clamp. The coded solutions were made such that a dose of 1 ml/kg provided either a DCA therapeutic level of 1mM

plasma concentration of DCA, or a placebo solution.
Immediately thereafter, an infusion of DCA at 12.5
mg/kg/hr or placebo in the same volume was initiated and
run for 24 hours. Based on the pharmacokinetics of DCA,
5 this was expected to maintain plasma levels of DCA in the
therapeutic range of (0.2-1mM). All blood samples were
analyzed by HPLC for DCA concentration.

6. Sample collections

Arterial blood samples were obtained from patients
10 at the following times:

- a. Immediately after the insertion of
arterial line in operating room (*i.e.*, at
beginning of surgery).
 - 15 b. Thirty minutes after the bolus of DCA has
been given, whether or not cardiopulmonary
bypass has been discontinued.
 - c. One hour after discontinuing
cardiopulmonary bypass.
 - 20 d. Six hours after discontinuing
cardiopulmonary bypass
 - e. Twelve hours after discontinuing
cardiopulmonary bypass.
 - f. Twenty four hours after discontinuing
cardiopulmonary bypass.
- 25 At the end of 24 hours, the DCA or placebo infusion was
discontinued.

7. Sample processing

Blood samples were collected from indwelling
arterial lines into citrate-containing tubes (0.5 ml

blood samples). The samples were spun in the microfuge, the plasma separated, and frozen immediately for later analysis. All plasma samples were stored at -80 degrees centigrade, until further processing. Plasma glucose and lactate were determined using a Sigma glucose kit and a spectrophotometric assay involving lactate dehydrogenase respectively. Plasma fatty acid levels were measured using an ELISA system and WAKO free fatty acid kit.

8. Inotrope Drug Score

In both the operating room at the end of cardiopulmonary bypass and in the intensive care unit, parenteral drugs were scored on an hourly basis with 1 point allotted for each level for each bolus or infusion given within the previous hour within the first 24 hours post-operatively. Thus at the end of 24 hours, high scores indicated poorer cardiac function.

9. Validation of Index

In this study, we anticipated a 30% decrease in Inotrope Score. Our intent was to maintain good or improve contractile function through the 24 hour period as compared to placebo, by providing an infusion of DCA throughout the 24 hour period following a bolus administration of DCA. By improving cardiac function, we anticipated a reduction in ICU time per patient.

10. Ascertainment of response variables

a. Data collection

The drug score charts in the operating room were filled out by the anesthetist. In the pediatric

intensive care unit, the research coordinator was responsible for completing drug score charts, corroborated by nursing, ICU flow sheets, and doctor's orders. Fatty acids, glucose, DCA, and lactate levels were determined with technicians blinded as to treatment category.

a) Data monitoring and safety issues

Careful attention was paid to safety precautions in this study. A data monitoring committee has the authority to terminate the study should have serious adverse side effects occurred. In previous studies, no adverse effects of DCA were noted.

b) Data Analysis

DCA was deemed beneficial if Inotrope Score was significantly lower in the Intervention patient compared to the placebo patients.

11. Statistical Analysis

Comparison of demographics between groups was done using unpaired t-tests (continuous variables) and Chi-square tests (discrete variables). Comparison of Cardiac functional Index between groups was done using a nonparametric unpaired test. Statistical significance is defined as $p < 0.05$. Data Handling and statistical analysis was performed by the Epicore Center.

25 Results of Study

Since DCA has a short-half life in the body this study was initiated in pediatric patients where a DCA bolus and infusion protocol was used over a 24 hour

period in the presence of other clinically recommended doses of hemodynamic drugs (Figures 7A and 7B). The goal of this study was to maintain therapeutic levels of DCA over a 24 hour period because it is known that poor
5 myocardial contractility and high lactate levels (10) persist for up to 24 hours in children after open heart surgery.

In a double-blinded randomized clinical trial involving 51 pediatric patients (age 3 days to 12 years)
10 requiring open-heart surgery were given either a DCA bolus or placebo followed by an infusion of DCA for 24 hours. During the course of this study, after the protocol was administered to first 10 patients in the Group A (out of the 24 patients), it became clear that
15 the original Group A infusion rate produced concentrations of DCA in excess of 1 mM by 24 hours. We therefore modified the Group A bolus infusion protocol, as described in the "Methods" section for Group B in this document. In the Group A, 12 patients received a DCA
20 bolus of 50 mg/kg followed by an infusion of DCA (25 mg/kg/hr) for 24 hours. In the Group B, 14 patients received a DCA bolus of 100mg/kg followed by an infusion of DCA (12.5 mg/kg/hr) for 24 hours.

The following observations were as follows from this
25 study: There was also a trend toward lower Inotrope Scores in the DCA groups over the 24 hour period as compared to placebo. There was also a trend toward less Intensive Care Unit (ICU) days in the DCA groups over the 24 hour period as compared to placebo. There was also a
30 trend toward less ventilator time in DCA Group A as

compared to placebo. This decrease in ventilator time was lower than what was observed from both the DCA Group B protocol and the DCA protocol of the Study described in Example B. Greater differences in ICU Time were observed in patients who had poorer initial function with more complex conditions and surgical procedures, which suggests that DCA may be more beneficial than placebo for these patients.

A subsequent review of the data obtained from the 51 patients in this study revealed the following. The change in dosing protocol in this study was initiated at patient number 25 (and not at patient number 20 as anticipated at the time of request for protocol change), and that the actual number of patients allocated to each group was 24 patients for the Group A, and 27 patients for the Group B. Subsequent review of the patient records and data of the 24 older, pediatric patients in the Group A revealed the inclusion of 1 infusion pump failure case. In the 27 younger, pediatric patients in the Group B, there were 3 infusion pump failure cases. In total, 4 only infusion pump failure cases were excluded in the subsequent data compilation. As a result of the infusion pump failure modifications, the final allocation of patients included in the final two groups in this document were as follows: Group A of n= 23 patients and Group B of n = 24 patients. The drug scoring compilation of data was set up for Inotrope Scoring, and not sodium bicarbonate scores. (Sodium bicarbonate is not considered an inotropic drug.) As a result, sodium bicarbonate scores were removed in the final compilation of the Inotrope Scoring data. Clinically recommended

doses of other hemodynamic drugs administered to both the placebo and drug patient groups were noted (see Figures 7A and 7B).

1. Inotrope Score

5 In this study, a trend in decreased Inotrope Score over the 24 hour period post-surgery was shown, similar to what was observed in the study described in Example B (Figure 4) over the 1 to 4 hour period. A trend to a decreased inotrope use was noted in both Group A, and
10 Group B patients receiving DCA. Data from the study, Group A (Figure 8) and Group B (Figure 9), show the effects of DCA bolus/infusion administration using the two dosing protocols on Inotrope Score over the 24 hour period. In the Group B (Figure 9), the decrease in
15 Inotrope Score (an average decrease of 51% per patient as compared to placebo) was greater than the results from the Group A (an average decrease of 44% per patient as compared to placebo). It should be noted that in this study, all patients in the A and B Groups on average
20 received lower Inotrope Scores than those reported for the patients in the study described in Example B patients, due to the involvement of a different cardiac surgeon.

2. ICU Time

25 In this study Group A, and Group B, a trend in decreased ICU time was similar to what was observed in the study described in Example B (Figure 5). A trend to decreased ICU time over the 24 hour period was noted in both Group A and Group B patients receiving DCA. Data

from the Group A (Figure 10) and Group B (Figure 11), show the effects of DCA bolus/infusion administration on ICU time, using the two different dosing protocols. In Group A, the reduction in ICU time (a decrease of 60
5 hours or 41% as compared to placebo), was greater than the results from both the study described in Example B (a decrease of 19 hours or 23% compared to placebo), and the Group B (a decrease of 50 hours, or 40% compared to placebo).

10 3. Ventilator Time

Data from the Group A and Group B showed that the trend in decreased ventilator time was similar to what was observed in the study described in Example B (Figure 6). A trend to decreased ventilator time over the 24 hour
15 period was noted in both Group A and Group B patients receiving DCA. Data from the Group A (Figure 12) and Group B (Figure 13) show the effects of DCA bolus/infusion administration on ventilator time using the two different dosing protocols. In Group A, the
20 reduction in ventilator time (a decrease of 46 hours or 47% as compared to placebo) was greater than the results from both the study described in Example B (a decrease of 12 hours or 27% compared to placebo) and the Group B (a decrease of 18 hours or 23% compared to placebo).

25 Conclusion

In summary, our findings support our first outcome measure to improve cardiac function through a surrogate measurement score for "cardiac index" which showed a reduced need for inotropes, and a reduced ICU time and
30 reduced ventilator time post-surgery as compared to

placebo. We have established through our three studies that DCA improves cardiac function and provides cardioprotection during reperfusion in both neonates and adults as additive and/or in combination therapy with
5 hemodynamic drugs. The data from these studies supports the use of DCA as a therapeutic approach for treating both the adult and pediatric cardiac surgical patients. The data also supports the combined use of DCA with inotropes in the presence of other clinically recommended
10 doses of hemodynamic drugs, and demonstrates that DCA can lessen the amount of inotropes needed post-surgery.

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We Claim:

1. A method of maintaining or improving cardiac function during or following a cardiac function disturbing event or a cardiac metabolism disturbing event
5 in a patient which method comprises administering to said patient a cardioprotective amount of dichloroacetate (DCA) and an inotropic drug, wherein DCA is administered to said patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about
10 12.5/mg/kg/hour for at least about 9 to 11 hours wherein said continuous infusion begins about 1/4 hour to within 1/2 hour after administration of said bolus.

2. A method according to claim 1 wherein said continuous infusion of DCA is at least about 25
15 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 10 hours.

3. A method according to claim 1 wherein said continuous infusion of DCA is for at least about 24 hours.

20 4. A method according to claim 3 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

5. A method according to claim 4 wherein said
25 continuous infusion begins about 1/4 hour after administration of the bolus.

6. A method according to claim 5 wherein said continuous infusion of DCA is at least about 25

mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 23 hours.

7. A method according to claim 5 wherein said continuous infusion of DCA is at least about 25
5 mg/kg/hour for about 4 to 6 hours, followed by at least about 12.5 mg/kg/hour for about 18 to 20 hours.

8. A method according to claim 5 wherein said continuous infusion of DCA is at least about 25
10 mg/kg/hour for about 12 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

9. A method of maintaining cardiac function at a predetermined level in a patient during or following a cardiac function disturbing event or a cardiac metabolism disturbing event and decreasing said patient's need for
15 inotropic drugs which method comprises administering to said patient a cardioprotective amount of DCA, wherein DCA is administered to said patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 12.5/mg/kg/hour for at least about
20 9 to 11 hours wherein said continuous infusion begins about 1/4 hour to about 1/2 hour after administration of said bolus.

10. A method according to claim 9 wherein said continuous infusion of DCA is at least about 25
25 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 10 hours.

11. A method according to claim 9 wherein said continuous infusion of DCA is for at least about 24 hours.

12. A method according to claim 11 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

5 13. A method according to claim 12 wherein said continuous infusion begins about 1/4 hour after administration of the bolus.

14. A method according to claim 13 wherein said continuous infusion of DCA is at least about 25
10 mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 22 hours.

15. A method according to claim 13 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 4 to 6 hours, followed by at least
15 about 12.5 mg/kg/hour for about 18 to 20 hours.

16. A method according to claim 13 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 11 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

20 17. A method of treating an ischemic, hypoxic or metabolic event or an event resulting in cardiac dysfunction in a patient which method comprises administering to said patient a cardioprotective amount of DCA and an inotropic drug, wherein DCA is administered
25 to said patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 12.5/mg/kg/hour for at least about 9 to 11 hours wherein said continuous infusion begins about 1/4 hour to about 1/2 hour after administration of said bolus.

18. A method according to claim 17 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 10 hours.

5 19. A method according to claim 17 wherein said continuous infusion of DCA is for at least about 24 hours.

20. A method according to claim 19 wherein said continuous infusion of DCA is at least about 25
10 mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

21. A method according to claim 20 wherein said continuous infusion begins about 1/4 hour after administration of the bolus.

15 22. A method according to claim 21 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 23 hours.

23. A method according to claim 21 wherein said
20 continuous infusion of DCA is at least about 25 mg/kg/hour for about 4-6 hours, followed by at least about 12.5 mg/kg/hour for about 18 to 20 hours.

24. A method according to claim 23 wherein said continuous infusion of DCA is at least about 25
25 mg/kg/hour for about 12 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

25. A method of maintaining or improving cardiac function during or following a cardiac function

disturbing event or a cardiac metabolism disturbing event in a patient which method comprises administering to said patient a cardioprotective amount of DCA and an inotropic drug, wherein DCA is administered to said patient in a
5 bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 12.5/mg/kg/hour for at least about 9 to 11 hours wherein said continuous infusion begins 0 to about 1/2 hour after administration of said bolus.

10 26. A method according to claim 25 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 10 hours.

15 27. A method according to claim 25 wherein said continuous infusion of DCA is for at least about 24 hours.

20 28. A method according to claim 27 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

29. A method according to claim 28 wherein said continuous infusion begins about 0 hour after administration of the bolus.

25 30. A method according to claim 25 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 23 hours.

31. A method according to claim 29 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 4 to 6 hours, followed by at least about 12.5 mg/kg/hour for about 18 to 20 hours.

5 32. A method according to claim 5 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 12 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

10 33. A method of maintaining cardiac function at a predetermined level in a patient during or following a cardiac function disturbing event or a cardiac metabolism disturbing event and decreasing said patient's need for inotropic drugs which method comprises administering to said patient a cardioprotective amount of DCA, wherein
15 DCA is administered to said patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 12.5/mg/kg/hour for at least about 9 to 11 hours wherein said continuous infusion begins 0 to about 1/2 hour after administration of said bolus.

20 34. A method according to claim 33 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 10 hours.

25 35. A method according to claim 34 wherein said continuous infusion of DCA is for at least about 24 hours.

36. A method according to claim 35 wherein said continuous infusion of DCA is at least about 25

mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

37. A method according to claim 36 wherein said continuous infusion begins about 0 hour after
5 administration of the bolus.

38. A method according to claim 37 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 23 hours.

10 39. A method according to claim 37 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for about 4 to 6 hours, followed by at least about 12.5 mg/kg/hour for about 18 to 20 hours.

40. A method according to claim 37 wherein said
15 continuous infusion of DCA is at least about 25 mg/kg/hour for about 12 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

41. A method of treating an ischemic, hypoxic or metabolic event or an event resulting in cardiac
20 dysfunction in a patient which method comprises administering to said patient a cardioprotective amount of DCA and an inotropic drug, wherein DCA is administered to said patient in a bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about
25 12.5/mg/kg/hour for at least about 9 to 11 hours wherein said continuous infusion begins 0 to about 1/2 hour after administration of said bolus.

42. A method according to claim 41 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for at least about one hour and at least about 12.5 mg/kg/hour for at least about 8 to 9 hours.

5 43. A method according to claim 41 wherein said continuous infusion of DCA is for at least about 24 hours.

44. A method according to claim 43 wherein said continuous infusion of DCA is at least about 25
10 mg/kg/hour for about 1 to about 12 hours, followed by continuous infusion of at least about 12.5 mg/kg/hour.

45. A method according to claim 44 wherein said continuous infusion begins about 0 hour after administration of the bolus.

15 46. A method according to claim 45 wherein said continuous infusion of DCA is at least about 25 mg/kg/hour for one hour, followed by at least about 12.5 mg/kg/hour for about 23 hours.

47. A method according to claim 45 wherein said
20 continuous infusion of DCA is at least about 25 mg/kg/hour for about 4 to 6 hours, followed by at least about 12.5 mg/kg/hour for about 18 to 20 hours.

48. A method according to claim 47 wherein said continuous infusion of DCA is at least about 25
25 mg/kg/hour for about 12 hours, followed by at least about 12.5 mg/kg/hour for about 12 hours.

49. A method of maintaining or improving cardiac function during or following a cardiac function

disturbing event or a cardiac metabolism disturbing event in a patient which method comprises administering to said patient a cardioprotective amount of DCA and a cardioprotective amount of an inotropic drug.

5 50. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is an ischemic event.

 51. A method according to claim 49 wherein hypotension is secondary in patients with ventricular
10 fibrillation (VF) or hemodynamically unstable ventricular tachycardia requiring an anti-arrhythmia drug.

 52. A method according to claim 51 further comprising administering an anti-arrhythmia drug selected from amiodarone (cordarone), desethylamiodarone or ion
15 channel blocker agent RSD 1235.

 53. A method according to claim 51 further comprising administering a vasopressor.

 54. A method according to claim 50 wherein said cardiac function disturbing event or cardiac metabolism
20 disturbing event is an acute myocardial infarction (AMI).

 55. A method according to claim 54 further comprising administering another agent which improves myocardial tissue perfusion and coronary flow in an infarct patient treated with a fibrinolytic drug.

25 56. A method according to claim 55 further comprising administering an agent selected from acetylsalicylic acid, an analgesic agent, an antipyretic

agent, an anti-inflammatory agent and a GP IIbIIIa inhibitor.

57. A method according to claim 56 wherein the agent selected from an analgesic agent, an antipyretic agent, and an anti-inflammatory agent is aspirin.

58. A method according to claim 56 wherein the GP IIbIIIa inhibitor is Clopidogrel.

59. A method according to claim 49 further comprising administering other agents during the event or shortly following the event, prior to surgery, or during surgery, or following surgery, selected from the group consisting of beta blockers, alpha adrenergic blockers, calcium channel blockers, dual action blocker (carvedilol), nitroglycerin, ACE Inhibitors, Angiotensin receptor blockers, Angiotensin II Antagonists, GPIIbIIIa inhibitors, diuretics (loop or thiazide), calcium sensitizers, phosphodiesterase inhibitors, digoxin, Nersiritide, vasodilators, neurohormonal agents (vasopressors, aldosterone receptor antagonists, endothelin receptor blockers, endopeptidase inhibitors, ET-1 antagonists, nitric oxide enhancing therapies (L-Arginine), natriuretic peptides (BNP), erythropoietin analogues, statins, matrix metalloproteinase inhibitors, advanced glycosylated end-product antagonists, insulin, potassium, glucose, GIK, vitamin B 6 isomers, a xanthine oxidase inhibitors, thrombin inhibitors, enoxaprin sodium, heparin, aspirin, anticoagulants, biguanides, sulfonylurease.

60. A method according to claim 50 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is stroke..

61. A method according to claim 50 or 60 further
5 comprising administering a tissue plasminogen activator (tPA) or a direct thrombin inhibitor.

62. A method according to claim 49, wherein said event is infarct or stroke in patients with or without diabetes, further comprising administering another agent
10 selected from insulin, glucose and potassium.

63. A method according to claim 49 further comprising administering another agent during the event or shortly following the event, prior to surgery, or during surgery, or following surgery.

15 64. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is acute heart failure or acute chronic heart failure.

65. A method according to claim 49 wherein said
20 cardiac function disturbing event or cardiac metabolism disturbing event is decompensated heart failure.

66. A method according to claim 65 wherein said inotropic drug is a B-type natriuretic peptide (BNP).

67. A method according to claim 66 wherein said
25 inotropic drug is Natreacor.

68. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism

disturbing event is heart failure in patients requiring an organ transplant.

69. A method according to claim 68 wherein said organ transplant is a heart transplant or lung
5 transplant.

70. A method according to claim 69 further compromising administration of a vasodilator drug, prostaglandin E1, adrenaline/noradrenaline, gluticosteriod or corticosteroid.

10 71. A method according to claim 69 compromising administering a prostaglandin E1 selected from misoprostol, and a combination of azathioprine, prednisolone and cyclosporin A.

72. A method according to claim 68 wherein said
15 organ transplant is a renal transplant.

73. A method according to claim 72 further compromising said drugs administering a vasodilator selected from a prostaglandin.

74. A method according to claim 73 wherein said
20 vasodilator is PGE1, and further compromising administering N-acetylcysteine (NAC: Apothecon).

75. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is caused by hemorrhagic shock, hypoxia
25 or trauma.

76. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is due to cardiomyopathy.

77. A method according to claim 76 wherein said
5 cardiomyopathy is diabetic myopathy.

78. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is due to HIV infection.

79. A method according to claim 49 wherein said
10 cardiac function disturbing event or cardiac metabolism disturbing event is due to malaria.

80. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is due to an acute coronary syndrome
15 (ACS).

81. A method according to claim 80 wherein said ACS is post-AMI, post Percutaneous Transluminal Coronary Angioplasty (PTCA) or angina.

82. A method according to claim 49 wherein said
20 cardiac function disturbing event or cardiac metabolism disturbing event is shock.

83. A method according to claim 82 wherein shock is secondary to hemorrhage, hypoxia, trauma or sepsis.

84. A method according to claim 49 wherein said
25 cardiac function disturbing event or cardiac metabolism disturbing event is associated with diabetes.

85. A method according to claim 49 wherein said cardiac function disturbing event or cardiac metabolism disturbing event is associated with the hypothalamic sensing of glucose and said administering may improve
5 glucose homeostasis in diabetes, or aging or obesity.

86. A method according to claim 85 further comprising administering another agent selected from insulin, glucose and potassium, biguanide, sulfonylurea, hormonal and nutritional supplement or nutraceutical.

10 87. A method of maintaining cardiac function at a predetermined level in a patient during or following a cardiac function disturbing event or a cardiac metabolism disturbing event and decreasing said patient's dose needed to give a cardioprotective amount of an inotropic
15 drug which method comprises administering to said patient a cardioprotective amount of DCA.

88. A method according to claim 87 wherein DCA and inotropic drug are administered in combination.

89. A method according to claim 87 wherein DCA is
20 administered within about 15 minutes of administering an inotropic drug.

90. A method according to any of claims 49, 87, 88 or 89 wherein said inotropic drug is selected from the group consisting of dobutamine, epinephrine, dopamine,
25 norepinephrine, phentolamine, digoxin, amrinone, milrinone, isoproterenol and enoximone.

91. A method according to any of claims 49, 87, 88 or 89 wherein DCA is administered to said patient in a

bolus of at least about 100 mg/kg followed by continuous infusion of DCA of at least about 25 mg/kg/hour for at least about 10 hours.

92. A method according to claim 91 wherein said
5 infusion of DCA is for at least about 24 hours.

93. A method according to claim 49 wherein said inotropic drug is selected from the group consisting of a beta-adrenergic receptor agonist, a photodiesterase 3 ("PDE3") inhibitor, an agent which increases cyclic AMP
10 levels, a sodium hydrogen (Na^+/H^+) exchange inhibitor, and a sodium calcium ($\text{Na}^+/\text{Ca}^{2+}$) exchange blocker.

94. A method according to claim 93 wherein said inotropic drug is an $\text{Na}^+/\text{Ca}^{2+}$ exchange blocker.

95. A method according to claim 49 wherein said
15 inotropic drug is a non-adrenegic vasopressor.

96. A method according to claim 95 wherein said inotropic drug is vasopressin.

97. A method according to claim 49 wherein said inotropic drug is an alpha-2-adrenegic agonist.

20 98. A method according to claim 97 wherein said inotropic drug is moxonidine or clonidine.

99. A method according to claim 49 wherein said inotropic drug is an endothelin 1 (ET-1) antagonist.

100. A method according to claim 99 wherein said ET
25 1 antagonist is bosetan or tezosentan.

101. A method according to claim 49 wherein said inotropic drug is an ion channel blocker.

102. A method according to claim 101 wherein said ion channel blocker is selected from a Na⁺ pump inhibitor or a Na⁺,H⁺ exchange inhibitor, a K⁺ inhibitor, and a multiple acting ion channel blocker (RSD 1235).

103. A method according to claim 49 wherein said inotropic drug is a calcium-sensitizing agent.

104. A method according to claim 103 wherein said inotropic drug is levosimendan.

105. A method according to claim 49 wherein said inotropic drug is a calcium channel blocker.

106. A method according to claim 105 wherein said inotropic drug is diltiazem or nifedipine or amlodipine or filopidine.

107. A method according to claim 49 wherein said inotropic drug is an angiotensin converting enzyme ("ACE") inhibitor or a dual acting angiotensin inhibitor (Duo ACE)

108. A method according to claim 107 wherein said inotropic drug is quinaprilat or enalapril or benazepril or lisinopril or captopril, or ramapril ortrandolapril.

109. A method according to claim 49 wherein said inotropic drug is a PDE3 inhibitor.

110. A method according to claim 109 further comprising administering a beta-adrenegic receptor agonist with said inotropic drug.

111. A method according to claim 49 wherein said
5 inotropic drug is an agent which increases cyclic AMP levels.

112. A method according to claim 49 wherein said inotropic drug is an Na^+, K^+ -ATPase inhibitor or a cardiac glycoside.

10 113. A method according to claim 112 wherein said inotropic drug is vandate, 2-methoxy-3,8,9-dihydroxy coumestan or digoxin.

114. A method according to claim 49 further comprising administering an agent which increases
15 arginine levels in combination with DCA and said inotropic drug.

115. A method of treating an ischemic, hypoxic or metabolic event or an event resulting in cardiac dysfunction in a patient which comprises administering to
20 said patient a cardioprotective amount of DCA and a cardioprotective amount of an inotropic drug.

116. A method according to claim 115 wherein said event is due to a cardiac surgical procedure, percutaneous intervention, acute myocardial infarction or
25 an acute coronary syndrome.

117. A method according to claim 116 wherein said event is a cardiac surgical procedure.

118. A method according to claim 115 wherein said event is an acute coronary syndrome selected from cardiogenic shock, hemorrhagic shock and trauma.

119. A method according to claim 115 wherein said
5 event results from sepsis, HIV or malaria.

120. A method according to claim 115 wherein said event occurs following cancer chemotherapy.

121. A method according to claim 120 wherein said cancer chemotherapy comprises administering a drug
10 selected from an alkalizing agent selected from busulphan, carmustine, chlorambucil, cyclophosphamid, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphelan, mesna, streptozocin, and thiotepa; and an antimetabolite selected from cytarabine, cladribine,
15 fluocouracel, gemcitabine, and methotrexate.

122. A method according to claim 115 wherein said event is due to or results from angina, hypertension, pulmonary hypertension, diabetic cardiomyopathy, cardiomyopathy, congestive heart failure or diabetes.

20 123. A method according to claim 115 wherein said event results in cognitive impairment.

124 A method according to claim 115 wherein said cardioprotective amount of DCA comprises a bolus of at least about 50 mg/kg followed by infusion of at least
25 about 12.5 mg/kg/hour.

125. A method according to claim 115 wherein said cardioprotective amount of DCA comprises a bolus of at

least about 100 mg/kg followed by infusion of at least about 25 mg/kg/hour.

126. A method according to claim 125 wherein DCA is infused for at least about 10 hours.

5 127. A method according to claim 125 wherein DCA is infused for at least about 24 hours.

128. A pharmaceutical composition comprising a cardioprotective amount of DCA and an inotropic drug selected from the group consisting of a beta-adrenergic
10 receptor agonist, a PDE3 inhibitor, an agent which increases cAMP levels, a Na^+ , H^+ exchange inhibitor, a Na^+ , Ca^{2+} exchange blocker, a non-adrenergic vasopressor, an alpha-2-adrenergic agonist, an ET-1 antagonist, an ion channel blocker(s), a calcium sensitizing agent, a
15 calcium channel blocker, an ACE inhibitor, a Na^+/K^+ -ATPase inhibitor, a Na^+ , K^+ exchange inhibitor, a cardiac glycoside, a natriuretic peptide (BNP), a prostaglandin E1, a GPIIb/IIIa inhibitor, acetylsalicylic acid, an analgesic, antipyretic, an anti-inflammatory agent, an
20 anti-arrhythmia agent, glucose, insulin and potassium, a tissue plasminogen activator, a sympathomimetic, and a pharmaceutically acceptable carrier.

129. A pharmaceutical composition according to claim 128 wherein said inotropic drug is selected from the
25 group consisting of a beta-adrenergic receptor agonist, a PDE3 inhibitor, an agent which increases cAMP levels, a Na^+ , H^+ exchange inhibitor, and a $\text{Na}^+/\text{Ca}^{2+}$ exchange blocker.

130. A pharmaceutical composition according to claim
129 wherein said inotropic drug is a $\text{Na}^+/\text{Ca}^{2+}$ exchange
blocker.

131. A pharmaceutical composition according to claim
5 130 wherein said inotropic drug is a non-adrenegic
vasopressor.

132. A pharmaceutical composition according to claim
131 wherein said inotropic drug is vasopressin.

133. A pharmaceutical composition according to claim
10 128 wherein said inotropic drug is an alpha-2-adrenegic
agonist.

134. A pharmaceutical composition according to claim
133 wherein said inotropic drug is moxonidine or
clonidine.

15 135. A pharmaceutical composition according to claim
128 wherein said inotropic drug is an endothelin 1 (ET-1)
antagonist.

136. A pharmaceutical composition according to claim
135 wherein said ET 1 antagonist is bosentan or
20 tezosentan.

137. A pharmaceutical composition according to claim
128 wherein said inotropic drug is an ion channel
blocker.

138. A pharmaceutical composition according to claim
25 137 wherein said ion channel blocker is selected from the
group consisting of a Na^+ pump inhibitor, a Na^+/H^+

exchange inhibitor, a K⁺ channel blocker, or a multiple acting ion channel blocker (RSD 1235).

139. A pharmaceutical composition according to claim 128 wherein said inotropic drug is a calcium-sensitizing agent.

140. A pharmaceutical composition according to claim 139 wherein said inotropic drug is levosimendan.

141. A pharmaceutical composition according to claim 128 wherein said inotropic drug is a calcium channel blocker.

142. A pharmaceutical composition according to claim 141 wherein said inotropic drug is selected from diltiazem, nifedipine, and amlodipine.

143. A pharmaceutical composition further to claim 128 comprising an angiotensin converting enzyme ("ACE") inhibitor or a duo acting antiotensin inhibitor (Duo ACE).

144. A pharmaceutical composition according to claim 128 and 143 wherein said inotropic drug is quinaprilat

145. A pharmaceutical composition according to claim 128 wherein said inotropic drug is a PDE3 inhibitor.

146. A pharmaceutical composition according to claim 145 wherein said PDE 3 inhibitor is Saterinone.

147. A pharmaceutical composition according to claim 145 further comprising a beta-adrenegic receptor agonist.

148. A pharmaceutical composition according to claim 128 wherein said inotropic drug is an agent which increases cyclic AMP levels.

5 149. A pharmaceutical composition according to claim 128 wherein said inotropic drug is an Na^+, K^+ -ATPase inhibitor or a cardiac glycoside.

150. A pharmaceutical composition according to claim 149 wherein said inotropic drug is selected from vandate, 2-methoxy-3,8,9-dihydroxy coumestan, and digoxin.

10 151. A pharmaceutical composition according to claim 128 further comprising administering an agent which increases arginine levels in combination with DCA and said inotropic drug.

15 152. A kit containing a pharmaceutical composition according to any of claims 128 to 151.

153. A kit according to claim 152 wherein said kit comprises a label or packaging insert containing instructions for use, in vitro, in vivo or ex vivo and components of said kit.

Figure 1

Pre-op and Post-op Cardiac Medications Used in Adult
Coronary Bypass Graft Patients in Study of Example A

CABG-1	PRE-OP MEDICATIONS			POST-OP MEDICATIONS						
	ACEI (Y=1;N=0)	ASA (Y=1;N=0)	Digoxin (Y=1;N=0)	Coumadin (Y=1;N=0)	Others (Y=1;N=0)	Nitrates (Y=1;N=0)	Vasodilators (Y=1;N=0)	Ca Antagonist (Y=1;N=0)	B-Blocker (Y=1;N=0)	Diuretics (Y=1;N=0)
Patient No.										
1	1	1	0	0	0	1	1	0	0	0
4	0	1	0	0	0	1	1	0	0	0
5	0	1	0	0	0	1	0	0	0	0
8	0	1	0	0	0	1	0	0	1	0
9	0	1	0	0	0	1	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	1	1	0	0	1
16	0	1	0	0	0	1	1	0	0	0
Mean										
SD										
17	1	1	0	0	0	1	1	0	0	1
18	0	1	0	0	0	1	1	0	0	0
2	1	1	0	0	0	1	1	0	0	1
3	0	1	1	1	0	1	1	0	1	1
6	0	1	0	0	0	0	1	0	0	0
7	0	1	0	0	0	1	1	0	0	0
10	0	0	0	0	0	0	0	0	0	0
12	0	1	0	0	0	1	0	0	0	0
14	1	1	0	0	0	0	0	0	1	0
15	0	0	0	0	0	1	1	0	1	0
Mean										
SD										

Figure 2

Example A - DCA administration of a 50mg/kg bolus, post-coronary bypass graft surgery (CABG) increases target heart enzyme activity in adult heart patients as compared to placebo

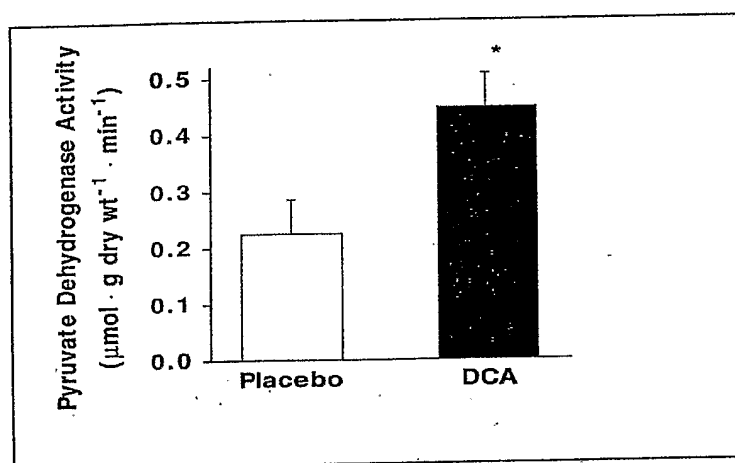


Figure 3

Example A - DCA administration of a 50mg/kg bolus, post coronary bypass graft surgery (CABG) in adult heart patients decreases plasma lactate levels as compared to placebo

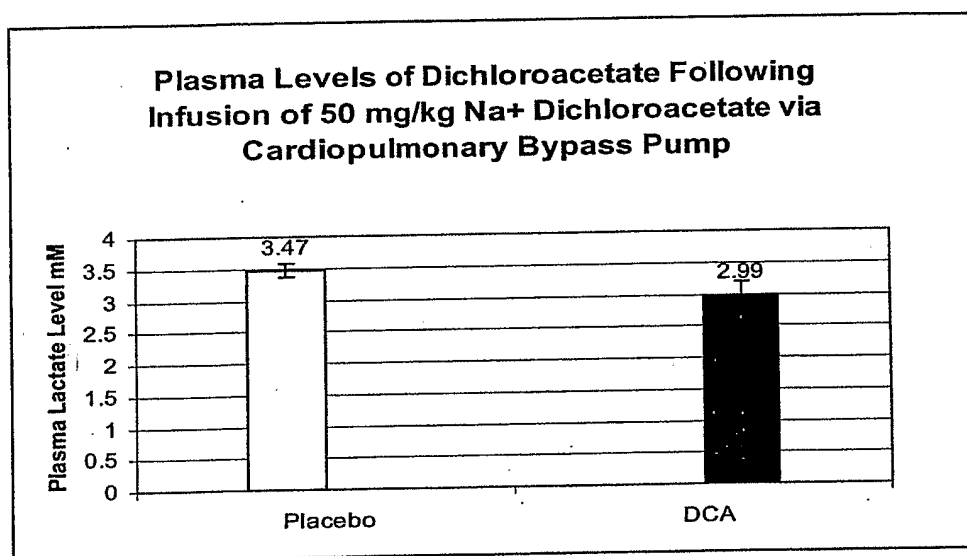


Figure 4

Example B - DCA administration as a 50kg/mg bolus, post-surgery in pediatric heart patients decreases 1 hour Inotrope Score as compared to placebo

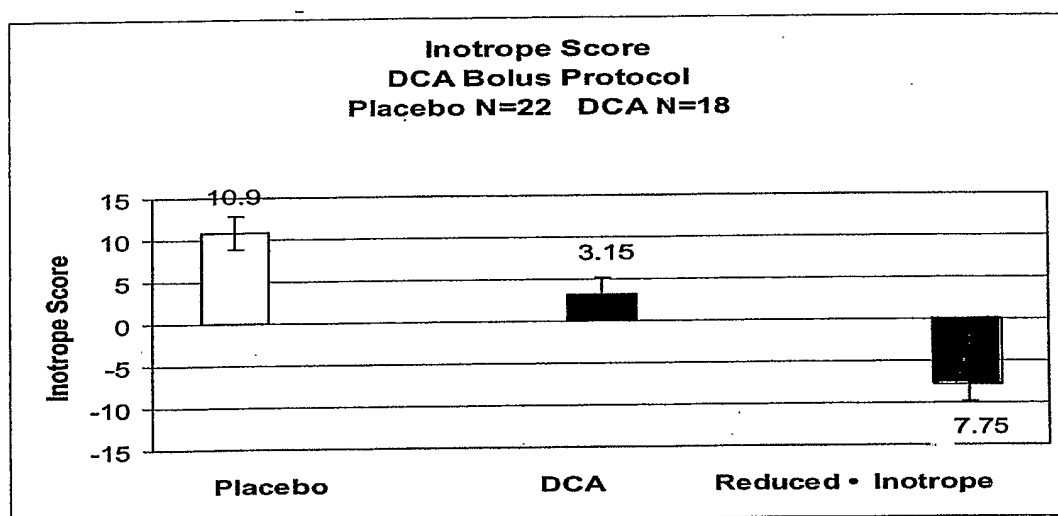


Figure 5

Example B - DCA administration as a 50kg/mg bolus post surgery in pediatric heart patients decreases ICU time as compared to placebo

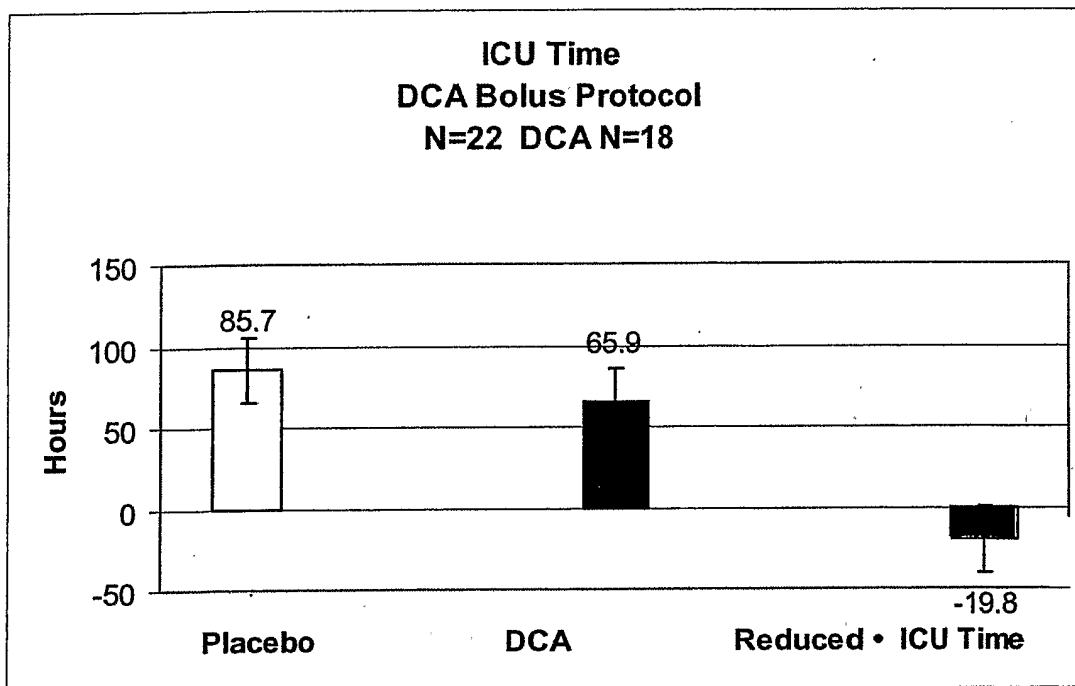


Figure 6

Example B - DCA administration as a 50kg/mg bolus, post-surgery in pediatric heart patients decreases ventilator time as compared to placebo

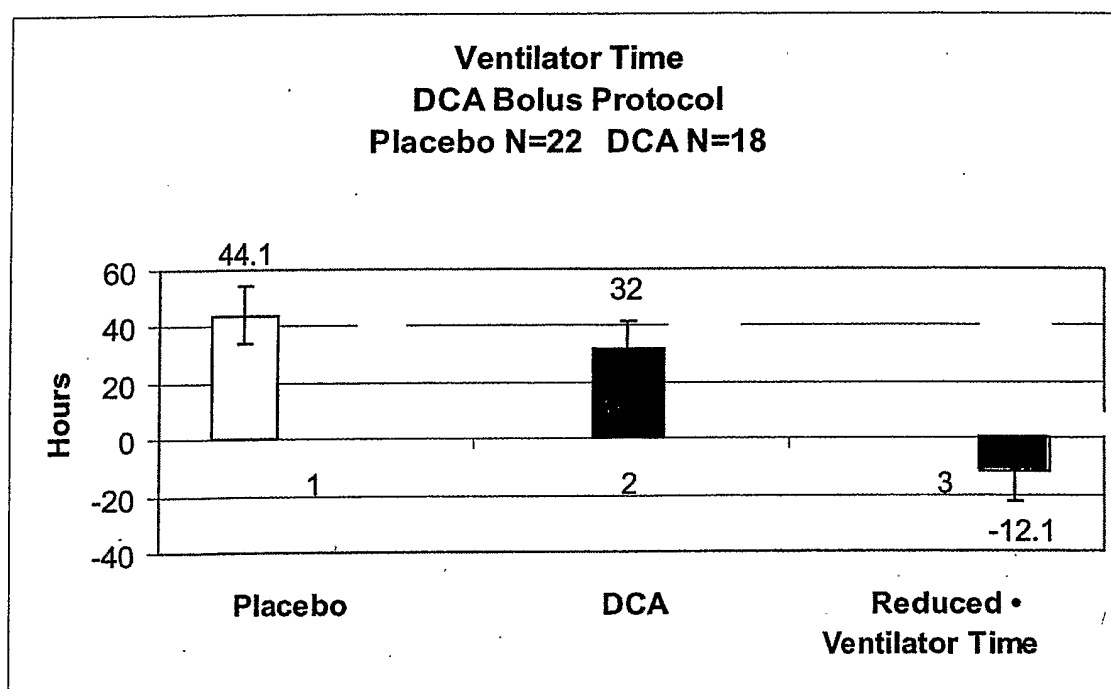


Figure 7A

Administration of Inotrope to patients of the Study of
Example C

(1 = yes, given; 0 = Not Given)

<u>Patent No.</u>	<u>Pre-Op Inotrope</u>	<u>Post-Op Inotrope</u>
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	0	0
9	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	1
17	0	0
18	0	0
19	0	0

Figure 7A continued

<u>Patent No.</u>	<u>Pre-Op Inotrope</u>	<u>Post-Op Inotrope</u>
20	0	0
21	1	0
22	0	0
23	1	0
24	0	0
25	0	0
26	0	0
27	0	0
28	0	0
30	0	0
31	0	0
32	0	0
33	1	1
34	0	0
35	0	0
36	0	0
37	0	0
39	0	0
40	0	0
41	0	0

Figure 7A continued

<u>Patent No.</u>	<u>Pre-Op Inotrope</u>	<u>Post-Op Inotrope</u>
42	0	0
44	0	0
45	0	0
46	0	0
47	0	0
48	1	1
49	0	0
50	0	0
51	0	0
52	0	0

Figure 7B

Ace Inhibitors	Inotrope	Vasodilator	Diuretic	Beta- Blocker	Anticoagulant	Heparin or Enoxaprin Sodium	Analgesic
	Dobutamine	Prostin	Lasix	Propranolol	Coumadin	Lovenex	Aspirin
Captopril	Epinephrine		Aldactazide	Atenolol		Enoxapram	Tylenol
Fosinopril	Dopamine		Ranitidine				
Enalapril	Norepinephrine						
	Phenylephrine						
	Phenatalomine						
	Amironone						
	Digoxin						

Figure 8

Example C - Effects of DCA administration as a 50mg/kg bolus and 25mg/kg/hour infusion, post-heart surgery in pediatric heart patients reduces Inotrope Score over 24 hours as compared to placebo

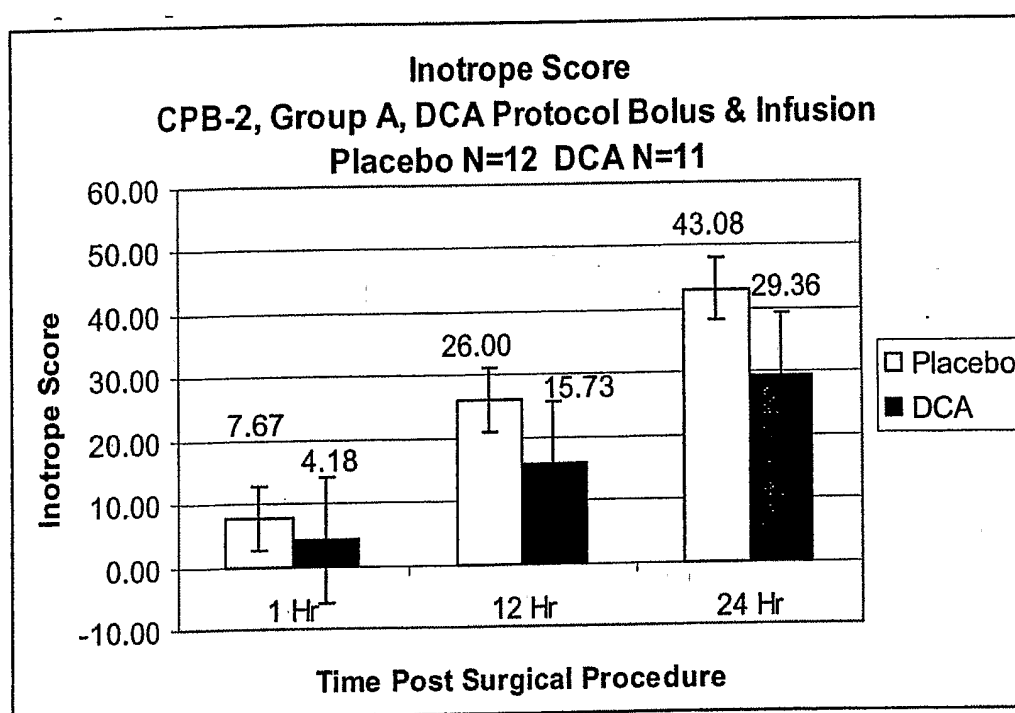


Figure 9

Example C - Effects of DCA administration as a 100mg/kg bolus and 12.5mg/kg/hour infusion, post-surgery in pediatric heart patients reduces Inotrope Score over 24 hours as compared to placebo

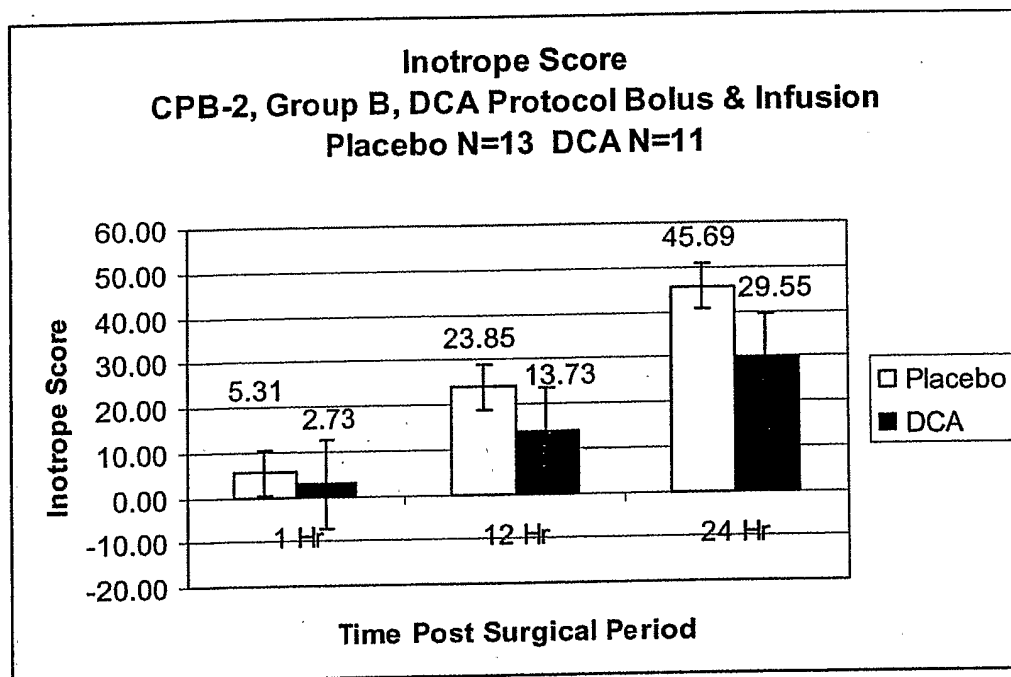


Figure 10

Example C - Effects of DCA administration as a 50mg/kg bolus and 25mg/kg/hour infusion, post-surgery in pediatric heart patients reduces ICU Time as compared to placebo

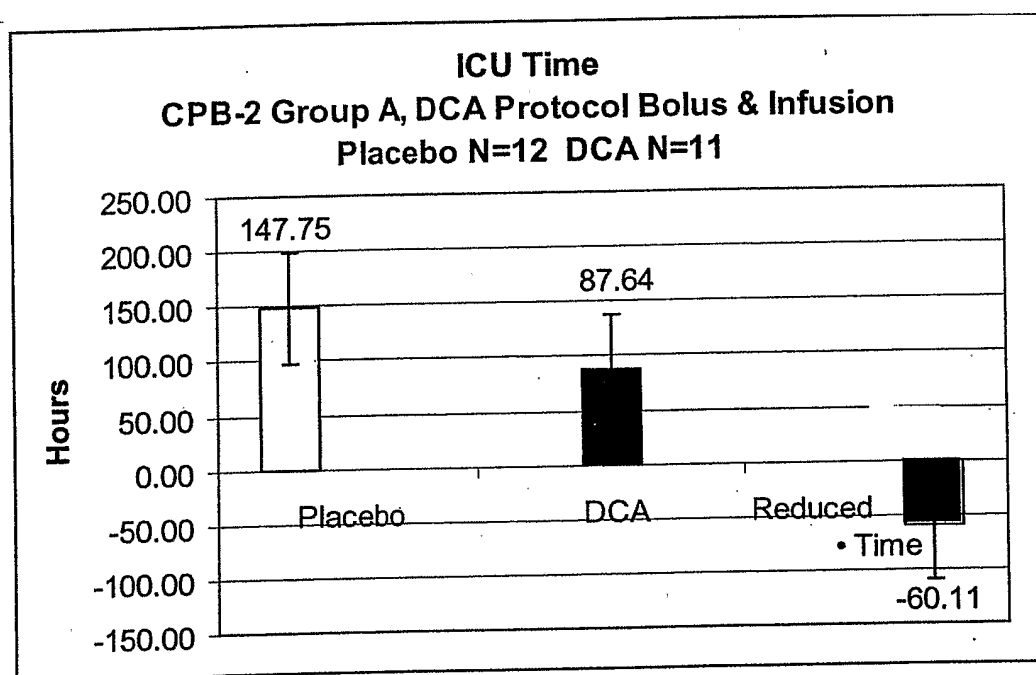


Figure 11

Example C - Effects of DCA administration as a 100mg/kg bolus and 12.5mg/kg/hour infusion post-surgery in pediatric heart patients reduces ICU Time as compared to placebo

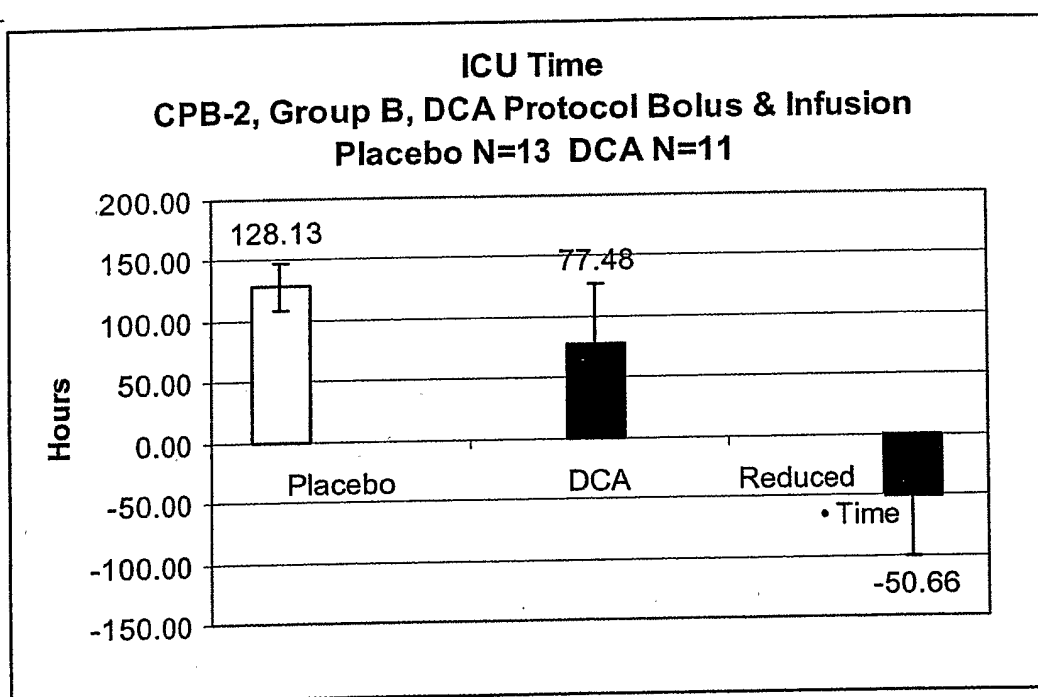


Figure 12

Example C - Effects of DCA administration as a 50mg/kg bolus and 25mg/kg/hour infusion, post-surgery in pediatric heart patients reduces Ventilator Time as compared to placebo

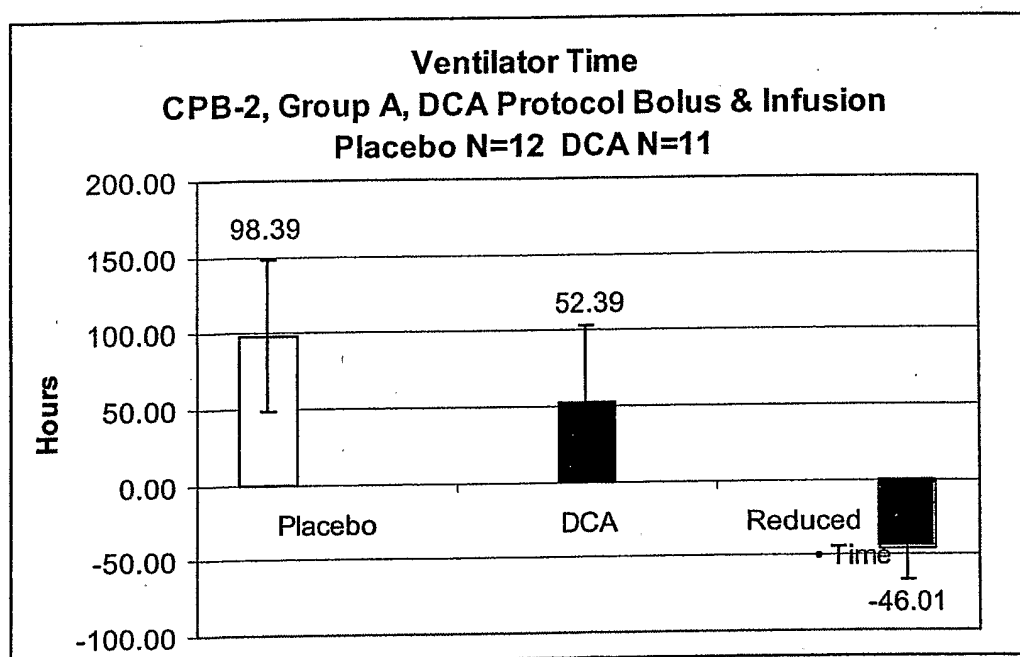
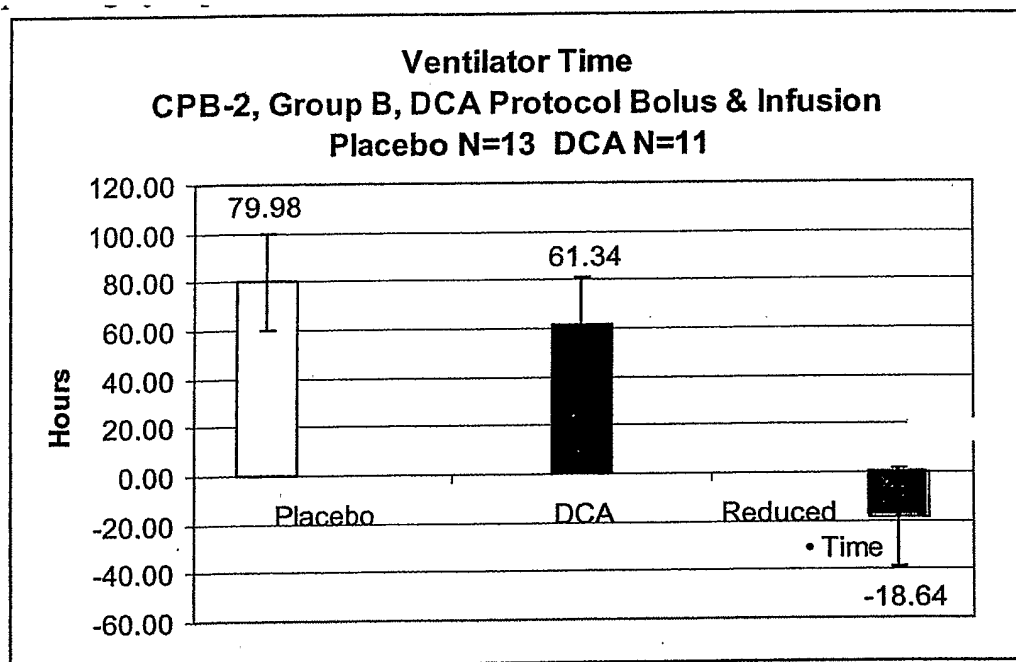


Figure 13

Example C - Effects of DCA administration as a 100mg/kg bolus and 12.5mg/kg/hour infusion post-surgery in pediatric heart patients reduces Ventilator Time as compared to placebo



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001894

A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>A61K 31/19</i> (2006.01) , <i>A61P 9/14</i> (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC																	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC: <i>A61K 31/19</i> (2006.01) , <i>A61P 9/14</i> (2006.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Canadian Patent Database, Delphion, PubMed, USPTO, Google™ dichloroacetate, intotrope, inotropic, cardiac, ischemia cardiac contractability, cardiovascular, stroke, hypoxia, cardiac surgery, hemorrhagic shock, trauma, dobutamine, calcium, ephedrine, epinephrine dopamine, phenyephedrine																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category*</th> <th style="width: 60%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 30%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td>US 6,693,133 B1 (LOPASHUCK ET AL.) 17 February 2004 see whole document</td> <td>1-153</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US 2004/0162346 A1 (LOPASHUCK ET AL.) 19 August 2004 see whole document</td> <td>1-153</td> </tr> <tr> <td style="text-align: center;">X</td> <td>CA 2,305,183 A1 (LOPASHUCK ET AL.) 15 April 1999 see whole document</td> <td>1-153</td> </tr> <tr> <td style="text-align: center;">X</td> <td>CA 2,490,636 A1 (LOPASHUCK) 31 December 2003 see whole document</td> <td>1-125 and 128-153</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 6,693,133 B1 (LOPASHUCK ET AL.) 17 February 2004 see whole document	1-153	X	US 2004/0162346 A1 (LOPASHUCK ET AL.) 19 August 2004 see whole document	1-153	X	CA 2,305,183 A1 (LOPASHUCK ET AL.) 15 April 1999 see whole document	1-153	X	CA 2,490,636 A1 (LOPASHUCK) 31 December 2003 see whole document	1-125 and 128-153
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X	CA 2,490,636 A1 (LOPASHUCK) 31 December 2003 see whole document	1-125 and 128-153															
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.																	
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"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 "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 "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 "&" document member of the same patent family																
Date of the actual completion of the international search 06 February 2006 (06-02-2006)	Date of mailing of the international search report 24 April 2006 (24-04-2006)																
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Tania Nish (819) 934-3592																

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☒ Claim Nos. : 1-127

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

Claims 1-127 are methods of medical treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. (Rule 39.1(iv)PCT)

Regardless, this Authority has carried out a search based on the alleged effects of the composition defined in the claims for the treatment of a cardiac function disturbing event or a cardiac metabolism disturbing event.

2. ☐ Claim 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. ☐ Claim Nos. :

because they are dependant 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 claim 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 claim 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001894

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BURNS ET AL.: "Inotropic interactions of dichloroacetate with amrinone and ouabain in isolated hearts from endotoxin-shocked rats" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY vol. 11 no. 4, 1988, Raven Press Ltd. pages 379-386 see whole document	1-153
X	COLLINS-NAKAI ET AL.: "Dichloroacetic acid (DCA) after open heart surgery in infants and children" CANADIAN JOURNAL OF CARDIOLOGY vol. 11 suppl. E, August 1995 page 106E see abstract 148	1-153
X	BERSIN ET AL.: "Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate" JACC vol. 23 no. 7, June 1994, Am. College of Cardiology pages 1617-24 see whole document, cited in application	1-153
X	BERSIN & STACPOOLE: "Dichloroacetate as metabolic therapy for myocardial ischemia and failure" AMERICAN HEART JOURNAL vol. 134 no. 5 pt 1, November 1997, Mosey-Year Book Inc. pages 841-855 see whole document	1-153
P,X	CA 2,489,853 A1 (LOPASHUCK & COLLINS-NAKAI) 16 July 2005 see whole document	1-153

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CA2005/001894

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