US 20070276210A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0276210 A1**

Gutierrez (43) **Pub. Date: Nov. 29, 2007**

(54) **APPARATUS AND METHOD FOR MEASURING MYOCARDIAL OXYGEN CONSUMPTION**

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(21) Appl. No.: **11/707,138**

(22) Filed: **Feb. 16, 2007**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/987,505, filed on Nov. 12, 2004, now Pat. No. 7,181,260.

(60) Provisional application No. 60/520,280, filed on Nov. 14, 2003.

Publication Classification

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **600/325**

(57) **ABSTRACT**

The present invention relates to a method to determine a cardiac characteristic determined at a proximal end and a distal end of a pulmonary artery catheter. The present invention also relates to a method of treating a patient based on a determination of a determined difference between a cardiac characteristic a proximal end and a distal end of a pulmonary artery catheter.

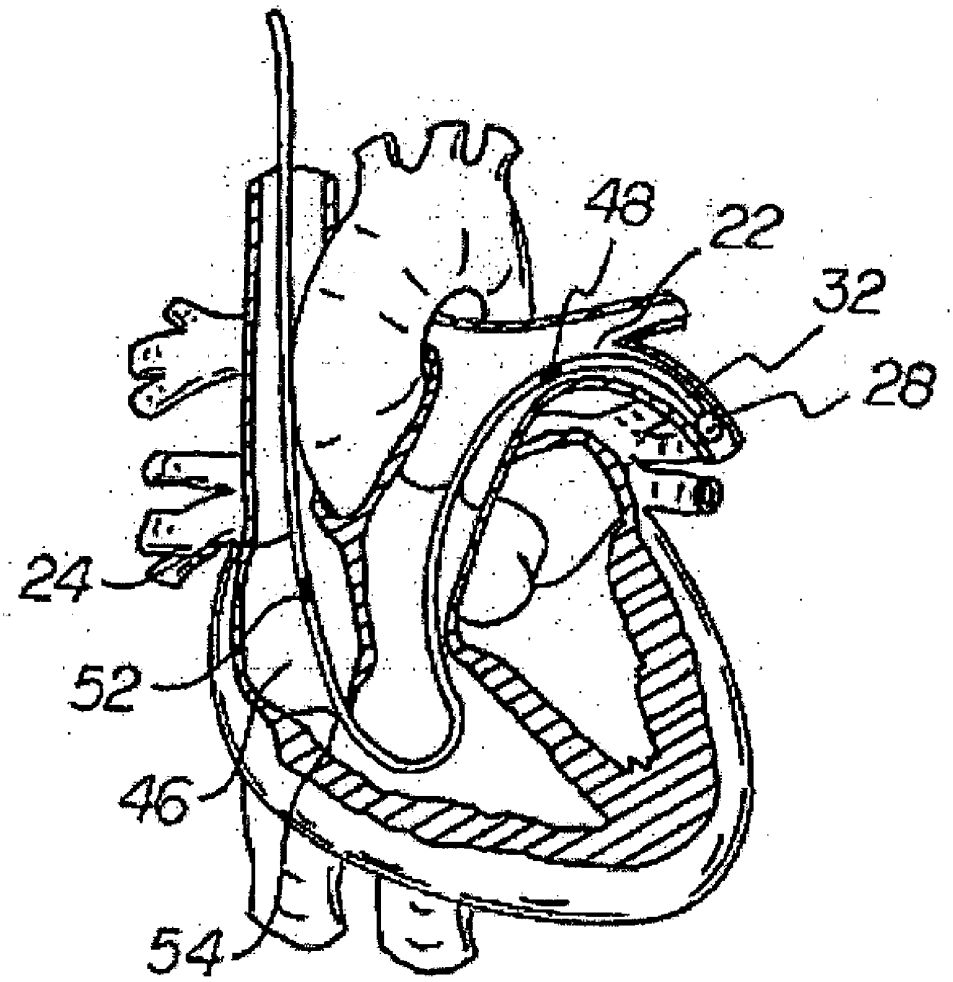


FIG. 1

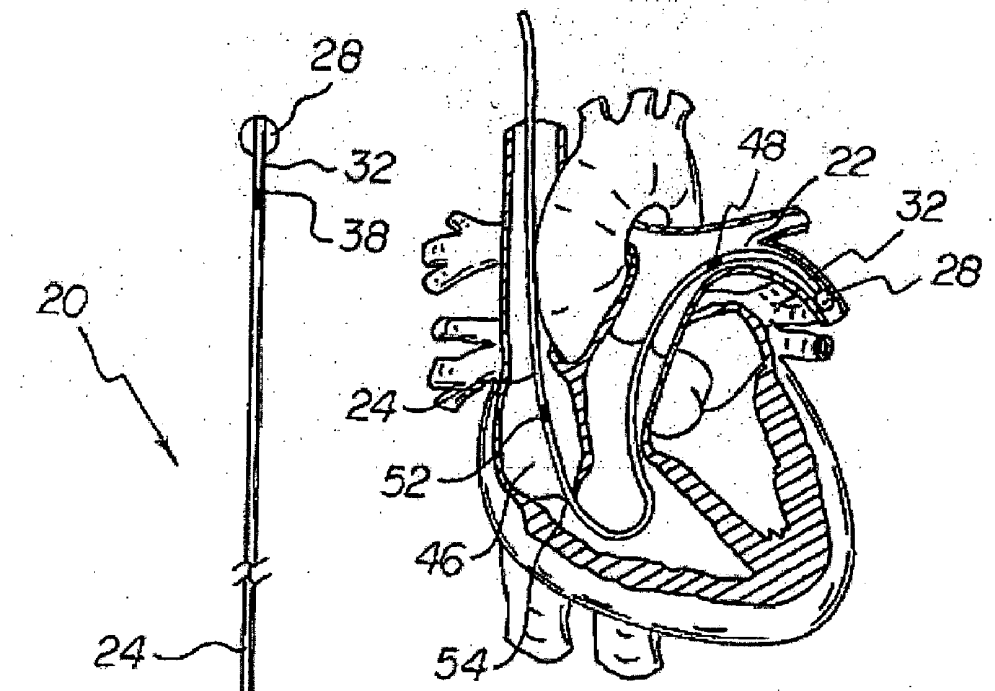


FIG. 2

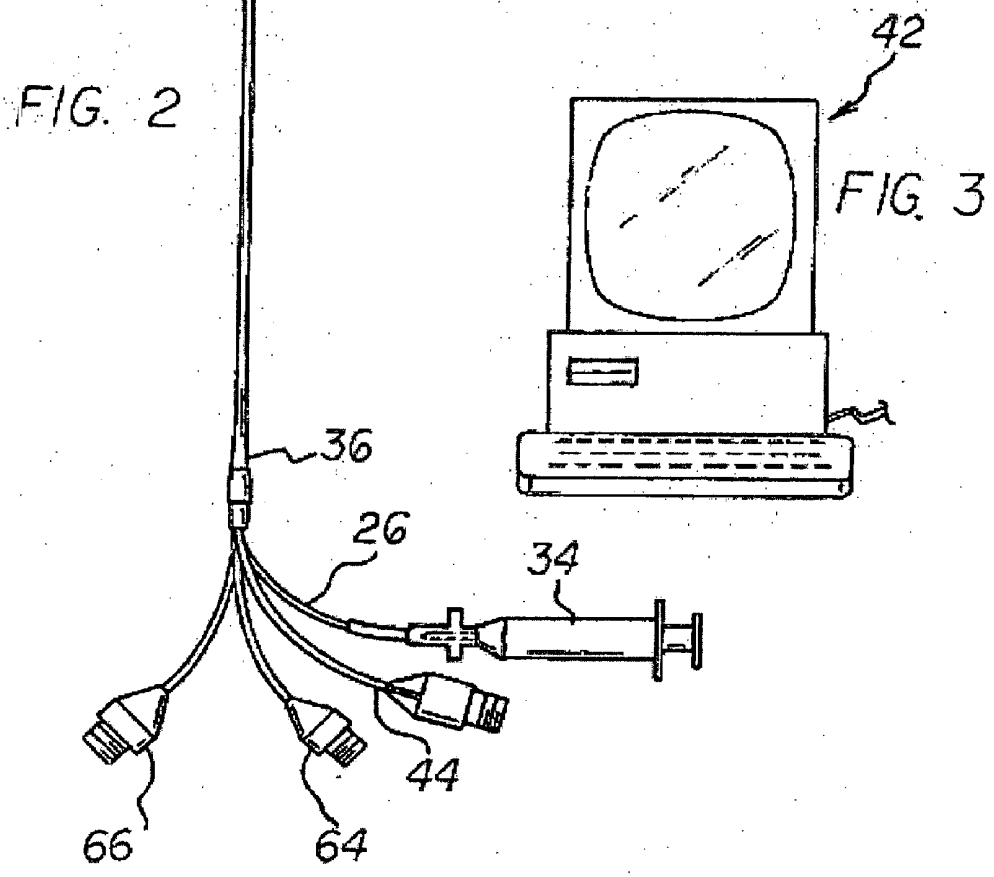


FIG. 3

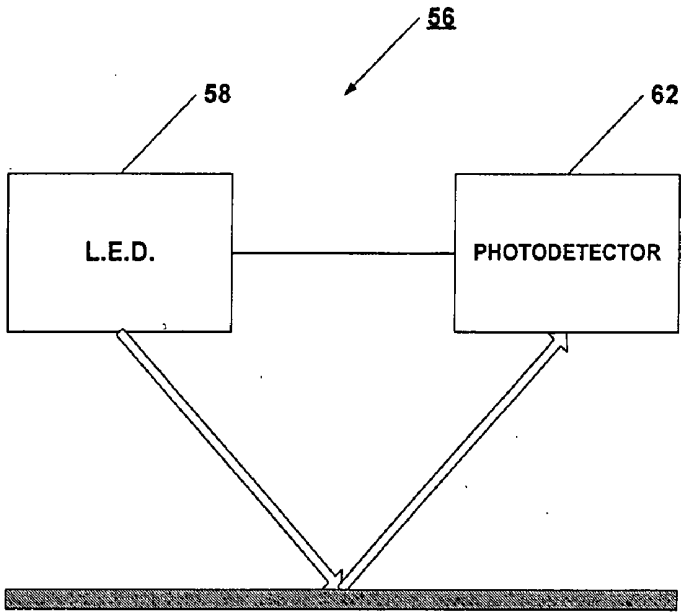

56
58
62
L.E.D.
PHOTODETECTOR

FIG 4

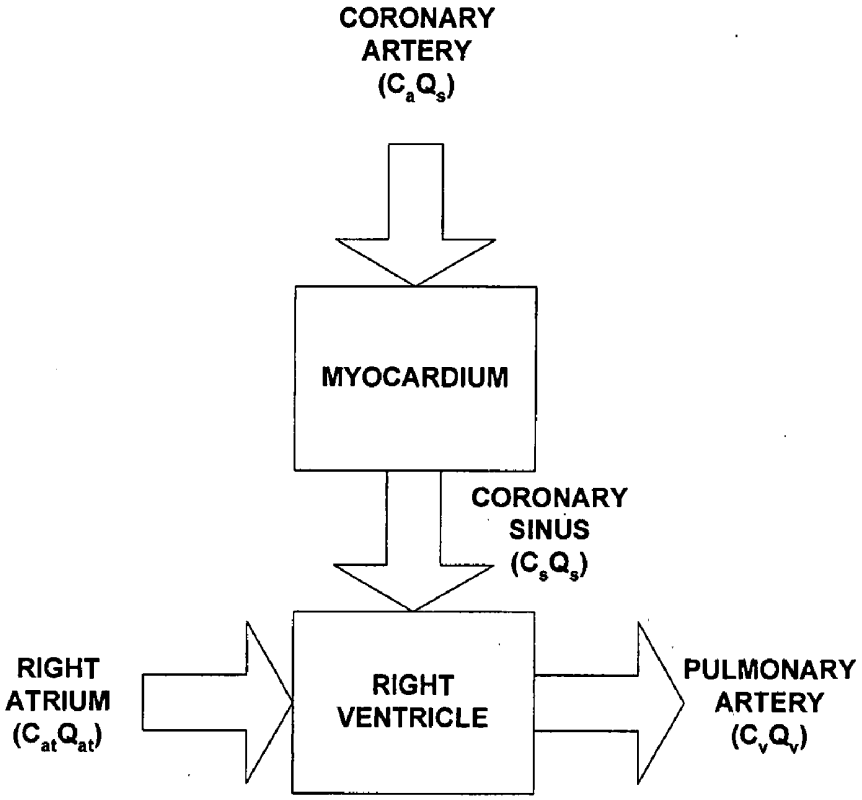

CORONARY ARTERY (C_aQ_s)
MYOCARDIUM
CORONARY SINUS (C_sQ_s)
RIGHT ATRIUM ($C_{at}Q_{at}$)
RIGHT VENTRICLE
PULMONARY ARTERY (C_vQ_v)

FIG. 5

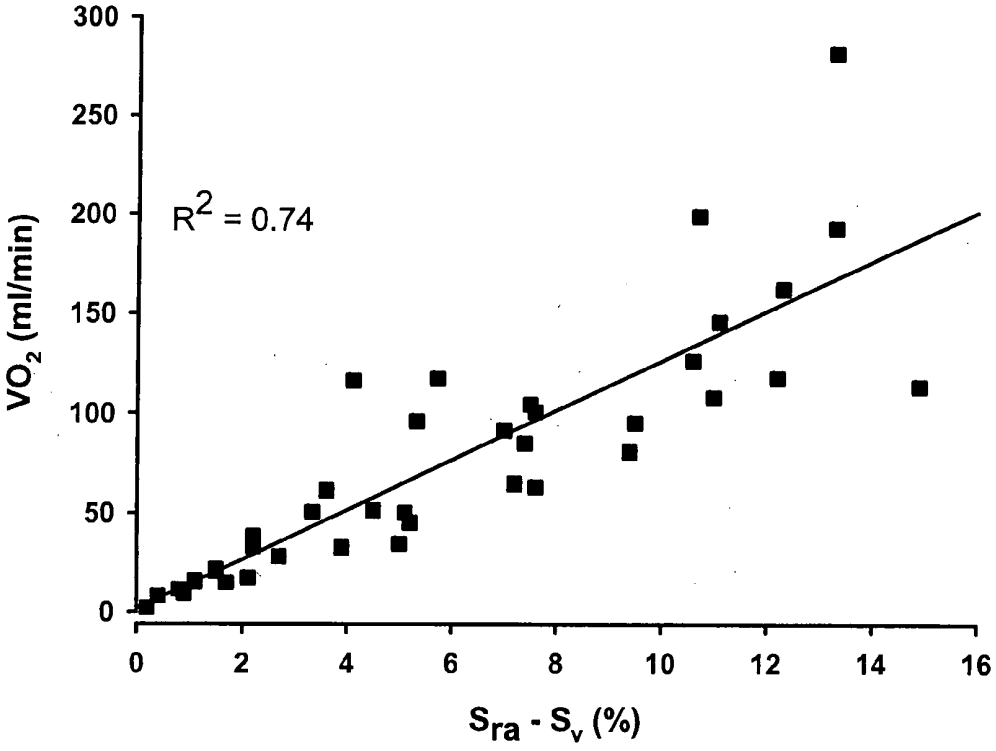


FIG. 6

Figure 7

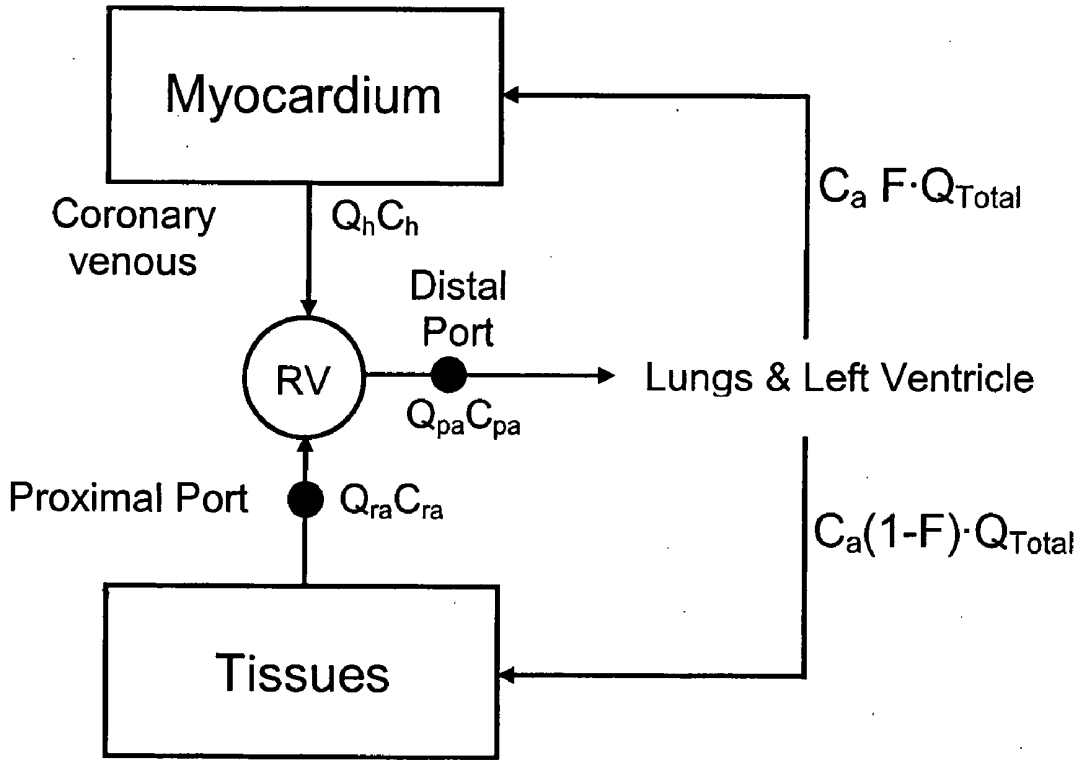

Myocardium
Coronary venous
Q_hC_h
C_a F·Q_{Total}
Distal Port
RV
Lungs & Left Ventricle
$Q_{pa}C_{pa}$
Proximal Port
$Q_{ra}C_{ra}$
$C_a(1-F)\cdot Q_{Total}$
Tissues

Figure 8

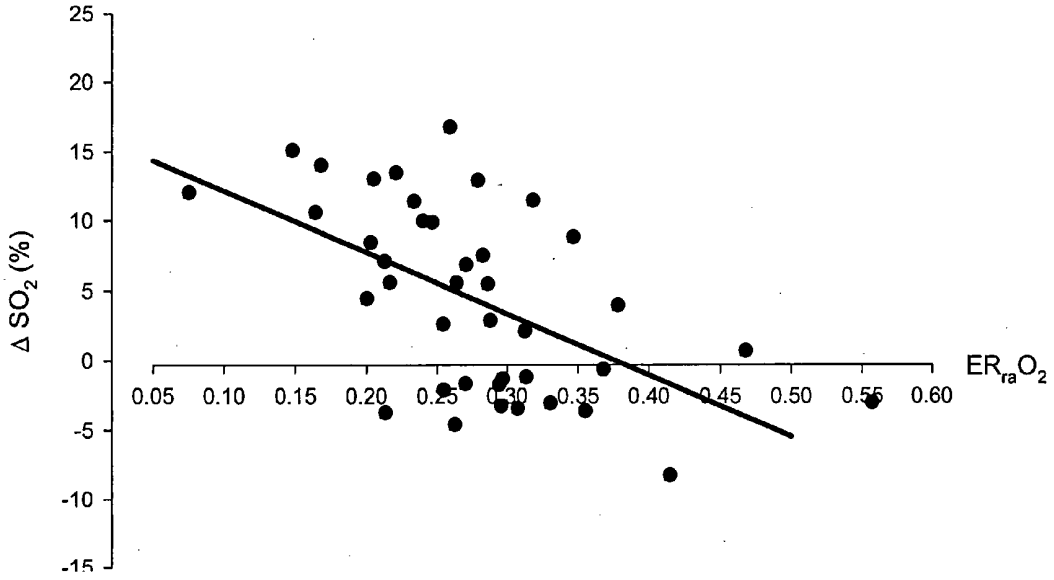

25
20
15
10
5
0
-5
-10
-15
Δ SO2 (%)
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
ERraO2

Figure 9

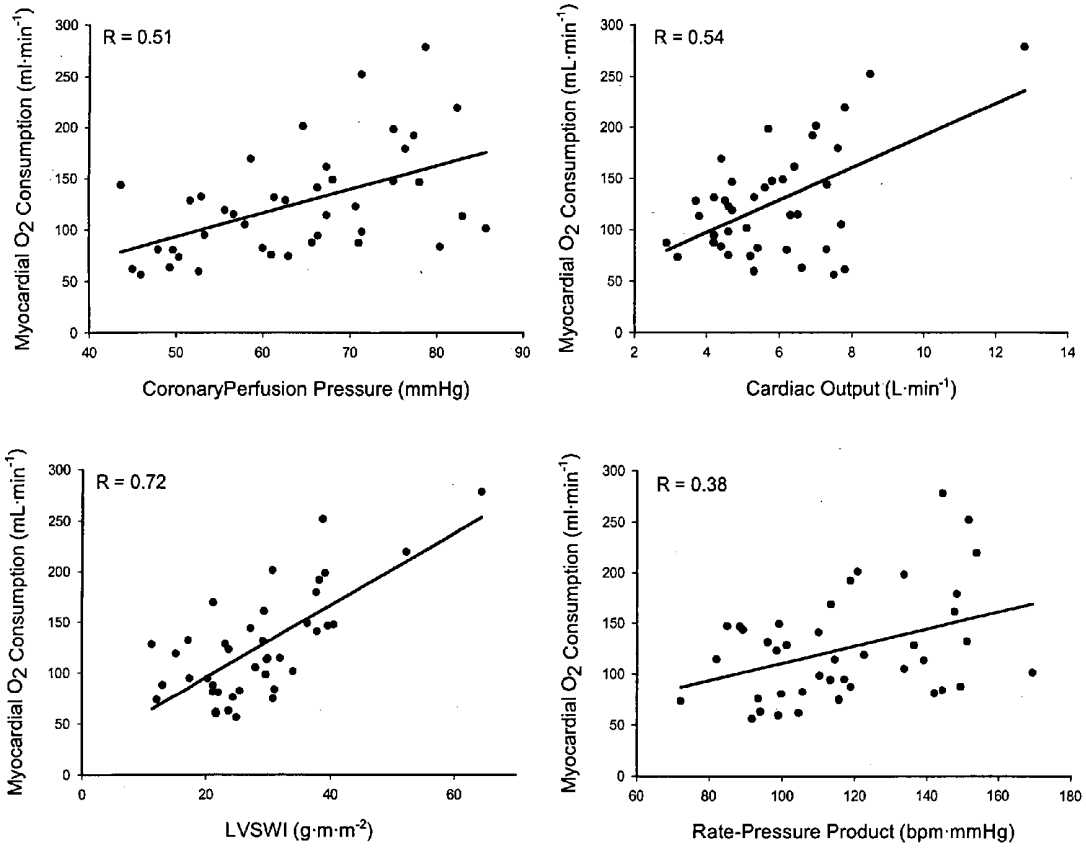

R = 0.51
Myocardial O2 Consumption (ml·min-1)
CoronaryPerfusion Pressure (mmHg)
R = 0.54
Myocardial O2 Consumption (mL·min-1)
Cardiac Output (L·min-1)
R = 0.72
Myocardial O2 Consumption (mL·min-1)
LVSWI (g·m·m-2)
R = 0.38
Myocardial O2 Consumption (ml·min-1)
Rate-Pressure Product (bpm·mmHg)

Figure 10

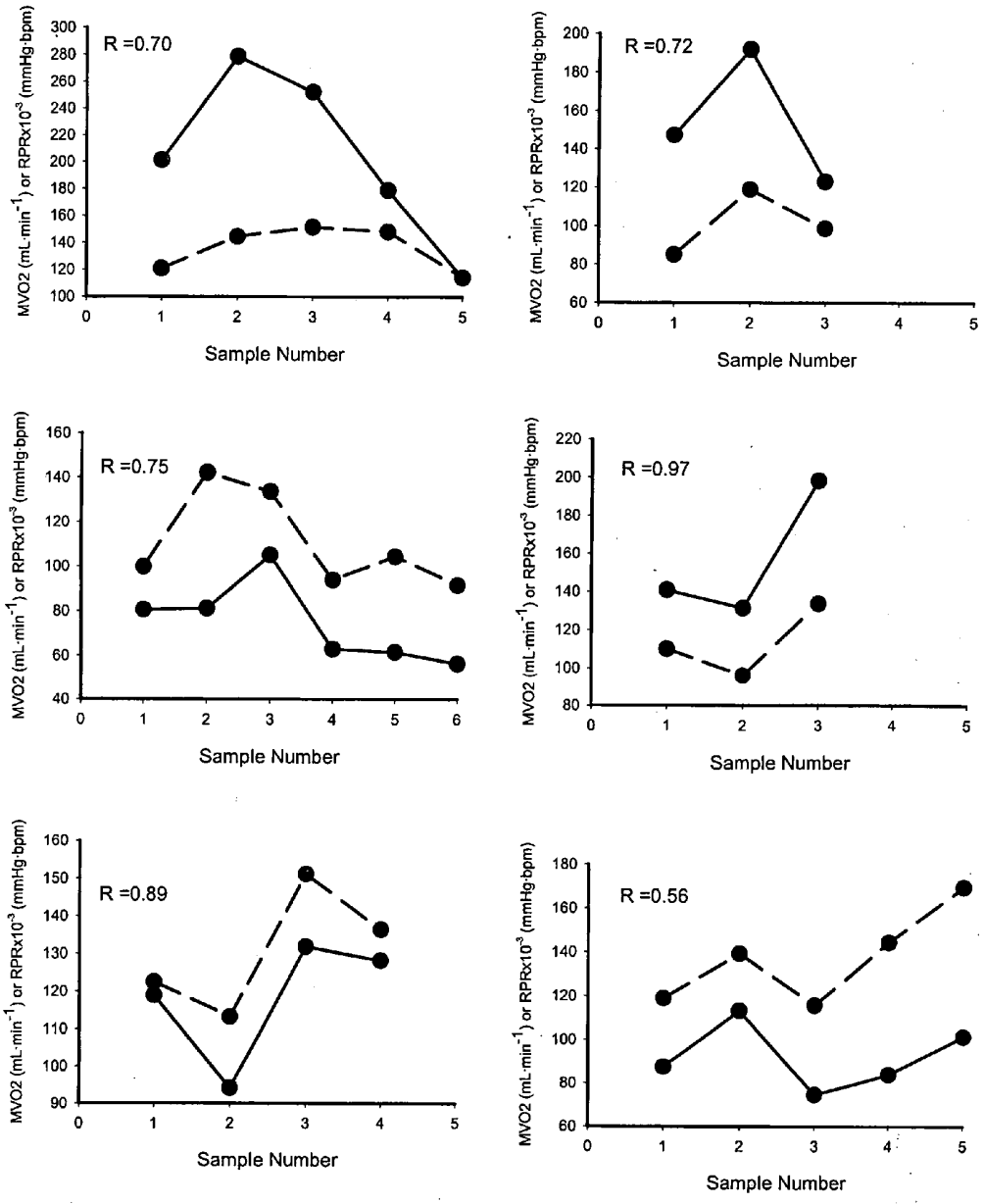
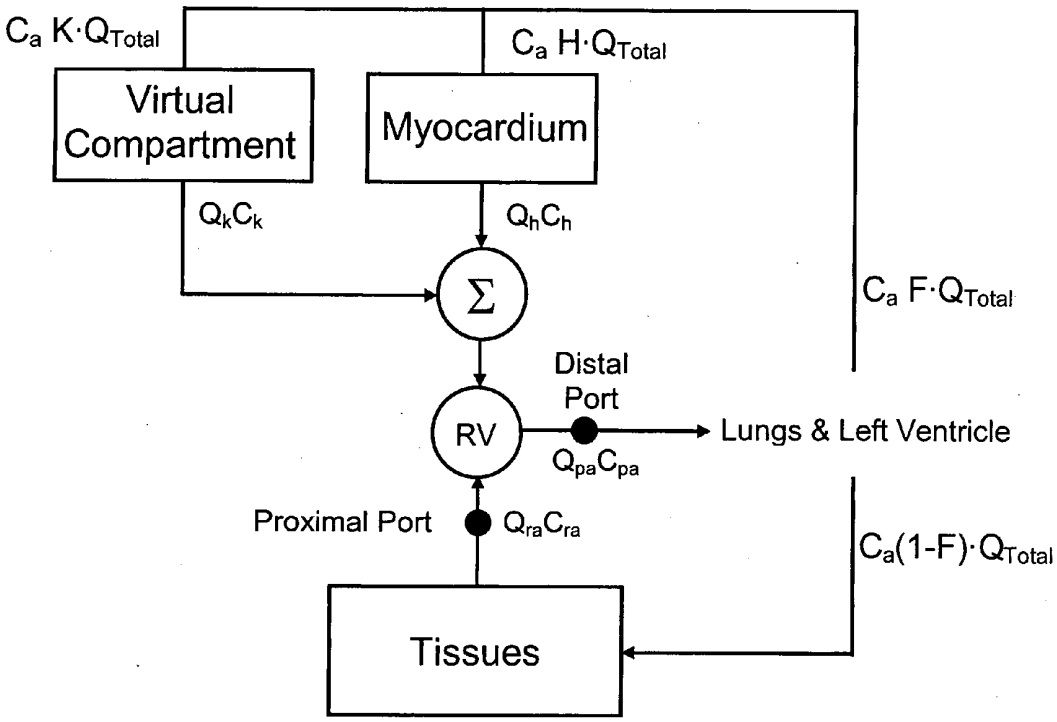

R =0.70
R =0.72
R =0.75
R =0.97
R =0.89
R =0.56
MVO2 (mL·min-1) or RPRx10-3 (mmHg·bpm)
Sample Number

Figure 11


C_a K·Q_{Total}
C_a H·Q_{Total}
Virtual Compartment
Myocardium
Q_kC_k
Q_hC_h
Σ
C_a F·Q_{Total}
Distal Port
RV
Lungs & Left Ventricle
$Q_{pa}C_{pa}$
Proximal Port
$Q_{ra}C_{ra}$
C_a(1-F)·Q_{Total}
Tissues

APPARATUS AND METHOD FOR MEASURING MYOCARDIAL OXYGEN CONSUMPTION

RELATED APPLICATION DATA

[0001] This invention claims priority from provisional application Ser. No. 60/520,280 filed on Nov. 14, 2003 entitled Novel Method to Measure Myocardial Oxygen Consumption in Critically 111 Patients, the contents of which are incorporated herein by reference, and from U.S. Ser. No. 10/987,505 that has a filing date of Nov. 12, 2004.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to an apparatus and method for measuring myocardial oxygen consumption. More particularly, the present invention relates to determining myocardial oxygen consumption by comparing oxygen saturation in atrial (or central veins) and mixed venous blood.

[0004] 2. Description of the Background Art

[0005] Pulmonary artery catheters ("PACs") are widely used for patient diagnosis and for hemodynamic and therapeutic monitoring. One of the most widely used PACs is the Swan-Ganz catheter. The Swan-Ganz catheter, a version of which is disclosed in U.S. Pat. No. 3,995,623 to Blake, includes a flexible tube (enclosing multiple lumina) that is designed to be flow-directed through a patient's heart by a distal balloon. The catheter is adapted to be delivered through the right atrium and right ventricle with the distal end positioned within the pulmonary artery.

[0006] The Swan-Ganz catheter includes first and second lumina for use in measuring blood pressures in the pulmonary artery and right atrium respectively. A third lumen is used for inflating the balloon at the distal end of the catheter. A fourth lumen is included for housing a thermistor that is used in monitoring blood temperature and in determining cardiac output. The fourth lumen also houses the wires associated with electrodes that are included for monitoring intraatrial and intraventricular electrograms. The Swan-Ganz catheter has been a useful tool in diagnosing complex cardiac arrhythmias.

[0007] A more recent PAC construction is disclosed in U.S. Pat. No. 6,532,378 to Saksena. In one embodiment, the PAC of Saksena includes a series of defibrillation electrodes interspersed with mapping electrode pairs at the distal end of the catheter. Proximal to the defibrillation and mapping electrodes are a series of sense electrodes and additional defibrillation electrodes. The catheter is used for indirect left atrial mapping from the left pulmonary artery and is also used in defibrillating or cardioverting the heart.

[0008] Each of the above referenced inventions is useful in providing a physician with information on the mechanical functioning of a patient's heart. However, none of the aforementioned PACs can be used to measure the rate of oxygen consumption by the heart, or myocardial VO2, whereby a physician may gain an understanding of the energy costs associated with the heart's performance. Measuring myocardial VO2 is significant because a decrease in myocardial VO2 may have serious consequences for critically ill patients. Heretofore, there has been no practical way to obtain myocardial VO2 measurements in critically ill patients.

SUMMARY OF THE INVENTION

[0009] It is an objective of the present invention to provide a method of determining a cardiac characteristic, such as, for example, the state of oxygenation of the heart, comprising: measuring a metabolite indicator at a distal end of a pulmonary artery catheter; measuring the metabolite indicator at a proximal end of the pulmonary artery catheter; and determining a cardiac characteristic based on the measurements of the metabolite indicator.

[0010] It is also an object of the present invention to provide a method of treating a patient comprising: measuring a metabolite indicator at a distal end of a pulmonary artery catheter; measuring the metabolite indicator at a proximal end of the pulmonary artery catheter; determining a cardiac characteristic based on the measurements of the metabolite indicator; and treating a patient based on the determination.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1** is a partial cross sectional view of a catheter usable in embodiments of the present invention.

[0012] FIG. **2** is a view of the catheter usable in embodiments of the present invention.

[0013] FIG. **3** is a view of a computer usable in embodiments of the present invention.

[0014] FIG. **4** is a block diagram illustrating an optical sensor usable in embodiments of the present invention.

[0015] FIG. **5** is a block diagram illustrating blood flow and oxygen content from the coronary artery and right atrium into the pulmonary artery.

[0016] FIG. **6** is a graph illustrating the relationship between myocardial consumption and differential oxygen saturation between atrial or central venous and mixed venous blood.

[0017] FIG. **7** illustrates a first-order mass transport model of the circulation.

[0018] FIG. **8** shows ΔSO2 plotted as a function of ERraO2. Also shown is the linear regression of the data (ΔSO2%=16.4-43.6 ERraO2; R=0.55; p<0.001). The intersection of this line with the abscissa defines the population mean myocardial O2 extraction ratio EmO2, in this case 0.38.

[0019] FIG. **9** shows a calculated MVO2 plotted as a function of coronary perfusion pressure, cardiac output, left ventricular stroke work index (LVSWI) and the rate-pressure product.

[0020] FIG. **10** shows sequential measures of MVO2 (solid line) and the rate pressure product (RPP×10-3; dashed line) plotted individually for study participants in whom three or more samples were obtained during the course of the study. Individual R values range from 0.54 to 0.97 with a weighted average correlation ρ=0.73.

[0021] FIG. **11** shows a second-order model of the circulation. The definitions of the various model parameters are shown in Table 1, and F is split into a flow fraction directed to the heart (H) and a flow fraction directed to a virtual compartment (K). The virtual compartment accounts for the

effect of incomplete mixing of IVC and SVC blood on the PAC proximal port blood sample.

[0022] Similar reference characters refer to similar parts throughout the several views of the drawings.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0023] The present invention relates to a pulmonary artery catheter ("PAG") and its use in determining a cardiac characteristic, such as, for example, myocardial oxygen consumption. Myocardial oxygen consumption is of critical importance because decreased myocardial energy utilization during acute illness may lead to tissue hypoperfusion, multiple organ failure, and eventually death. The inventor has discovered that myocardial oxygen consumption is a function of the difference in oxygen levels in atrial (or central veins) and mixed venous blood. The inventor has further discovered that differences in lactate, glucose or any other measurable blood concentration metabolite in atrial or central venous blood and mixed venous blood can also be used in determining myocardial energy metabolism.

[0024] The measurements necessary to calculate myocardial oxygen consumption are carried out by way of a PAC. FIG. **1** illustrates PAC **20** positioned within the pulmonary artery **22** of a patient's heart. As is conventional, PAC **20** of the present invention is constructed from an elongated flexible tube **24**. Tube **24**, which may be coated with a material to facilitate its insertion into a patient's vein, houses a series of lumina each of which serves a different diagnostic or therapeutic purpose.

[0025] For example, one lumen **26** is used to selectively inflate or deflate a balloon **28** at the distal end **32** of PAC **20**. Balloon **28** is preferably formed from a flexible material that expands upon receiving a fluid through lumen **26**. This fluid can be selectively injected into or withdrawn from balloon **28** via a syringe **34** at the proximal end **36** of PAC **20**. When inflated, balloon **28** allows PAC **20** to be "flow-directed" to a patient's heart.

[0026] PAC **20** additionally includes a thermistor **38** positioned adjacent to balloon **28**. The use of thermistors in PACs is known in the art and is generally described in U.S. Pat. No. 3,995,623 to Blake. Electricat leads (not shown) are used to couple thermistor **38** to a microprocessor **42**, or other diagnostic equipment, as will be described in greater detail hereinafter. An additional lumen **44** is included to shield the leads of the thermistor **38**. Thermistor **38** is used to monitor blood temperature and also allows total cardiac output to be determined by way of thermodilution. As will be elaborated upon hereinafter, total cardiac output is one factor used in calculating myocardial oxygen consumption.

[0027] One of the other factors needed to determine myocardial oxygen consumption is the difference in oxygen content between the right atrium **46** and the pulmonary artery **22** (i.e. between atrial (or central veins) and mixed venous blood). This difference is measured via two oxygen sensors positioned along the length of PAC **20**. Namely, a first oxygen sensor **48** is located at a distal end **32** of PAC **20**, while second sensor **52** is located proximal to the first. Locating second sensor **52** approximately 30 centimeters or more from distal end **32** of PAC **20** is preferred. With PAC **20** properly positioned within a patient's heart, first sensor **48** is positioned for readings within pulmonary artery **22** and second sensor **52** is positioned for readings within right atrium **46**. Ideally, second sensor **52** will be located about 3-4 centimeters above the tricuspid valve **54**. Nonetheless, oxygen saturation can also be measured from the superior vena cava, upstream from the atrium. This is because measuring oxygen saturation in a superior vena cava (central venous blood) provides the same information as measuring atrial blood.

[0028] The sensors can measure blood oxygen content in any number of ways. For example, chemical sensors can be employed in making the measurements. Additionally, the sensors need not be located on the length of PAC **20**, rather direct blood sampling may be used in making the necessary measurements. In the preferred embodiment, however, optical sensors **56** are employed. One suitable optical sensor is described in U.S. Pat. No. 4,684,245 to Goldring. The sensor described in the '245 patent includes a series of light emitting diodes ("LEDs") and a photodetector.

[0029] LEDs **58** are used to radiate infrared light into an adjacent blood sinus whereby the sensor's photodetector **62** can detect infrared absorption by the blood. The oxygen level in the blood can be determined from the level of infrared absorption. The optical sensors **56** are operatively coupled to microprocessor **42** for use in storing and processing the detected oxygen levels. The catheter includes additional lumina (**64**, **66**) for housing the leads to optical sensors **48** and **52**.

[0030] The present invention can employ any microprocessor **42** suitable for carrying out the algorithms described herein. The microprocessor can either be carried on-board PAC **20** or it can be a physically separate stand alone computer, such as a laptop. Microprocessor **42** is used in computing the oxygen consumption by the heart or myocardial VO2 on the basis of the following equation:

$$V0_2 = Qv(Cat - Cv) + QvF_s(Ca - Cat) \quad \text{Eq. 1}$$

[0031] where,

[0032] Q_v=pulmonary artery blood flow or total cardiac output; this value is obtained from thermistor **38**.

[0033] Cat=Oxygen (Oz) content in atrial (or central veins) blood; this value is obtained from second oxygen sensor **52** located within the right atrium **46**.

[0034] Cv=Oxygen (**62**) content in the pulmonary artery blood; this value is obtained from first oxygen sensor **48** located within pulmonary artery **22**.

[0035] C_a=Oxygen (02) content in the coronary artery (arterial saturation); this value is obtained from a pulse oximeter, through a noninvasive and standard technique known to most Intensive Care Units and anyone skilled in the art;

[0036] F_s=fraction of total blood flow going to the myocardium; this value is unknown for any particular patient, but it can safely be approximated to be between 0.05 and 10.

[0037] Equation 1 is derived from the principle of conservation of mass known as Fick's Principle as noted in the mass transport model depicted in FIG. **5** and the following equation:

$$VO_2 = CaQs - C_S Q_S \quad \text{Eq. 2}$$

[0038] The various O2 contents referenced in Equation 1 are based on the well known composition of O2 within blood. That is, total O2 is comprised of a percentage of O2 bound to hemoglobin and a percentage of O2 dissolved in plasma. The following equation reflects the known composition of O2 within blood:

O2 Content=1.34×hemoglobin concentration×O2 saturation+0.0003 PO2

[0039] As can be observed from Equation 3, the percentage of O2 from dissolved oxygen is quite small and can be neglected. In doing so, Equation 1 can be simplified as follows:

$$(VO_2)=KQvKSat-Sv)+Fs(Sa-Sat)] \quad \text{Eq. 4}$$

[0040] Here,

[0041] K=1.34×hemoglobin concentration.

[0042] Sat=Oxygen saturation in atrial (or central veins) blood.

[0043] S_v=Oxygen saturation in the pulmonary artery blood.

[0044] S_a=Arterial Oxygen saturation.

A close approximation to VO2 is obtained by:

$$VO_2=KQ_v(S_{at}-Sv) \quad \text{Eq. 5}$$

Microprocessor **42** can employ either Equations 1 or 4 in computing myocardial VO_2 consumption.

[0045] FIG. **6** is a graph illustrating data taken from 50 patients in whom a single determination of VO_2 was made. FIG. **6** is a graph showing the same data but shows VO_2 plotted as a function of the difference in O_2 saturation between the first and second oxygen sensors. VO_2 was calculated using Equation 4 with Fs=0.05.

[0046] FIG. **6** illustrates that VO_2 is proportional to the difference in the saturation between the proximal and distal oxygen sensors. Therefore, the difference in O2 saturation between atrial (or central veins) and mixed venous blood (S_at-S_v) could be used to monitor relative changes in VO2 in a given patient without the need to measure Qv or hemoglobin saturation. It is also possible to monitor changes in VO2 continuously by use of infrared optics placed in the tip and the atrial (or central veins) region of the PAC.

[0047] The principles presented herein can also be used to measure atrial (or central veins) and mixed venous blood differences in lactate, glucose and any other measurable blood concentration metabolite to serve as a measure of myocardial metabolism.

[0048] This is because the healthy myocardium generates its energy supply from the oxidation of fatty acids with the balance of energy production derived from the oxidation of glucose and lactate. Under aerobic conditions there is net lactate extraction from the coronary circulation with the oxidation of lactate accounting for 10% to 20% of the myocardial energy production, a proportion that increases substantially in septic patients. Given the heart's penchant for lactate as a metabolic substrate, coronary venous blood lactate concentration usually is lower than central venous blood lactate concentrate. The mixing of these effluents in the right ventricle should result in a declining blood lactate concentrate gradient from right atrium to pulmonary artery.

[0049] The metabolic response of the heart to acute illness often determines patient survival. Uncompensated cardiac failure can lead to systemic hypoperfusion, tissue hypoxia, multiple system organ failure and death. To assure tissue perfusion, current treatment of sepsis and other shock states calls for the infusion of fluids, vasopressors and inotropic agents. These interventions, while increasing cardiac output and systemic oxygen delivery (DO_2), are also likely to increase cardiac work and perhaps affect adversely myocardial aerobic metabolism

[0050] Mechanical parameters of myocardial performance, such as contractility and cardiac output, are measured routinely in critical ill patients using echocardiography or, more invasively, with a PAC. On the other hand, there is no practical technique available with which to monitor myocardial energy metabolism in the ICU. Given the heart's predilection for oxidative phosphorylation as the main source of ATP, myocardial energy generation may be inferred from its rate of O_2 uptake (MVO_2) Therefore, a method capable of measuring MVO_2 in critically ill patients could provide the means with which to monitor the effect of therapeutic interventions on cardiac energy metabolism. This monitoring modality would be particularly useful when treating patients in septic or cardiogenic shock, conditions usually associated with impaired myocardial function

[0051] Presently, measurement of MVO_2 in the clinical setting is an onerous task, one that requires knowledge of coronary sinus blood O_2 saturation ($S_{cs}O_2$), as well as of total coronary blood flow. $S_{cs}O_2$ may be measured from blood samples drawn from a catheter placed in the coronary sinus, a demanding procedure in the best of hands. Moreover, accurate measures of coronary sinus blood flow are exceedingly difficult to obtain More accurate techniques, such as magnetic resonance imaging[7] and contrast echocardiography have been used to estimate total coronary blood flow, but these techniques are not suitable for ICU monitoring.

[0052] Others have reported the existence of an O_2 saturation gradient (ΔSO_2) from right atrium to pulmonary artery in critically ill patients. The magnitude of ΔSO_2 is approximately 5%, although wide variations are found among individuals or even in the same person when measurements are taken at different times The mechanism resulting in ΔSO_2 is not known, but it is probable that mixing of right atrial (or central veins) with coronary venous blood plays an important role in its development. On this basis, it is reasonable to hypothesize that ΔSO_2 represents a physiological signal that bears some degree of relationship to coronary venous SO_2 and therefore, to MVO_2.

[0053] Should the above hypothesis hold true, then it may be possible to use the PAC to monitor MV_2 in critically ill individuals by computing ΔSO_2 from blood samples drawn from the catheter's proximal and distal ports. The purpose of this study was to explore this possibility by developing a mathematical expression relating ΔSO_2 to MVO_2, and comparing the results of this expression to parameters of myocardial energy utilization in a heterogeneous group of critically ill individuals.

[0054] The derivation of the equations used to calculate MVO_2 is shown below. These equations are based on the first-order mass transport model of FIG. **7**, where 'Q' represents blood flow and 'C' the O_2 content of blood. The

subscripts 'a', 'ra', 'pa' and 'h' refer to arterial, right atrial (or central veins), pulmonary artery and coronary venous blood, respectively.

[0055] The equation used to calculate MVO_2 is derived using the first-order mass transport model shown in FIG. 7, where 'Q' represents blood flow and 'C' the O_2 content of blood. Referring to FIG. 7, the definitions of the various model parameters are shown in Table 1. The model assumes perfect mixing of blood from the superior and inferior vena cava prior to reaching the Proximal Port sampling site, with further mixing with coronary venous blood occurring in the right ventricle. O2 consumption takes place in the "Tissues" and "Myocardium" compartments. Sampling of mixed venous blood occurs in the Distal Port located in the pulmonary artery. From conservation of flow and conservation of mass principles,

$$Q_{pa}=Q_{ra}+Q_h \tag{6a}$$

and

$$Q_{ra}C_{ra}+Q_hC_h=Q_{pa}C_{pa} \tag{7a}$$

Combining the above equations yields,

$$Q_{ra}C_{ra}+Q_hC_h=(Q_{ra}+Q_h)C_{pa} \tag{8a}$$

According to Fick's Principle, myocardial O_2 consumption is,

$$MVO_2=Q_h(C_a-C_h) \tag{9a}$$

Solving (4a) for C_h, and substituting into (3a),

$$Q_{ra}(C_{ra}-C_{pa})=Q_h[C_{pa}-C_a+MVO_2/Q_h] \tag{10a}$$

Taking Q_{pa} as the total cardiac output (Q_{total}) and defining F as the fraction of Q_{total} directed to the heart, $F=Q_h/Q_{total}$, yields the following expression for MVO_2,

$$MVO_2=Q_{total}[C_{ra}-C_{pa}+F(C_a-C_{ra})]\text{ml}\cdot\text{min}^{-1} \tag{11a}$$

Dividing the above expression by the myocardial O_2 delivery ($C_aQ_h=FC_aQ_{total}$) yields the myocardial O_2 extraction ratio,

$$ER_mO_2=[(C_{ra}-C_{pa})/F+C_a-C_{ra}]/C_a \tag{12a}$$

Neglecting the effect of plasma dissolved O_2 on the calculation of blood O_2 contents, and noting that $\Delta SO_2=S_{ra}O_2-S_{pa}O_2$, yields expressions for MVO_2 and of ER_mO_2 in terms of ΔSO_2 and the measured O_2 saturations,

$$MVO^2=13.9\cdot[Hb]\cdot Q_{pa}[\Delta SO_2+F(S_aO_2-S_{ra}O_2)]\ \text{ml}\cdot\text{min}^{-1} \tag{13a}$$

$$ER_mO_2=[\Delta SO_2/F+S_aO_2-S_{ra}O_2]/S_aO_2 \tag{14a}$$

where [Hb] is the blood hemoglobin concentration.

According to the model, MVO_2 is calculated as,

$$MVO^2=13.9\cdot[Hb]\cdot Q_{pa}[\Delta SO_2+F(S_aO_2-S_{ra}O_2)]\ \text{ml}\cdot\text{min}^{-1} \tag{15}$$

Where F is the fraction of the cardiac output directed to the myocardium; $\Delta SO_2=S_{ra}O_2-S_{pa}O_2$; and [Hb] is the blood hemoglobin concentration. The myocardial O_2 extraction ratio is,

$$ER_mO_2=[\Delta SO_2/F+S_aO_2-S_{ra}O_2]/S_aO_2 \tag{16}$$

Equation (16) contains two undefined unknowns, ER_mO_2 and F. These parameters may be estimated by solving equation (16) for ΔSO_2,

$$\Delta SO_2=F\cdot S_aO_2\cdot(ER_mO_2-ER_{ra}O_2) \tag{17}$$

where $ER_{ra}O_2=1-S_{ra}O_2/S_aO_2$. Equation (17) traces a line with slope $F\cdot S_aO_2$ whose intercept (at $\Delta SO_2=0$) equals ER_mO_2.

[0056] The above was validated using a prospective, sequential study conducted at The George Washington University Hospital intensive care unit. The Institutional Review Board approved of the study and informed consent was obtained from the patient or from the next of kin. Critically ill individuals older than 18 years of age of either sex in whom a PAC was required to guide fluid therapy were enrolled in the study. Excluded were patients with uncorrected valvular incompetence or intra-cardiac shunts. Physicians not involved in the study determined the clinical need for using PACs in these patients. PACs were inserted using standard technique through the internal jugular or femoral approach. All patients had an arterial line inserted as part of their ICU management. After discarding the first 2 ml of blood, one ml aliquots were drawn in random order and in rapid succession from the arterial line and the proximal and distal ports of the PAC. The latter samples were drawn with the catheter balloon deflated. This was followed by measurement of heart rate, arterial, pulmonary artery, central venous, and PA occlusion pressures (PAOP) and cardiac output in triplicate by the thermodilution method. Measurements were obtained within 24 hours of catheter insertion and daily thereafter, until the PAC was removed. Blood samples were immediately analyzed in triplicate for oxyhemoglobin concentration ([Hb]) and O_2 saturation (IL682 CO-Oximeter, Instrumentation Laboratories, Lexington, Mass.).

[0057] In analyzing the obtained data, Cardiac index (CI), myocardial perfusion pressure (PP), rate-pressure product (RPP), left ventricular stroke work index (LVSWI), systemic O_2 delivery (DO_2), systemic O_2 consumption (VO_2), and the systemic O_2 extraction ratio (ERO_2) were computed according to standard formulae. Paired Student's t-test was used to compare $S_{ra}O_2$ to $S_{pa}O_2$. The relationship of MVO_2 to the various computed and measured parameters was analyzed by Spearman's correlation analysis. Data are shown as mean±SD with $p<0.05$ taken as a significant difference.

[0058] Sixteen critically patients with various medical and post-surgical conditions were enrolled in the study. Descriptive demographic data for the group and number of samples taken per patient are shown in Table 2. Table 2, presents the descriptive demographics and number of blood samples sets obtained in the patients enrolled in the study (n=16); and CABG=Coronary artery bypass grafting.

TABLE 2

No.	Sex	Age	Diagnosis	APACHE II	Samples
1	F	69	Acute respiratory failure	12	1
2	M	75	Pneumonia	9	1
3	M	55	Acute myocardial infarction	10	2
4	M	80	Post CABG	18	1
5	M	58	Heart failure	7	2
6	F	45	Post CABG	2	1
7	M	48	Sepsis, multiple myeloma	23	5
8	F	56	Sepsis, pneumonia, breast cancer	23	6
9	F	72	Post CABG	11	2
10	M	76	Post CABG	10	2
11	M	49	Pneumonia	9	4
12	F	76	Aortic valve repair	8	3

TABLE 2-continued

No.	Sex	Age	Diagnosis	APACHE II	Samples
13	M	85	Pulmonary hypertension	15	3
14	M	72	Heart failure	10	2
15	M	75	Pulmonary hypertension	5	1
16	M	68	Heart failure	15	5

[0059] The mean age was 66±12 years and the APACHE II score 16±6. Eleven were men. The number of samples per patient varied according to the time the PAC remained in place, ranging from one to six, yielding 41 sets of simultaneous arterial, RA and PA samples.

[0060] Table 3 shows the combined hemodynamic and O_2 transport data for all study participants. Table 3 presents Hemodynamic and systemic O_2 transport parameters; and PAOP=Pulmonary artery occlusion pressure; SVRI=Systemic vascular resistance index; PVRI=Pulmonary vascular resistance index; PRP=Double product; LVSWI=Left ventricular stroke work index; DO_2=Systemic O_2 delivery; VO_2=Systemic O_2 consumption; ERO_2=Systemic O_2 extraction ratio.

TABLE 3

	Mean ± SD	Median	Min	Max
Body Temperature (° C.)	36.6 ± 0.7	36.5	35.0	38.1
Heart rate (bpm)	98 ± 15	96	67	130
Cardiac Output ($L \cdot min^{-1}$)	5.8 ± 1.8	5.4	2.9	12.8
Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)	3.1 ± 0.9	3.1	1.5	6.8
Mean Arterial Pressure (mmHg)	84 ± 12	83.0	63.0	110
Mean Pulmonary Pressure (mmHg)	34 ± 11	33	12	56
PAOP (mmHg)	20 ± 8	18	6	45
Central Venous Pressure (mmHg)	19 ± 10	19	1	37
SVRI ($dynes \cdot sec^{-1} \cdot cm^{-5}$)	1773 ± 605	1648	874	3378
PVRI ($dynes \cdot sec^{-1} \cdot cm^{-5}$)	385 ± 250	313	110	998
Stroke Volume (mL)	60 ± 18	58	30	113
Rate Pressure Product × 10^{-3} ($mmHg \cdot beats \cdot min^{-1}$)	118 ± 24	114	72	170
LVSWI ($g \cdot m \cdot m^{-2}$)	28 ± 11	28	11	64
Hemoglobin ($g \cdot dL^{-1}$)	10.1 ± 1.6	10.0	7.3	14.1
VO_2 ($ml \cdot min^{-1}$)	238 ± 65	211	129	390
DO_2 ($ml \cdot min^{-1}$)	761 ± 219	718	360	1,294
$ER_{pa}O_2$	0.32 ± 0.08	0.32	0.18	0.53

[0061] Referring to Table 3, there was a wide variation in all parameters, reflecting the heterogeneity of clinical diagnoses in the patient population. Table 4 shows arterial, RA and PA blood O_2 saturations and ΔSO_2. $S_{ra}O_2$ was greater than $S_{pa}O_2$($p<0.01$) with ΔSO_2=4.3±6.8%. There was a wide dispersion of individual ΔSO_2 values, ranging from −8.2% to 16.8%.

[0062] FIG. **8** shows ΔSO_2 plotted as a function of $ER_{ra}O_2$ (computed as $1-S_{ra}O_2/S_aO_2$). Also shown is the linear regression of the data ($\Delta SO_2\%=16.4-43.6\ ER_{ra}O_2$; R=0.55; $p<0.001$). The intercepts of this regression line are ΔSO_2=16.4% for $ER_{ra}O_2=0$ and $ER_{ra}O_2$=0.38 for $\Delta SO_2=0$. The latter corresponds to the condition where $ER_mO_2=ER_{ra}O_2$. The myocardial flow fraction F was computed from equation (17) using values for $ER_{ra}O_2=0$; ΔSO_2=16.4, ER_mO_2=0.38 and S_aO_2=95.6% (the group's mean S_aO_2 from Table 3), resulting in F=0.45. Table 5 lists myocardial O_2 transport parameters calculated using equations (15) and (16) with F=0.45. In Table 5, shows computed myocardial oxygenation parameters assuming F=0.45. The coronary perfusion was calculated as F·Qtotal, and in Table 5, MDO2=Myocardial O2 delivery; MVO2=Myocardial O2 consumption (from equation 10); EmO2=Myocardial O2 extraction ratio (from equation 14).

[0063] FIG. **9** shows calculated MVO_2, corresponding to each set of blood SO_2 measurements (F=0.45), plotted as a function of PP, CO, LVSWI and RPP, respectively. MVO_2 decreased with decreasing PP (MVO_2=2.3 PP−19.8; R=0.51; $p<0.001$); and increased in concert with the parameters of cardiac performance CO, LVSWI and RPP. MVO_2 was most closely related to LVSWI (MVO_2=3.6 LVSWI+25.7; R=0.72; $p<0.001$); with less robust associations noted for CO (MVO_2=15.9 CO+36.0; R=0.54; $p<0.01$); and RPP (MVO_2=0.8 RPP+26.4; R=0.38; $p<0.02$). A stronger relationship between MVO_2 and RPP emerges when comparing these variables in individual subjects. This is illustrated in FIG. **10**, where sequential measures of RPP and MVO_2 are plotted individually for study participants in whom three or more samples were obtained during the course of the study. Individual R values ranged from 0.54 to 0.97 with a weighted average correlation ρ=0.73. The high individual correlation values shown in FIG. **10** suggests that the dispersion of combined data around the correlation line for RPP and MVO_2 (FIG. **9**) reflects mainly the heterogeneous nature of the patient population studied, although other factors also may be involved

[0064] The clinical complexity of placing a coronary sinus catheter, as well as the precarious condition of the patients enrolled in the study, precluded the direct measure of MVO_2. Instead, MVO_2 derived from equation (15) was compared to CO, LVSWI and RPP. These hemodynamic parameters are related to the rate of myocardial energy utilization and served as surrogates for direct measures of MVO_2. The significant degree of association found between calculated MVO_2 and these cardiac performance parameters supports the hypothesis that ΔSO_2 mirrors alterations in myocardial energy utilization.

[0065] The most striking correlation was that noted between MVO_2 and LVSWI (R=0.72), a marker of cardiac contractility. Although it may be argued that this relationship could have resulted in part from coupling of shared data, since both the calculation of LVSWI and MVO_2 include the cardiac output term, the lesser robustness noted between CO and MVO_2 (R=0.51) belies this argument.

[0066] The significant correlation noted between RPP and MVO_2 in individual subjects (ρ=0.73) also supports the hypothesis that ΔSO_2 is related to myocardial energy utilization. RPP is used widely as an index of aerobic myocardial metabolism, based on human and experimental studies that show a strong correlation between RPP and cardiac O_2 uptake. It should be noted that the calculation of RPP (systolic BP×HR) does not incorporate any of the terms used in the calculation of MVO_2, thus eliminating the possibility of data coupling.

[0067] Application of the clinical data to the mass transport model of FIG. **15** resulted in a value for F, the fraction of the cardiac output directed to the heart, of 0.45. For a mean population cardiac output of 5.8 L/min (Table 3), this

F value predicts a mean coronary flow of 2.6±0.8 L/min, a value that is exceedingly high when compared to published data from experimental and clinical studies. Dhainaut J F, Huyghebaert M F, Monsallier J F, Lefevre G, Dall'Ava-Santucci J, Brunet F, Villemant D, Carli A, Raichvarg D. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. *Circulation* 1987;75:533-541, measured coronary sinus flow with a thermodilution technique in septic shock patients and reported it to be approximately 0.2 L/min, corresponding to F=0.03. Cunnion R E, Schaer G L, Parker M M, Natanson C, Parrillo J E. The coronary circulation in human septic shock. *Circulation* 1986;73:637-644, reported coronary venous flow in individuals with septic shock of 0.45 L/min, with some patients having flows approaching 1.0 L/min. This value, however, results in F=0.10, still far less than that predicted by the model.

[0068] A possible explanation for the wide discrepancy noted in calculated and measured F values is that clinical measures of coronary sinus flow underestimate total coronary venous flow. Coronary venous flow is usually assumed to equal coronary sinus flow, the latter obtained by thermodilution tracer techniques, an error-prone method. Moreover, even when measured accurately, coronary sinus flow may underestimate total coronary venous flow. The great cardiac and middle cardiac veins drain into the coronary sinus in only 50% of human hearts and the major epicardial veins drain into the coronary sinus in only 20% of cases. Measures of coronary blood flow obtained simultaneously by phase-contrast magnetic resonance and PET scanning shows that coronary sinus flow accounts for only 65% the total left ventricular venous flow. This difference, however, is not large enough to explain the discrepancy between the model-predicted and clinical estimates of coronary blood flow.

[0069] Perhaps a more likely explanation for the high predicted value of F is that the equations of the model described by FIG. **7** oversimplify a highly complex hydrodynamic system, resulting in an overestimate of myocardial blood flow. This first-order model assumes perfect blending of IVC and SVC blood occurring prior to central venous blood reaching the location of the PAC proximal port. Further, mixing of central venous and coronary venous blood occurs exclusively within the right ventricle. The real situation is more complicated. Instead, the anatomical relationship of the inferior vena cava (IVC), the superior vena cava (SVC) and the coronary sinus is such that they empty their venous contents in close proximity in the right atrium. Moreover, this is a dynamic system in which catheter motion may alter the position of the proximal port within the right atrium from beat to beat. In this intricate hydrodynamic system, the position of the proximal port of the PAC, relative to the coronary sinus is of great, and so far not well understood significance.

[0070] Another complicating factor in describing the process by which blood mixes in the right atrium is the possibility that $(SO_2)_{SVC}$ may differ from $(SO_2)_{IVC}$, depending on the patient's clinical condition. Reportedly, $(SO_2)_{SVC} \leqq (SO_2)_{IVC}$ in individuals not in shock, whereas the opposite occurs in shock states. For example, the condition where $(SO_2)_{SVC} >> (SO_2)_{IVC}$, coupled with imperfect mixing of the central venous flows, could result in ΔSO_2 being related mainly to the mixing of SVC and IVC blood streams. Under these conditions the first-order model would yield values for MVO_2 and F higher than those warranted by the actual physiological condition.

[0071] A mathematical model accounting for the above mentioned caveats is a difficult undertaking. Shown in FIG. **11** is a more complex, but less well defined mass transport model that accounts for incomplete mixing and different O_2 saturations for SVC and IVC. According to this model, F is now split into a flow fraction directed to the heart (H) and a flow fraction directed to a virtual compartment (K). The virtual compartment accounts for the effect of incomplete mixing of IVC and SVC blood on the PAC proximal port blood sample. In this model, the value of H may be defined to conform to published reports, as long as the relationship K=F−H is maintained.

For the model configuration shown in FIG. **11** (derivation not shown),

$$S_hO2=[S_{pa}O_2-S_{ra}O_2(1-F)+S_kO_2(H-F)]/H \quad (18)$$

and

$$ER_hO_2-1-[S_{pa}O_2-S_{ra}O_2(1-F)+S_kO_2(H-F)]/H\cdot S_aO_2) \quad (19)$$

where S_k is the venous saturation of the virtual compartment. As a first approximation, S_k may be assigned a value of $S_{ra}+\Delta_{CV}$, where Δ_{CV} is the difference between $(SO_2)_{SVC}$ and $(SO_2)_{IVC}$.

[0072] Application of data obtained in the current study to equation (19) is not possible, since it requires several unwarranted assumptions, in particular regarding values for the unknown parameters H and Δ_{CV}. On the other hand, the model of FIG. **11** does provide a theoretical construct to be tested in future studies that include simultaneous drawing of right atrial (or central veins), pulmonary artery, IVC, SVC and coronary sinus blood samples. From a clinical perspective, however, increasing the model's complexity may be of marginal utility in the management of critically ill patients. The first-order model, imperfect as it may be, appears capable of reflecting changes in MVO_2 taking place in these individuals.

[0073] A standard PAC can serve to monitor myocardial O_2 uptake. The PAC is a widely used monitoring device and adoption of the simple technique described should is relatively easy. Moreover, it would not be a difficult task to adapt current in vivo oximetry technology to measure ΔSO_2, thus allowing for continuous monitoring of MVO_2 while reducing sources of measuring error. The bioenergetic information provided by ΔSO_2 also may be supplemented by measuring the RA to PA concentration gradients of other parameters involved in myocardial energy metabolism, such as lactate[25,26], CO_2, glucose and free fatty acids.

[0074] Additional clinical and experimental studies are required to fully understand the physiological principles that relate ΔSO_2 to myocardial O_2 uptake at the heart's rate of energy utilization. These studies should include mapping of central venous, right atrial (or central veins) and coronary sinus blood O_2 saturations under various pathological conditions, as well as the direct measures of MVO_2. This information should better define the relationship of the mass-transport models presented here, and even the relevance of the models themselves, to the determination of MVO_2 in critically ill individuals.

[0075] The present disclosure includes that contained in the appended claims, as well as that of the foregoing description. Although this invention has been described in its preferred form with a certain degree of particularity, it is understood that the present disclosure of the preferred form has been made only by way of example and that numerous changes in the details of construction and the combination and arrangement of parts may be resorted to without departing from the spirit and scope of the invention.

What is claimed is:

1. A method of determining a cardiac characteristic comprising:

a) measuring a metabolite indicator at a distal end of a pulmonary artery catheter;

b) measuring the metabolite indicator at a proximal end of the pulmonary artery catheter; and

c) determining a cardiac characteristic based on the measurements of the metabolite indicator.

2. A method of determining a cardiac characteristic according to claim 1, wherein the metabolite indicator includes at least one of: SO_2, Lactate, and Glucose.

3. A method of determining a cardiac characteristic according to claim 1, wherein the metabolite indicator includes and indicator that indicates a difference in a metabolite concentration between the distal and proximal ports of the pulmonary artery catheter.

4. A method of treatment comprising:

a) measuring a metabolite indicator at a distal end of a pulmonary artery catheter;

b) measuring the metabolite indicator at a proximal end of the pulmonary artery catheter;

c) determining a cardiac characteristic based on the measurements of the metabolite indicator; and

d) treating a patient based on the determination.

5. A method of treatment according to claim 4, wherein the metabolite indicator includes at least one of: SO_2, Lactate, and Glucose.

6. A method of treatment according to claim 4, wherein the metabolite indicator includes and indicator that indicates a difference in a metabolite concentration between the distal and proximal ports of the pulmonary artery catheter.

* * * * *

专利名称(译)	用于测量心肌耗氧量的装置和方法		
公开(公告)号	US20070276210A1	公开(公告)日	2007-11-29
申请号	US11/707138	申请日	2007-02-16
[标]申请(专利权)人(译)	古铁雷斯GUILLERMO		
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IPC分类号	A61B5/00 A61B5/028 A61B5/029		
CPC分类号	A61B5/028 A61B5/029 A61B5/14532 A61B5/6853 A61B5/14546 A61B5/1459 A61B5/412 A61B5/14542		
优先权	60/520280 2003-11-14 US		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及一种确定在肺动脉导管的近端和远端确定的心脏特征的方法。本发明还涉及一种基于确定肺动脉导管的近端和远端的心脏特征之间的确定差异来治疗患者的方法。