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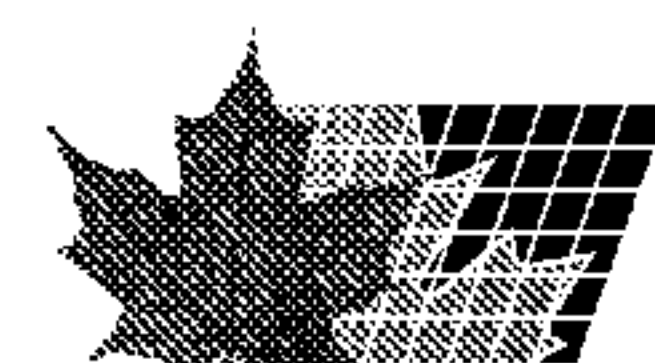
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(72) Inventeur/Inventor:
Stanko, Ronald T., US
(73) Propriétaire/Owner:
University of Pittsburgh Medical Center, US
(74) Agent: MACRAE & CO.

(54) Titre : PROCEDE DE TRAITEMENT D'UN PATIENT SOUFFRANT D'UN TRAUMATISME CARDIAQUE
(54) Title: METHOD FOR TREATING A MEDICAL PATIENT FOR CARDIAC TRAUMA

(57) **Abrégé/Abstract:**

A method for treating a medical patient prior to or during heart trauma, e.g., myocardial infarction, angina and ischemia. An effective dosage of pyruvate is introduced into the patient to increase the patient's cardiac output and stroke volume, to decrease the patient's heart rate and to reduce the oxygen demand of the patient's heart. The dosage may be introduced intravenously into the patient or orally as a component of the patient's diet. The oral feeding method is especially useful for surgical patients prior to surgical procedures which are likely to encourage cardiac trauma and useful for patients exhibiting symptoms of chronic congestive heart failure.



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(71) Applicant: UNIVERSITY OF PITTSBURGH MEDICAL
CENTER [US/US]; 3459 Fifth Avenue, Pittsburgh, PA
15213 (US).(72) Inventor: STANKO, Ronald, T.; 3459 Fifth Avenue, Pitts-
burgh, PA 15213 (US).(74) Agent: KECK, Harry, B.; 415 Lawyers Building, Pittsburgh,
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(54) Title: METHOD FOR TREATING A MEDICAL PATIENT FOR CARDIAC TRAUMA

(57) Abstract

A method for treating a medical patient prior to or during heart trauma, e.g., myocardial infarction, angina and ischemia. An effective dosage of pyruvate is introduced into the patient to increase the patient's cardiac output and stroke volume, to decrease the patient's heart rate and to reduce the oxygen demand of the patient's heart. The dosage may be introduced intravenously into the patient or orally as a component of the patient's diet. The oral feeding method is especially useful for surgical patients prior to surgical procedures which are likely to encourage cardiac trauma and useful for patients exhibiting symptoms of chronic congestive heart failure.

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DESCRIPTIONMETHOD FOR TREATING A MEDICAL PATIENT FOR CARDIAC TRAUMATECHNICAL FIELD

The present invention provides a method (a) for treating a medical patient to prepare the patient for surgical procedures involving the heart, lungs, veins, arteries or other vital organs, which procedures are accompanied by cardiac trauma, i.e., ischemia, and (b) for treating a medical patient experiencing cardiac trauma. The invention provides for introducing an effective dosage of pyruvate into the patient's bloodstream prior to and/or during the cardiac trauma.

BACKGROUND ART

Pyruvate and mixtures of pyruvate with dihydroxyacetone have been described for a number of beneficial results:

U.S. Patent 4,158,057 describes oral administration of pyruvate and dihydroxyacetone to prevent excessive accumulation of fatty deposits in a mammal liver due to ethanol ingestion.

U.S. Patent No. 4,351,835 describes oral administration of pyruvate and dihydroxyacetone to reduce an expected weight gain

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from a given diet or to induce a weight loss in a mammal. The patent also describes oral administration of pyruvate and dihydroxyacetone to athletes prior to strenuous athletic events to increase endurance and/or performance.

U.S. Patent No. 4,415,575 describes oral administration of pyruvate and dihydroxyacetone to increase the body protein concentration in a mammal.

U.S. Patent No. 4,458,937 describes oral administration of pyruvate to a mammal to induce a weight loss or reduce an expected weight gain from a given diet.

U.S. Patent No. 4,645,764 describes oral administration to a living being of pyruvate and dihydroxyacetone to induce a weight loss or to reduce an expected weight gain from a given diet and for inhibiting body fat while increasing body protein concentration.

U.S. Patent No. 4,812,478 describes oral administration of dihydroxyacetone to an animal to induce a weight loss or to reduce an expected weight gain from a given diet.

These described results of oral administration of pyruvate and pyruvate with dihydroxyacetone are of great interest for medical patients who ingest ethanol; medical patients having fatty liver deposits or tendencies toward fatty liver deposits; medical patients who are obese or have a tendency toward obesity; normal subjects desiring to lose body weight or to retard body weight increase; normal patients, particularly athletes, who desire to increase endurance; and medical patients having diabetic tendencies.

U.S. Patent No. 4,874,790 describes the use of pyruvate as a treatment for patients having diabetic tendencies.

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The use of pyruvate to treat ischemia and to increase inotropism in hearts has been described:

K.E. SOMMERS et al, PYRUVATE IMPROVES POSTISCHEMIC
MIOCARDIAL FUNCTION AND ATP RECOVERY: A 31P NMR
SPECTROSCOPY STUDY,
SURGICAL FORUM VOL XLI, 1990, pages 241-3;

R.M. MENTZER, JR. et al, EFFECT OF PYRUVATE ON REGIONAL
VENTRICULAR FUNCTION IN NORMAL AND STUNNED
MYOCARDIUM,
ANN. SURG. May 1989, pages 629-634;

ROLF BUNGER et al, PYRUVATE-ENHANCED PHOSPHORYLATION
POTENTIAL AND INOTROPISM IN NORMOXIC AND
POSTISCHEMIC ISOLATED WORKING HEART,
EUR. J. BIOCHEM, Feb. 1989, pages 221-233.

DISCLOSURE OF INVENTION

Surgical procedures involving the heart, lungs, veins, arteries and other vital organs are accompanied by heart trauma, especially ischemia. Ischemia is defined as a lack of oxygen in an organ; heart ischemia is defined as a lack of oxygen in the heart.

According to the present invention the adverse effects of ischemia are offset by introducing a therapeutic quantity of pyruvate into the blood stream of the patient prior to the surgical procedure to increase the patient's cardiac output, to increase the patient's heart stroke volume and, unexpectedly, to reduce the oxygen demand of the patient's heart.

The treatment may be initiated several weeks prior to scheduled surgery and may be continued to and through the surgical procedure. For unscheduled surgery, the treatment may commence as soon as feasible prior to and throughout the surgical procedure. For cardiac trauma which may or may not result in surgery, the treatment may begin as soon as cardiac trauma symptoms are suspected.

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The pyruvate may be in the form of organic salts, e.g., calcium or sodium salts of pyruvic acid; or esters of pyruvic acid such as ethyl amino pyruvate.

Cardiac trauma also occurs in medical patients. Many patients seek medical attention when experiencing chest pains, angina, myocardial infarction and other cardiac disorders. The standard treatment for such patients is to introduce liquid solutions intravenously into the patient's circulatory system. Such liquid solutions are available in a variety of compositions. Some liquid solutions contain vitamins and selected minerals and sugars. The liquid solutions also may contain specific pharmaceuticals as anti-coagulants, blood thinners, and the like. The patient may also receive dosages of inotropic agents such as dopamine, dobutamine or isuprel. The known inotropic agents increase the contractility of the heart and increase the heart rate, but also increase the oxygen demand of the heart. The inotropic agents may be included in the saline solutions which are available.

Adding pyruvate to such saline solutions provides a convenient system for introducing pyruvate into the cardiac trauma patient. Pyruvate, like known inotropic agents increases the contractility of the heart and increases the heart rate. However the pyruvate does not increase the oxygen demand of the heart, but unexpectedly lowers the oxygen demand of the heart.

A medical patient who is about to undergo surgical procedures which are likely to encourage cardiac trauma, e.g., ischemia, preferably is prepared for the surgical procedure by oral dosages of pyruvate for a treatment period of several days to several weeks prior to the scheduled surgery. Typical surgical procedures which are likely to develop cardiac trauma include surgery involving the heart, lungs, veins, arteries, or other vital organs. A preferred pyruvate oral dosage is from 5 to 15 percent of the patient's caloric intake throughout the treatment period.

The pyruvate dosage has been observed to increase the heart output and to increase the stroke volume of the heart and concurrently to reduce the oxygen requirement of the heart. These three benefits enable the heart to perform its normal functions more easily. These benefits to the cardiac trauma patient will improve opportunities for effective treatment in the cases of genuine cardiac malfunctions and will cause no objectionable side effects in patients having false symptoms of cardiac trauma.

Heart output (or cardiac output) has been defined as the quantity of blood pumped by the left ventricle into the aorta each minute. Heart output for young healthy adult males averages 5.6 liters per minute. The stroke volume is the quantity of blood pumped by each beat of the left ventricle. The heart rate is the number of heart beats per minute. The product of heart rate (beats/minute) and stroke volume (volume/beat) yields the cardiac output (volume/minute).

Preferred Embodiments

In a preferred procedure, a medical patient experiencing cardiac trauma receives a liquid drip solution immediately containing from about 2-20 grams pyruvate per liter of solution. The pyruvate may be in the form of metal salts of pyruvic acid or may be in the form organic esters of pyruvic acid, for example, ethyl amino pyruvate. The saline drip is continued until the patient is normalized. If immediate surgery is indicated, the liquid drip will continue throughout the surgery and thereafter until the patient is normalized.

An alternative procedure, when time is available, is to provide oral dosages of pyruvate for days or weeks prior to an anticipated cardiac trauma, e.g., prior to scheduled surgery. Immediately prior to and during surgery, the saline drip should be employed.

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As a further alternative, patients having chronic congestive heart failure symptoms may take effective oral dosages of pyruvate to decrease heart rate, to increase stroke volume and to reduce the oxygen demand of the heart. Liquid pyruvate in drinks is preferred. Pyruvate in a confection is a convenient alternative, e.g., cookies, candies. Pyruvate may be substituted in whole or in part for digitalis in treating chronic congestive heart failure patents.

EXAMPLE I

A control group of 20 human patients was fed a mixture of sodium and calcium pyruvate continually over a period of 6 weeks. The patients received 26-44 grams of pyruvate daily corresponding to about 7% of the total caloric intake of each patient over the six-week period.

At the end of the six-week period, the heart rate for the patients (beats/minute) decreased 9%. The diastolic blood pressure decreased 6%. The rate pressure product (rpp), measured as the product of systolic blood pressure and heart rate, decreased 13%.

The rate pressure product (rpp) is known to be an indirect measure of the oxygen requirement of the heart. Hence the oxygen demand of the patients was decreased.

EXAMPLE II

In another experiment, eight human subjects were fed sodium and calcium pyruvate for a period of one week continually at the rate of 15% of the total calories of each patient. The total pyruvate did not exceed 400 calories daily for any one patient per day.

Prior to and following the treatment period, the subjects carried out arm exercise for 90 minutes or leg exercise for 60

minutes. At the end of the exercise, the cardiac output of each subject was measured. The cardiac output (liters/minute) increased by 2.3%. The cardiac stroke volume (ml/min) increased by 5%.

The cardiac output and stroke volume of each subject was measured before and after the one week period. The increases are reported in TABLE I:

TABLE I

<u>SUBJECT</u>	<u>CARDIAC OUTPUT INCREASE %</u>	<u>STROKE VOLUME INCREASE %</u>
1	2.0	4.5
2	1.7	4.3
3	1.0	4.8
4	1.0	2.9
5	0	1.0
6	6.8	10.9
7	5.2	10.7
8	1.0	1.0
—		
X (average)	2.3 ± 0.8	5.0 ± 1.4
Deviation	p < 0.05	p < 0.05

The deviation ($p < 0.05$) indicates that the reported values are statistically significant.

By increasing the cardiac output and stroke volume and reducing the cardiac oxygen demand, the patient's heart experiences increased effectiveness without increase in effort (which equates to exercise).

Oral ingestion of pyruvate preferably is in the form of a liquid food containing the pyruvate. Liquid diet preparations are especially useful. The pyruvate may be included in solid foods, such as confections, e.g., cookies, cakes, candies.

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EXAMPLE III

Six laboratory dogs, weight about 17 Kg each, were individually anaesthetized. Blood tubes were inserted into the (a) aorta; (b) vena cava; and (c) femoral artery of each dog. A pressure sensor was placed in the left ventricle of each dog. An EKG was installed for each dog to record the EKG waves.

A pyruvate infusion was introduced into the superior vena cava of each dog. The concentration of pyruvate started at 0.25 mg/minute/Kg of dog weight and increased as shown in TABLE II.

TABLE II
INFUSION CONCENTRATION

<u>Time (Minutes)</u>	
0-15	0.25 mg/minute/Kg dog weight
15-30	0.5
30-45	1.0
45-60	2.0
60-75	4.0
75-90	8.0
90-105	16.0

Note that the test continued for 105 minutes with the pyruvate concentration doubled every 15 minutes.

Throughout the test:

- (a) Sensors measured blood flow (volume/time).
- (b) The heart rate (beats/minute) were measured.
- (c) Diastolic blood pressure (gms/area).
- (d) Blood samples were taken from an artery and from a vein. Oxygen analyses of the two samples established the oxygen demand.

In all cases the oxygen demand decreased throughout the text.

Relevant observations are set forth in TABLE III.

TABLE III

PYRUVATE TESTS WITH ANAESTHETIZED DOGS

All individual tests were averaged and normalized.

<u>Time (Minutes)</u>	<u>Pyruvate Concen- tration</u>	<u>$\Delta p/\Delta t$</u>	<u>Content O₂</u>	<u>Content CO₂</u>	<u>Cardiac Output</u>	<u>Heart Rate</u>
	(a)	(b)				
0	0	1.00(c)	1.00(c)	1.00(c)	1.00(c)	1.00(c)
18	0.25	0.99	0.95	0.95	0.92	0.99
33	0.50	0.98	0.99	0.93	0.98	0.98
49	1.00	0.96	0.90	0.84	0.93	0.95
64	2.00	0.86	0.90	0.93	0.92	0.88
80	4.00	1.02	0.98	0.84	1.01	0.86
96	8.00	1.14	0.98	0.87	1.03	0.82
107	16.00	1.45(d)	1.05(e)	0.94(e)	1.17	0.83

(a) - Mg pyruvate/minute/Kg dog weight.

(b) - Change in blood pressure with time indicates the contractility of the heart.

(c) - Arbitrary "normal" value.

(d) - The contractility increased 45% after the pyruvate became effective.

(e) - The difference between oxygen content and CO₂ content indicates the oxygen utilization. There was a 10% decrease (1.05 - 0.94).

The dog tests of EXAMPLE III indicate that cardiac output increases, heart rate decreases and oxygen demand decreases when sufficient pyruvate is in the animal's blood system.

Note that the initial effects of pyruvate at low concentrations did not predict the favorable effects of pyruvate after a suitable concentration was delivered.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. For use in oral or intravenous administration in humans
5 to increase the cardiac output of a human, in need thereof without concurrently increasing the cardiac oxygen demand of said human, an effective dosage of pyruvate.
2. For use in continuous oral administration in a patient
10 over a preparation period prior to a surgery likely to result in cardiac trauma to increase the cardiac output of a patient in preparation for the surgery without concurrently increasing said patient's cardiac oxygen demand, an effective dosage of pyruvate.
3. The dosage of pyruvate of claim 2 wherein the pyruvate
15 dosage provides 5-15 weight percent of the patient's total caloric intake over said preparation period.
4. The dosage of pyruvate of claim 1 wherein the pyruvate is included in a liquid drip solution containing 2 to 20 weight percent pyruvate.
- 20 5. The dosage of pyruvate of claim 3 wherein the pyruvate is included in a confection.
6. The dosage of pyruvate of claim 1 wherein the pyruvate is a metal salt of pyruvic acid.
7. The dosage of pyruvate of claim 1 wherein the pyruvate
25 is an organic ester of pyruvic acid.
8. The dosage of pyruvate of claim 7 wherein the pyruvate is ethyl amino pyruvate.

9. For use in intravenous administration by a liquid drip solution throughout a surgery involving the heart or other vital organ to increase the cardiac output of a medical patient
5 experiencing the surgery without concurrently increasing the cardiac oxygen demand of said patient, an effective amount of pyruvate.