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(54) Title: APPARATUS AND METHODS OF BIOELECTRICAL IMPEDANCE ANALYSIS OF BLOOD FLOW
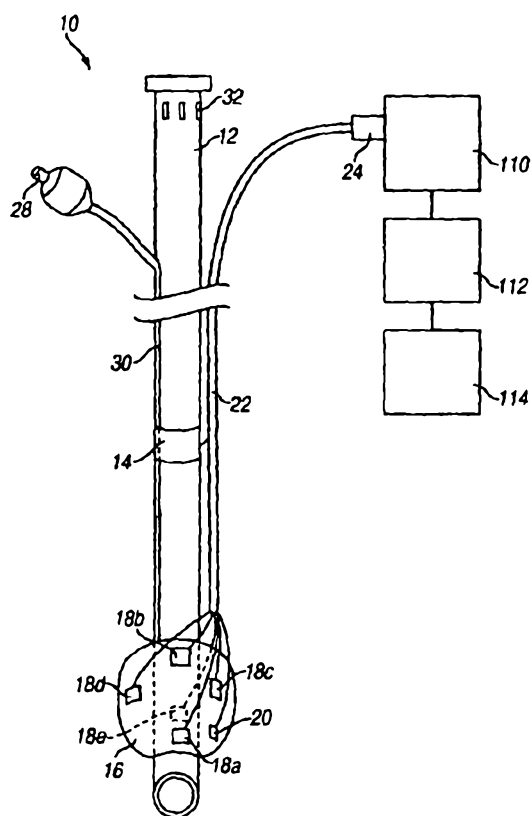
(57) Abstract: Apparatus and methods are provided for monitoring cardiac output using bioelectrical impedance techniques in which three orthogonal pairs of sense electrodes (18a-18e) are placed in the trachea or esophagus in the vicinity of the aorta, while an excitation current is injected into the intervening tissue mass via a current electrode (20), so that bioelectrical impedance measurements based on the voltage drop sensed by the sense electrodes reflect voltage changes induced primarily by blood flow dynamics. Methods are provided for computing cardiac output from bioelectrical impedance values using a multi-parameter algorithm derived using stepwise multiple linear regression or other optimization techniques. Apparatus and methods are also provided so that the measured cardiac output may be used to control administration of intravenous fluids or medication to an organism or to optimize a heart rate controlled by a pacemaker.

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APPARATUS AND METHODS OF BIOELECTRICAL
IMPEDANCE ANALYSIS OF BLOOD FLOW

Field Of The Invention

The present invention relates generally to
5 apparatus and methods for non-invasively measuring
cardiac output and, more particularly, to apparatus and
methods for measuring cardiac output using
bioelectrical impedance analysis techniques.

10 Background Of The Invention

Knowledge of cardiac output is crucial in the
care of critically ill patients, as well as patients
with chronic heart disease requiring monitoring of
medication. For many years the standard of cardiac
output measurement has been pulmonary artery
15 catheterization. Previously known catheterization
techniques, as described, for example, in U.S. Patent
Nos. 3,915,155, 3,726,269 and 3,651,318, involve
periodic injection into the patient's bloodstream of a
bolus of saline, during which thermodilution
20 measurements are performed to determine cardiac output.
Such techniques cannot generally be used for continuous
monitoring. Moreover, such catheterization techniques
pose significant risk to the patient, including

malignant arrhythmias, pulmonary artery rupture, and in
rare cases, death.

     Consequently, for many years work has been
underway to develop less invasive apparatus and methods
5 for monitoring cardiac output. For example, as an
alternative to catheterization methods, Doppler
ultrasound techniques have been adapted to measure the
velocity of blood flow. If the diameter of a vessel,
its flow profile, and the angle of the ultrasound beam
10 relative to the vessel can be determined, Doppler
ultrasound measurements of the ascending aorta, either
externally (from the suprasternal notch) or internally
(from within the trachea) can be used as a measure of
cardiac output.

15   U.S. Patent 4,671,295 describes an example of
such methods and apparatus, wherein an ultrasound
transducer is mounted on the tip of an endotracheal
tube so that Doppler measurements of blood flow from a
point (pulse wave mode) or path (continuous wave mode)
20 along the ultrasound beam can be measured. The method
described in the patent requires multiple measurements
within the blood vessel, a priori knowledge of the
blood flow pattern and cross-sectional area of the
vessel, and the relative angulation of the blood
25 vessel. In addition, the measurement is highly
dependent upon the exact placement of the transducer.
These drawbacks have resulted in the slow adoption of
Doppler ultrasound cardiac output techniques.

     A yet further technique which the prior art
30 has sought to apply to the measurement of cardiac
output is bioelectrical impedance analysis ("BIA").
BIA has recently gained wide use as a method for
measuring body composition and physiological metrics.
BIA involves passing a low level electrical alternating
35 current ("AC") through body tissues between multiple

electrodes, measuring the voltage difference between multiple locations on the tissue, and then calculating the electrical impedance (electrical resistance plus reactance) of the stimulated tissue.

5   Generally, BIA apparatus employ two current electrodes to conduct a low level excitation current through body tissue. As current flows in the tissue, a potential difference develops across the tissue which is proportional to the value of the AC current and the

10   tissue impedance. The tissue impedance may be calculated by disposing two sense electrodes between the current electrodes and measuring the voltage difference between the two sense electrodes.

        Current flows predominantly through body

15   materials with high conductivity, such as blood. Less current flows through muscle, which has an intermediate conductivity, while the conductivity of fat, air and bone is much lower than that of either blood or muscle. Because the resistance to current flow is a function of

20   the conductivity and cross-sectional area of the conducting volume, volumes having a larger cross-sectional area have lower electrical resistance.

        It is also known that the impedance of the conducting volume and the measured medium metrics

25   (i.e., static parameters such as fat or water content, and dynamic metrics, such as blood flow) are dependent upon the placement of the electrodes and the conducting path between the electrodes. Thus, the greater the distance between the electrodes, the more likely that

30   extraneous variables will affect the measurement.

        Previously known BIA methods generally correlate the measured voltage drop between the sense electrodes to tissue impedance using relatively simple algorithms based on simplified models of body

35   structure, for example, by assuming that the body is

composed of simple cylindrical resistive volumes.
Temporal cyclical variations in the body impedance are
then assumed to result from physiological events such
as blood flow and breathing.

5   Measurements of the electrical impedance, and
particularly, the time-varying nature of electrical
impedance, may therefore provide a non-invasive
indicator of physiological events. Various algorithms
have been developed to isolate specific physiological
10 parameters, such as cardiac output, from the measured
bioelectrical impedance, as described, for example, in
W.G. Kubicek, et al., "Development And Evaluation Of An
Impedance Cardiac Output System," Aerospace Medicine,
Vol. 37, pp. 1208-1212 (1966) and U.S. Patent
15 No. 3,340,862, which is incorporated herein by
reference.

        Despite the application of BIA methods for
measuring cardiac output, no simple continuous BIA -
based cardiac output measurement device has gained
20 widespread acceptance. Many existing BIA devices use
external or internal electrodes to measure
bioelectrical impedance for large volumes, for example,
the whole body or thoracic segments. Because the
excitation current diffuses throughout the entire
25 volume, making use of any and all conductive paths,
differences between individual patients, and even for
the same patient over time, may inhibit standardizing
the BIA metrics.

        Moreover, it is known that while BIA
30 measurements of cardiac output provide good correlation
for normal patients and those hemodynamically stable
patients, there is poorer correlation for critically
ill patients and patients in heart failure, as
described, for example, in R. J. Detemeter et al., "The
35 Use Cf Noninvasive Bioelectric Impedance To Determine

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Cardiac Output: Factors Affecting Its Accuracy," Am. J.
Noninvasive Cardiol., Vol. 2, pp. 112-118 (1988).

     An example of an attempt to overcome the
variabilities encountered when taking bioelectrical
5 impedance measurements across large volumes is
described, for example, in U.S. Patent No. 4,870,578.
That patent describes BIA apparatus for monitoring
cardiac output by using external electrodes that
measure the electrical resistance of a segment of the
10 thorax and includes circuitry to account for
respiratory-induced voltage changes. As acknowledged
in that patent, the respiratory-induced voltage changes
are typically much greater than the cardiac-induced
voltage changes.
15   Other devices that attempt to account for the
effect of non-cardiac physiological events on
bioelectrical impedance include arranging multiple
electrodes on esophageal catheters to measure thoracic
bioelectric impedance, as described, for example, in
20 U.S. Patent Nos. 4,852,580 and 4,836,214. Both patents
describe multi-electrode arrays inserted into the
esophagus to provide an impedance measurement
reflecting blood flow in the descending aorta. It may
be difficult for such devices to provide true isolation
25 of cardiac-induced voltage changes from those induced
by other physiological events. In addition, these
systems do not ensure that the multiple electrodes make
positive contact with the esophageal wall.

     BIA measurements have also been employed to
30 provide a metric of cardiac output by measuring
physiologic effects other than blood flow. For
example, U.S. Patent No. 4,953,556 describes a BIA
arrangement including an internal electrode mounted on
an esophageal catheter and an external electrode which
35 is disposed above the apex of the heart. The apparatus

described in that patent attempts to use BIA measurements to determine cardiac wall motion and lung motion, from which an estimate of cardiac output and pulmonary activity can be obtained.

5   BIA measurements taken across small volumes, such as just the ascending aorta, are typically highly dependent on the position and orientation of the electrodes that are used to measure the impedance. For example, a pair of electrodes positioned orthogonally 10 to the flow will provide radically different measurements than a pair of electrodes that are placed parallel to the direction of flow. Given the complex curvature of the aorta, it can be very difficult to align and orient a pair of electrodes to provide useful 15 BIA measurements.

In view of the foregoing, it would be desirable to provide apparatus and methods for accurately, non-invasively and continuously measuring cardiac output using BIA techniques.

20   It further would be desirable to provide apparatus and methods for measuring cardiac output in critically ill patients using BIA techniques that overcome the inaccuracies arising from measuring voltage changes across whole body or large volume 25 thoracic segments.

It also would be desirable to provide apparatus and methods for measuring cardiac output using BIA techniques that are less dependent on the precise positioning and orientation of the electrodes 30 than previously known BIA cardiac output measurement devices and methods.

It also would be desirable to provide inexpensive apparatus and methods for measuring cardiac output using BIA techniques that overcome the drawbacks

of previously known BIA cardiac output measurement
devices and methods.

It would further be desirable to provide
apparatus and methods for continuously monitoring
5   cardiac output so as to permit the measured cardiac
output to be employed as a metric for controlling and
maintaining other aspects of a patient's health.

Summary Of The Invention

In view of the foregoing, it is an object of
10 this invention to provide apparatus and methods for
accurately, non-invasively and continuously measuring
cardiac output using BIA techniques.

It is another object of this invention to
provide apparatus and methods for measuring cardiac
15 output in critically ill patients using BIA techniques
that overcome the inaccuracies arising from measuring
voltage changes across the whole body or large volume
thoracic segments.

It also is an object of the present invention
20 to provide apparatus and methods for measuring cardiac
output using BIA techniques that are less dependent on
the precise positioning and orientation of the
electrodes than previously known BIA cardiac output
measurement devices and methods.

25   It is yet another object of the present
invention to provide inexpensive apparatus and methods
for measuring cardiac output using BIA techniques that
overcome the drawbacks of previously known BIA cardiac
output measurement devices and methods.

30   It is still another object of this invention
to provide apparatus and methods for continuously
monitoring cardiac output that permit the measured
cardiac output to be employed as a metric for

controlling and maintaining other aspects of a patient's health.

These and other objects of the invention are accomplished in accordance with the principles of the
5 invention by providing BIA cardiac output monitoring apparatus adapted to be disposed within a patient's trachea or esophagus in close relation to the aorta to acquire cardiac output information. Preferred embodiments of the apparatus of the present invention
10 include: 1) multiple sense electrodes configured to be placed in the patient's trachea or esophagus in the vicinity of the aorta, wherein the sense electrodes are arranged in pairs along three orthogonal axes; and 2) a current electrode and a ground electrode disposed
15 within the patient's trachea or esophagus.

In accordance with the principles of the invention, current conducted between the current electrode and the ground electrode flows throughout the intervening thoracic mass, and passes preferentially
20 through blood because of its high conductivity, relative to other body materials. The sense electrodes primarily sense the voltage drop in the blood in the aorta. Because the impedance of the blood in the aorta changes with the-volume of blood flowing through the
25 aorta, the measured voltage drop between the sense electrodes varies with blood flow. Time-varying differences in the sensed voltage, therefore, primarily are caused by blood flow dynamics, rather than respiratory or non-cardiac related physiological
30 effects.

Measuring the impedance along three orthogonal axes enables a three-dimensional impedance field to be computed, which in turn is used to compute a stroke volume. Use of three-dimensional BIA
35 measurements and algorithms provides a degree of

invariance to the precise positioning and orientation
of the sense electrodes.

Methods in accordance with the present
invention overcome the inaccuracies of the gross

5   physiologic models employed in previously known BIA
cardiac methods, by avoiding the simplified algorithms
for the ventricular stroke volume based on whole thorax
BIA measurements. In particular, the methods of the
present invention employ multiple linear regression or

10 other optimization techniques such as adaptive
filtering or neural networks to derive a multi-
parameter algorithm that relates impedance measurements
made in the vicinity of the aorta along three
orthogonal axes to ventricular stroke volume. This

15 multi-parameter algorithm provides an accurate metric
for stroke volume that is substantially invariant to
the position and orientation of the sense electrodes.

In further aspects of the present invention,
apparatus for monitoring a patient's cardiac output may

20 be used to control administration of intravenous fluids
and medication to a patient or to optimize heart rate
for those patients having pacemakers.

Brief Description Of The Drawings

Further features of the invention, its nature

25 and various advantages will be more apparent from the
accompanying drawings and the following detailed
description of the preferred embodiments:

FIGS. 1A and 1B are idealized models of the
volumes upon which previously known bioelectrical

30 impedance algorithms are based;

FIGS. 2A and 2B are a vertical frontal view
of the upper portion of a human body and a front view
of the ascending aorta, the esophagus and the trachea,
respectively;

FIG. 3 shows a first embodiment of the
apparatus of the present invention for endotracheal
use, including three orthogonal pairs of sense
electrodes for making a three-dimensional impedance
5   measurement;

FIG. 4 is a flowchart of a method used in
accordance with the principles cf the present invention
to derive a multi-parameter algorithm relating
impedance measurements to ventricular stroke volume;

10   FIG. 5 shows a second embodiment cf the
apparatus of the present invention for esophageal use;

FIGS. 6A and 6B are, respectively, schematic
diagrams showing systems for administering fluids or
medication to a patient and for controlling heart rate
15   for patients having pacemakers, respectively,
constructed in accordance with the principles of the
present invention; and

FIG. 7 is a graph showing results obtained
using apparatus and methods in accordance with the
20   present invention in animals.

Detailed Description Of The Invention

The present invention relates generally to
BIA apparatus for use in measuring cardiac output in
patients, including critically ill and heart-diseased
25   patients, as well as patients undergoing elective
surgery. The apparatus and methods of the present
invention overcome drawbacks observed in previously
known attempts to use whole body or large volume
thoracic BIA measurements to measure cardiac output, by
30   providing apparatus and methods that are not based upon
the gross modeling of physiological events implicit in
such previously known BIA measurement techniques.
Additionally, the BIA measurement apparatus and methods
of the present invention are easier to use and provide

greater invariance to placement and orientation of
electrodes than previously known BIA measurement
apparatus and techniques.

     In a first embodiment of the apparatus and
5 methods of the present invention, three orthogonal
pairs of sense electrodes disposed on an endotracheal
tube are used to measure a three-dimensional impedance
field. The electrodes are placed in contact with a
patient's airway (e.g., trachea and/or bronchus) in
10 close relation to the aorta, so that changes in
bioelectrical impedance can be closely correlated to
cardiac events, without significant effects due to non-
cardiac physiologic events. Excitation AC current is
injected into the body between a current electrode and
15 a ground electrode disposed along the endotracheal
tube. A second embodiment uses a similar arrangement
of electrodes disposed along an esophageal tube or
esophageal stethoscope.

     In both embodiments, a three-dimensional
20 bioelectrical impedance field is computed from the
voltage drop measured between the pairs of sense
electrodes. The bioelectrical impedance is in turn
correlated to blood flow through the ascending aorta.
Because the ascending aorta has no other branches other
25 than the coronary arteries, blood flow through the
ascending aorta may be closely correlated to cardiac
output.

     It is known in the medical literature that
BIA measurements of cardiac output in general show good
30 correlation for normal patients and hemodynamically
stable patients, but much poorer correlation for
critically ill patients, and patients in heart failure,
as discussed in the above-mentioned Detemeter paper.
It has been discovered that the reason for this poorer
35 correlation in the latter cases is that the theoretical

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basis underlying the use of whole body or large volume
thoracic measurements may be incorrect.

While the present invention finds ready
application in monitoring cardiac output in critically-
5   ill and heart diseased patients, it may be
advantageously used for all intubated patients,
including pediatric cases. For example, apparatus
constructed in accordance with the present invention
may be readily employed in asymptomatic patients
10   undergoing elective surgery. As many as 95% of post-
operative deaths in the latter population result from
hemodynamic failure.

Previously known techniques derive the
equation for ventricular stroke volume ("SV") from the
15   assumption that a time-varying column of blood, in
parallel with the other conducting material in the
thorax, changes from zero to the full stroke volume
during the cardiac cycle. The column of blood is
assumed to be the length between the electrodes used to
20   obtain the BIA measurements, with effects on the BIA
measurements due to respiration accounted for, for
example, as discussed in the aforementioned U.S. Patent
No. 4,870,578.

FIG. 1A illustrates a typical previously
25   known BIA algorithm. Cardiac output is estimated from
the bioelectrical impedance measurement $I(t)$, where it
is assumed that changes in the bioelectrical impedance
coincidental with the heart electrical activity (as
represented by an electrocardiograph output) are the
30   result of blood flow $F(t)$. A transfer function $T(t)$ is
then based upon empirical formulae derived from
measurements taken on healthy, hemodynamically stable
subjects. The bioelectrical impedance $I(t)$ is then
computed as:

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$$I(t) = F(T)*T(t) \tag{1}$$

It has been determined, however, that the
foregoing assumption regarding the column of blood
ignores the branched, multiple and complex paths
5   present in the arterial system. Moreover, the
distribution of blood and fluids between different
physiologic "compartments" in the idealized thoracic or
whole body model and body regions are different in
normal and critically ill patients.
10   FIG. 1B illustrates that the thoracic
approach to BIA measurement must account for transfer
functions appropriate to each of the multiple blood
flow paths through the volume, so that bioelectrical
impedance I(t) should be computed as:

15                  $$I(t) = \sum F_i(t)*T_i(t)*W_i \tag{2}$$

where W_i are weights corresponding to *a priori*
knowledge of the relative distribution of flow through
the various segments of the volume, e.g., the aorta,
20   and arterial segments and other fluid chambers.
Moreover, the weights W_i may be different for different
patients, may be different for chronically ill as
opposed to healthy subjects, and may be variable even
within a given patient, e.g., due to changes in heart
25   rate.
It has been discovered, however, that
equation (1) may be used accurately for any patient
provided that the transfer function T(t) is correlated
to measured blood flow (e.g., using a flow meter) so
30   that the effect of the distribution weights W_i can be
essentially eliminated. Accordingly, applicant has
concluded that BIA measurements should be taken very

close to a major blood vessel or artery, so that
between the electrodes of the BIA apparatus there are
few or no branching vessels or adjacent vessels. The
present invention therefore involves the use of BIA
5   measurements in the vicinity of blood vessels meeting
the foregoing requirements, especially the ascending
aorta.

          Referring to FIG. 2A, the upper portion of a
human body 100 is shown in outline with the
10   corresponding locations of aorta 101, esophagus 102,
trachea 103, and bronchi 104a and 104b (all shown in
dotted line) and suprasternal notch 105. These
internal vessels and organs are more clearly depicted
in FIG. 2B. With reference to FIGS. 2A and 2B, the
15   outflow tract of the left ventricle of the heart is
ascending aorta 101a. Segment 101b of the artery (the
aortic arch) passes in front of right bronchus 104a, in
front of trachea 103 and then arches behind left
bronchus 104b into the descending aorta 101c, which
20   leads towards the lower part of the body.

          Since ascending aorta 101a passes in close
proximity to bronchi 104a and 104b and trachea 103, it
is possible to obtain a BIA measurement across
ascending aorta 101a, with relatively little
25   intervening tissue, by positioning sense electrodes at
this location. AC voltage applied to the patient's
tissue by current electrodes, positioned in proximity
to the patient's ascending aorta, causes an AC current
to flow in the patient's tissue. The measured voltage
30   difference between the sense electrodes is then
employed to compute tissue impedance. Because the
first branches from the aorta (other than the coronary
arteries) are from aortic arch 101b, downstream of the
measurement location, the measurement of blood flow

from ascending aorta 101a accurately measures the
volume of blood ejected from the left ventricle.

In previously-known BIA measurement systems,
the orientation of electrodes on or near the aorta are
5   expected to have a large effect on both the magnitude
and the type of signal produced by the sense
electrodes. For example, experiments using a rigid
plastic pipe have shown that electrodes placed
orthogonal to flow generate a signal that varies
10 linearly with flow in the pipe, while electrodes placed
parallel to flow detect changes in flow and the
presence or absence of turbulence. As will of course
be appreciated, the intra-thoracic aorta is not a
straight rigid pipe. As can be seen in FIGS. 2A
15 and 2B, the aorta in the region of interest makes a
complex (i.e. more than 180 degree) turn. Since the
orientation of the electrodes with respect to flow is
important, and it is difficult to identify the exact
orientation of an electrode with respect to the aorta,
20 previously-known BIA methods are believed not to
produce reliable or reproducible results.

In accordance with the principles of the
present invention, the impact of electrode orientation
—   on BIA measurement -apparatus and methods -is reduced by
25 measuring a three-dimensional impedance field, and
using algorithms that relate the three-dimensional
impedance field to cardiac output. Measurement of the
three-dimensional impedance field is accomplished using
three orthogonal pairs of sense electrodes positioned
30 near the aorta, as discussed in detail hereinbelow.

It will be understood by one skilled in the
art that as used herein, the three orthogonal pairs of
sense electrodes are substantially orthogonal, but need
not be precisely orthogonal in a mathematical sense.
35 Considerable variation from a precise orthogonal

relationship between the pairs of the electrodes is
acceptable, and will provide clinically useful results.

   Referring now to FIG. 3, a first embodiment
of a BIA measurement device built in accordance with
5 the principles of the present invention is described.
Measurement apparatus 10 includes endotracheal tube 12,
including inflatable cuff 16 disposed near a distal end
of endotracheal tube 12, and a lumen for ventilating
the patient. Additionally, endotracheal tube 12
10 includes shaft electrode 14, which serves as an
electrical ground electrode for measurement
apparatus 10. Sense electrodes 18a-18e are mounted on
inflatable cuff 16 to form three orthogonal pairs of
sense electrodes. Additionally, current electrode 20
15 is mounted on inflatable cuff 16.

   All of the electrodes, including shaft
electrode 14, sense electrodes 18a-18e, and current
electrode 20 are connected via cable 22 and
connector 24 to impedance recorder 110. Cable 22 may
20 comprise a shielded cable containing multiple
conductors or a ribbon cable, and may be disposed
within endotracheal tube 12, parallel to endotracheal
tube 12, or wrapped around endotracheal tube 12.
Measurement apparatus 10 also includes digital
25 sampler 112, and computer 114.

   Sense electrodes 18a-18e, current
electrode 20, and shaft electrode 14 are preferably
composed of a conductive silver ink, printed or silk
screened onto a polyethylene backing. Sense
30 electrodes 18a-18e and current electrode 20 are
preferably each 6mm square, while shaft electrode 14
preferably comprises a 15mm wide band disposed on the
shaft of endotracheal tube 12. All of the electrodes
have a smooth surface, and are atraumatic to the
35 tracheal mucosa.

The interior of inflatable cuff 16 is in
fluid communication with insufflation port 28 via
lumen 30 of endotracheal tube 12. When inflated,
inflatable cuff 16 retains endotracheal tube 12 in
5   position within the patient's airway, and provides a
substantially airtight seal, thereby preventing
inadvertent movement of the endotracheal tube.
Inflatable cuff 16 also urges sense electrodes 18a-18e
and current electrode 20 into contact with the interior
10   wall of the trachea. Inflatable cuff 16 may be
inflated using conventional inflation means (i.e., a
gas filled syringe) connected to insufflation port 28
via lumen 30. Alternatively, inflatable cuff 16 may be
replaced by another suitable type of expandable member
15   for urging the sense electrodes against the interior
wall of the patient's airway, such as an expanding
mandrel, or other mechanical arrangement.
        The proximal end of endotracheal tube 12,
i.e., the end manipulated by the clinician, may include
20   reference marks 32 on the circumference of the tube
that reflect the circumferential orientation of
endotracheal tube 12 within the patient's trachea. The
reference marks may be used to assist in placement of
the sense electrodes and current electrode.—
25   Endotracheal tube 12 may also include a depth marker
(not shown) to assist in determining the proper depth
of placement.
        In use, endotracheal tube 12 is inserted into
the patient through the oral or nasal cavity, past the
30   epiglottis and into the trachea in accordance with
standard intubation practice. Alternatively, access to
the trachea may be had through a surgical opening at
the suprasternal notch by conventional tracheotomy.
        Endotracheal tube 12 is positioned so that
35   inflatable cuff 16 is located near the aorta, and

inflatable cuff 16 is inflated, causing sense
electrodes 18a-18e and current electrode 20 to contact
the tracheal mucosa. Shaft electrode 14 contacts the
oral mucosa several centimeters above the aorta, and
5   serves as a ground electrode.

An alternating current, preferably a
sinusoidal current having a predetermined frequency, is
applied between current electrode 20 and shaft
electrode 14 by impedance recorder 110. The
10   alternating current preferably has an amplitude of
approximately 2 mA, and a frequency in the range
of 5 KHz to 1 MHZ, typically 100 KHz. It should be
noted that at frequencies below 1 KHz, cardiac
stimulation can occur.

15   Signals indicative of a drop in voltage
between the two electrodes of each of the orthogonal
pairs of electrodes are received at impedance
recorder 110. The first orthogonal pair of electrodes
comprises sense electrodes 18a and 18b, the second
20   orthogonal pair of electrodes comprises sense
electrodes 18c and 18d, and the third orthogonal pair
comprises sense electrodes 18a and 18e.

These impedance signals are digitally sampled
at fixed intervals, preferably approximately 400 —
25   samples per second, by digital sampler 112. The
digital samples are provided to computer 114, which may
record the samples, display graphs of the samples,
apply algorithms in accordance with the principles of
the present invention to determine cardiac output, and
30   apply any additional algorithms to the digital samples.

Impedance recorder 110, digital sampler, and
computer 112 may also record and digitize
electrocardiogram (ECG) signals for use in determining
cardiac output. Various parameters related to the ECG

signal may be used in the algorithms described hereinbelow.

As will be described hereinbelow, numerous algorithms may be applied to determine ventricular stroke volume (SV) based on impedance measurements. SV may be continuously computed and updated on a display (not shown) associated with computer 114, and may consist of a running average of the current and a user-selectable number of preceding cardiac cycles. Cardiac output may then be computed as the product of the instantaneous average SV and the heart rate, and also displayed numerically.

The three-dimensional impedance field is determined by combining the measurements from the three orthogonal pairs of sense electrodes. Hereinafter, the impedance signal will be referred to as Z, with Z_x, Z_y, and Z_z being the impedance signals along each of the three orthogonal axes. Z_0 will be used to refer to the steady state impedance, with Z_{0x}, Z_{0y}, and Z_{0z} being the steady state impedance along each of the three orthogonal axes. A signal corresponding to the difference between the impedance and the mean of the impedance signal over time will be referred to hereinafter as DZ, while signals representing this difference along each of the three axes will be referred to hereinafter as DZ_x, DZ_y, and DZ_z, respectively. These signals are combined according to one of the algorithms detailed hereinbelow to provide a metric for cardiac output. The three-dimensional impedance field (DZ_{3D}) may be calculated from these measurements as:

$$DZ_{3D} = \sqrt{DZ_x^2 + DZ_y^2 + DZ_z^2} \qquad (3)$$

While there are numerous previously known
methods for computing cardiac output from a measurement
of impedance, and many different parameters that assist
in correlating impedance and stroke volume (SV), many
5   of these equations do not properly account for
positional artifacts.

For example, SV may be calculated according
to the Kubicek equation, equation (4), as:

$$SV_K = \rho(L/Z_0)^2 * DZ_{Max}(RVET) \qquad (4)$$

10 where:

SV_k =   ventricular stroke volume as computed by
the Kubicek algorithm, ml;

ρ =   resistivity of blood (in normal
patients, about 150-200 ohm-cm/s, and
15   can be corrected for each patient as a
function of hematocrit);

L =   distance between the sense electrodes,
typically known as a manufacturing
parameter, cm;

20 Z_0 =   steady state impedance between the sense
electrodes, ohms;

DZ_{Max} =   the maximum magnitude of the change of
impedance (DZ); and

RVET =   right ventricular ejection time.

25   As given in equation (4), the Kubicek
equation is applied to a single pair of sense
electrodes, that measure only a single impedance
signal. As a result, the calculated stroke volume
given by the Kubicek equation is highly position and
30 orientation dependent.

The Bernstein-Sramek formula relating SV to
impedance has a basic form similar to the form of the

Kubicek equation. The Bernstein-Sramek formula may be
expressed as:

$$SV_{BS} = \frac{V_{EPT}}{Z_0} \times \frac{dZ}{dt}MAX \times (VET \tag{5}$$

where:

5   SV_{BS} =   Ventricular stroke volume, calculated by
                            the Bernstein-Sramek formula, ml.

         V_{EPT} =   volume of the electrically participating
                            tissue, which varies according to
                            height, weight, and gender of the
10   patient. V_{EPT} may be calculated as:
                                $V_{EPT} = \delta * (0.17H)^3/4.25$
                            where H is the height of the patient (in
                            cm), and δ is a scaling factor, relating
                            height, weight, ideal weight, and
15   relative blood volume index. It should
                            be noted that this formulation of the
                            Bernstein-Sramek formula assumes ρ, the
                            blood resistivity to be a constant.

         Z_0 =   steady state impedance between the sense
20   electrodes, ohms.

         $\frac{dZ}{dt}MAX$ =   the maximum magnitude of the change of
                            impedance with time.

         VET   =   ventricular ejection time.

         As with the Kubicek algorithm described
25 above, the formulation of the Bernstein-Sramek
    algorithm given in equation (5) is expressed in terms
    of a single impedance value. The results of the
    Bernstein-Sramek algorithm also are highly dependent on
    the position and orientation of the sense electrodes.

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To overcome these drawbacks of previously-known formulas, a new formulation of the Kubicek formula (equation (4)) was derived, which uses a Simpsons' integral from the start of ejection to the
5 end of ejection. This new formulation may be expressed as:

$$SV = m \times \int_{BET}^{EET} DZ\, dt \qquad (6)$$

where:

SV   =   Ventricular stroke volume, calculated
10   using equation (6).

m   =   An empirically derived parameter giving
         the slope of the relationship between
         the stroke volume calculated in ohms*sec
         and true stroke volume in ml. The units
15   of m are (ml)/(ohms*sec). The effects
         of inter-electrode distances, as well as
         other calibration data are lumped into
         the parameter m.

DZ   =   The change in impedance from the mean.
20   BET =   The beginning of ejection time.

EET =   The end of ejection time.

To reduce this dependency of the parameter m in equation (6) on the orientation and positioning of the sense electrodes, a three-dimensional version of
25 the algorithm has been formulated as:

$$SV_{S3D} = \left[\left(m_x \times \int_{BET}^{EET} DZ_x\, dt \right)^2 + \left(m_y \times \int_{BET}^{EET} DZ_y\, dt \right)^2 + \left(m_z \times \int_{BET}^{EET} DZ_z\, dt \right)^2 \right]^{\frac{1}{2}} \qquad (7)$$

where:

SV_{S3D}	=	Ventricular stroke volume, computed using equation (7).
m_x, m_y, and m_z	=	Empirically determined scaling factors along each of three orthogonal axes.
DZ_x, DZ_y, and DZ_z	=	The change in impedance from the mean along each of three orthogonal axes, as measured by the apparatus of the present invention.
BET	=	The beginning of ejection time.
EET	=	The end of ejection time.

The empirically determined scaling factors m_x, m_y, and m_z recognize the fact that no simple physical model can adequately relate the impedance signal and cardiac output. Each of the three individual x, y, and z terms in the three-dimensional formulation of the equation (7) may be used separately as an indicator of stroke volume, but equation (7) normalizes the effect of sense electrode position and orientation.

In accordance with the principles of the present invention, a three-dimensional equation based on the maximum of the first derivative of the change in impedance also may be derived:

$$SV_{Diff-3D} = \left[\left(m_{xD} \frac{dDZ_x}{dt} MAX \right)^2 + \left(m_{yD} \frac{dDZ_y}{dt} MAX \right)^2 + \left(m_{zD} \frac{dDZ_z}{dt} MAX \right)^2 \right]^{\frac{1}{2}} \quad (8)$$

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where:

$SV_{Diff-3D}$ = Ventricular stroke volume, computed using equation (8).

m_{xD}, m_{yD}, and m_{zD} = Empirically derived scaling factors related to the change in flow over time.

DZ_x, DZ_y, and DZ_z = change in impedance from the mean along each of three orthogonal axes.

Equation (8) provides a differential term, that represents three-dimensional changes in flow velocity with time. As before, the three empirically derived m parameters recognize the lack of a simple physical model relating impedance with cardiac output. Once again, each of the three individual terms for each of the axes may be useful in computing the ventricular stroke volume.

Other parameters also may be useful for computing stroke volume from an impedance signal. For example, it is possible to determine whether there is turbulence in the flow from the timing of the impedance signal. This information is useful, since the presence of turbulence indicates a high flow rate, with velocities exceeding the Reynolds number. Conversely, the absence of turbulence indicates a lower flow rate.

When turbulence is present, the duration of high points in the impedance signal is longer, and the signal takes longer to decay. These characteristics can be measured using two turbulence-related parameters. The first of these, τ_{85}, represents the time spent at 85% or more of peak flow. The time spent at 85% or more of peak amplitude is longer in beats with turbulent flows. The second parameter, τ_d

represents the decay time, and measures the time
between 95% of the peak amplitude of the signal on the
up-slope, and 60% of the peak amplitude on the
downslope.

5   In addition to the above-listed formulas and
parameters, many other parameters may be of use in
correlating impedance with cardiac output. For
example, the signals I_1, I_2, I_3, I_4, and I_5, which
represent the potential between each of the five sense

10   electrodes 18a-18e and ground, may be useful. Other
potentially useful parameters include ejection time,
time to peak of the first derivative of the DZ signal,
and other timing parameters derived from the impedance
signal. Signals relating to an ECG, such as the timing

15   of the R wave (i.e., the maximum peak of the ECG
signal) may also be used.

          A measurement of arterial pressure may also
be used to improve the accuracy of the multiparameter
model of the present invention. If arterial pressure

20   is included as a parameter in the multiparameter model
described hereinbelow, correlations may be improved,
and error may be reduced.

          Animal studies using pigs have shown that
there are correlations between the impedance-signal

25   (Z), the change in impedance from the mean (DZ), the

integral of the signal ($\int_{BET}^{EET} DZ\,dt$), and the maximum

differential ($\frac{dDZ}{dt}$ MAX) of the signal and the true

cardiac output. Three-dimensional forms of these
signals, provided by the apparatus and methods of the

30   present invention, have a degree of invariance to

position and orientation of the sense electrodes that
are used to take the measurements. Additional
parameters, such as the turbulence parameters T_{85} and
T_d, as well as the other parameters discussed above are
5   also useful.

          Initial animal studies have shown that none
of the foregoing individual correlations are
sufficiently robust to provide an invariant
relationship between impedance and true cardiac output
10   across individual animals, without calibration, when
used with the three-dimensional impedance measurement
device of the present invention. In accordance with
the principles of the present invention, it is
therefore desirable to use optimization techniques,
15   such as linear regression, adaptive filtering, or
neural networks to generate an algorithm that uses a
combination of the equations and parameters described
above to correlate impedance as measured along three
orthogonal axes with cardiac output.

20   In accordance with the principles of the
present invention, an algorithm may be generated using
stepwise multiple linear regression with all of the
equations and parameters that individually correlate
with stroke volume. The algorithm generated by this
25   technique has the form:

$$SV = C + \sum w_i \times f_i \qquad\qquad (9)$$

where:
        SV   =   ventricular stroke volume;
        C   =   a constant value determined by the
30   linear regression;

w_i = weights assigned to the equations and/or parameters by the linear regression; and

f_i = selected ones of the equations and/or parameters for correlating impedance with ventricular stroke volume, as discussed hereinabove.

Referring to FIG. 4, a flowchart of the method of selecting independent variables for the stepwise multiple linear regression process used to derive an algorithm is discussed. At step 201, data are collected for multiple subjects under a variety of occlusion conditions. The data include impedance measurements along each of three axes, as discussed hereinabove, the I_1 - I_5 measurements, and other parameters for the algorithms described hereinabove. Additionally, data are collected on the actual stroke volume, using, for example, a transit time flow probe.

At step 202, the data are used with the various algorithms to compute a predicted stroke volume for each of the algorithms. These results, as well as the measurements of impedance, I_1 - I_5, and other parameters that correlate with stroke volume are used as independent variables in the stepwise multiple linear regression.

At step 203, the stepwise multiple linear regression equation begins with no independent variables. At step 204, the independent variable with the highest F test is added to the equation, in a manner similar to forward selection.

At step 205, backwards elimination is performed on the set of independent variables to test for redundancy. If a redundant variable is detected, it is eliminated.

Finally, at step 206, the forward selection (step 204) and backward elimination (step 205) are repeated until all of the independent variables have been added to the equation, or have been eliminated

5 from the equation.

This technique combines the best characteristics of forward selection and backward elimination. The first variable added is the strongest predictor of the dependent variable and redundant

10 independent variables are eliminated. This method is used to determine which parameters will be included in the final multi-parameter algorithm for stroke volume.

Once the final multi-parameter algorithm for stroke volume is determined, it may be used with the

15 apparatus of the present invention to monitor cardiac output by programming computer 114 to continuously apply the final multi-parameter algorithm to compute the stroke volume from the data collected by the sense electrodes. Cardiac output may then be computed as the

20 product of the instantaneous average stroke volume and the heart rate.

Other optimization techniques also may be used to derive a multi-parameter algorithm for stroke volume. Some of the techniques which were tried as

25 alternatives to stepwise multiple linear regression included use of a multilayer perceptron neural network, and an algorithm that used fuzzy logic to determine signal quality, and to select a multi-parameter algorithm derived through multiple linear regression

30 according to the available high quality signals. These techniques provided results that were similar to the results obtained using the multi-parameter algorithm derived using the stepwise multiple linear regression method described hereinabove.

        Referring now to FIG. 5, an alternative
embodiment of the three-dimensional impedance
measurement device of the present invention is
described, which is designed for esophageal use, rather
5   than tracheal use. This embodiment may be
advantageously used, for example, in previously
intubated patients. Extubating a patient having an
endotracheal tube to replace it with a tube having
sensors for measuring impedance in accordance with the
10 principles of the present invention may involve an
unacceptable degree of discomfort or risk to the
patient. By using the embodiment shown in FIG. 5,
however, in which a set of electrodes is added to an
esophageal stethoscope, impedance measurements may be
15 used to compute cardiac output in previously intubated
patients without disturbing an endotracheal tube that
is already in place.
        Measurement apparatus 50 comprises an
esophageal stethoscope, including tube 53, stethoscope
20 balloon 54 disposed at a distal end of tube 53, and
thermister 56. Shaft electrode 58, which serves as an
electrical ground electrode for measurement
apparatus 50, is mounted on tube 53. Inflatable
cuff 60 also is mounted on tube 53, and sense
25 electrodes 62a-62e are mounted on inflatable cuff 60 to
form three orthogonal pairs of sense electrodes.
Additionally, current electrode 64 is mounted on
inflatable cuff 60.
        All of the electrodes, including shaft
30 electrode 58, sense electrodes 62a-62e, and current
electrode 64 are connected via cable 66 and
connector 68 to impedance recorder 110. Cable 66 may
comprise a shielded cable containing multiple
conductors or a ribbon cable, and may be disposed
35 within tube 53, parallel to tube 53, or wrapped around

tube 53. Measurement apparatus 50 also includes
digital sampler 112, and computer 114.

As in the embodiment of FIG. 3, sense
electrodes 62a-62e, current electrode 64, and shaft
5   electrode 58 preferably are composed of a conductive
silver ink, printed or silk screened onto a
polyethylene backing. Sense electrodes 62a-62e and
current electrode 64 preferably are each 6mm square,
while shaft electrode 58 preferably comprises a 15mm
10 wide band. It will be understood by one skilled in the
relevant arts that other dimensions may be used, and
that the size of inflatable cuff 60 and the sizes and
spacing of the electrodes may be larger in the
esophageal embodiment than in the endotracheal
15 embodiment described hereinabove, due to the larger
diameter of the esophagus.

The interior of inflatable cuff 60 is in
fluid communication with insufflation port 70 via
lumen 72. When inflated, inflatable cuff 60 retains
20 the esophageal stethoscope in position within the
patient's esophagus, thereby preventing inadvertent
movement. Inflatable cuff 60 also urges sense
electrodes 62a-62e and current electrode 64 into
contact with the interior wall of the esophagus.
25 Inflatable cuff 60 may be inflated using conventional
inflation means (i.e., a gas filled syringe) connected
to insufflation port 70 via lumen 72. Alternatively,
inflatable cuff 60 may be replaced by another suitable
type of expandable member for urging the electrodes
30 against the interior wall of the patient's esophagus,
such as an expanding mandrel, or other mechanical
arrangement.

In addition to measuring impedance signals
through electrodes, the esophageal stethoscope of
35 measurement apparatus 50 may be used for ascultation

and temperature measurements. To accommodate use of
these functions, measurement apparatus 50 includes
stethoscope hookup 74, and thermister lead 76.
Preferably, stethoscope hookup 74 and thermister

5   lead 76 may be connected to standard recording
equipment.

In use, tube 53 is inserted through the mouth
into a patient's esophagus, and positioned so that
inflatable cuff 60 is located near the aorta.

10   Inflatable cuff 60 is then inflated, causing sense
electrodes 62a-62e and current electrode 64 to contact
the interior wall of the patient's esophagus. Shaft
electrode 58 contacts the esophagus several centimeters
above the aorta, and serves as a ground electrode.

15   An alternating current, preferably a
sinusoidal current having a predetermined frequency, is
applied between current electrode 64 and shaft
electrode 58 by impedance recorder 110. The
alternating current preferably has an amplitude of

20   approximately 2 mA, and a frequency in the range of 5
KHz to 1 MHz, typically 100 KHz.

As for the endotracheal embodiment discussed
hereinabove, signals indicative of a drop in voltage
- -between the two electrodes of each of the orthogonal

25   pairs of electrodes are received at impedance recorder
110. The first orthogonal pair of electrodes comprises
sense electrodes 62a and 62b, the second orthogonal
pair of electrodes comprises sense electrodes 62c
and 62d, and the third orthogonal pair comprises sense

30   electrodes 62a and 62e.

These impedance signals are digitally sampled
at fixed intervals, preferably approximately 400
samples per second, by digital sampler 112. The
digital samples are provided to computer 114, which may

35   record the samples, display graphs of the samples,

apply algorithms in accordance with the principles of the present invention to determine cardiac output, or apply any other algorithms to the digital samples.

A multi-parameter algorithm similar to that
5   discussed hereinabove computes the stroke volume based on impedance measurements. The algorithm may be derived using stepwise multiple linear regression, in the manner described hereinabove.

Further alternative embodiments of the
10 present invention also may include additional sensors to enable other types of quantitative analysis. For example, diodes suitable for employing blood oximetry techniques based on near infrared light absorption also may be disposed on the endotracheal tube to measure
15 blood oxygen saturation levels. In particular, multiple light emitting diodes, including one or more red-light and infrared emitting diodes, may be disposed on the endotracheal tube, on the inflatable cuff or member, or both, for obtaining blood oxygen saturation
20 measurements using transreflectance oximetry techniques, as described, for example, in U.S. Patent No. 5,099,842, the entirety of which is incorporated herein by reference.

Referring now to FIG. 6A, use of the
25 apparatus of the present invention is described as a controller for the administration of fluids, or of medication, such as dobutamine, dopamine, epinephrine, norepinephrine, nitroprusside, or other substances for medical management of hemodynamics. In FIG. 6A,
30 cardiac output is measured by apparatus 17C, which may be either of the foregoing embodiments, and includes tube 171 disposed in patient 190, either in the trachea or the esophagus. Apparatus 170 is used to monitor hemodynamic status and as a metric to control the
35 administration of fluids or medication intravenously

via lumen 172 coupled to fluid supply system 173.
Computer 174, which may be the same computer that
computes cardiac output from the impedance values
output by impedance recorder 110 and digital

5   sampler 112, controls fluid supply system 172. The
apparatus of FIG. 6A provides a closed-loop system
wherein the amount of fluid or other medication
injected into the patient is controlled by the cardiac
output computed as described hereinabove.

10   Referring now to FIG. 6B, use of the
apparatus of the present is described as a controller
for pacemaker 180. Generally, it is desirable to
maximize cardiac output for the lowest possible heart
rate, since the lower the heart rate, the lower the

15   myocardial oxygen consumption. In the arrangement of
FIG. 6B, cardiac output is measured by apparatus 181,
which may be any of the foregoing embodiments, and
includes tube 182 disposed in patient 190, either in
the trachea or the esophagus. The output of

20   apparatus 181 is used, in conjunction with
computer 183, as a metric to control the setting of
pacemaker 180 as described hereinafter.

             A baseline cardiac output measurement is
first obtained and then the heart-rate is reduced by a

25   predetermined amount, e.g., two beats/min, while the
cardiac output is continuously monitored by
apparatus 181. As long as the cardiac output increases
or remains unchanged, the heart rate is periodically
further lowered by the predetermined amount, for

30   example, by 2 beats/min every 15 minutes. The process
of reducing heart rate while monitoring cardiac output
is continued until either a minimum desired heart rate
is obtained or the cardiac output measured by
apparatus 181 begins to decrease. If the cardiac

output is determined to have decreased, the heart rate
is returned to the preceding higher rate.

Example

When the above described stepwise multiple
5   linear regression technique was applied to data taken
from ten pigs, using the apparatus of the present
invention, the resulting multi-parameter algorithm
contained weighted terms for 53 parameters, including
I_1, I_2, I_3, I_4, I_5, Z_{0x}, Z_{0y}, Z_{0z}, equation (7), each of
10 the x, y, and z terms of equation (7), equation (8),
and each of the x, y, and z terms of the equation (8),
and other parameters relating to timing, and to the ECG
signal. The resulting algorithm was able to compute a
stroke volume from the various impedance measurements
15 while maintaining a high degree of invariance to exact
positioning and rotation of the sense electrodes, and
an ability to be used across individuals without need
for recalibration for each individual in which the
device was used.
20   Table 1 shows the list of independent
variables (i.e., parameters) in the equation that
resulted from stepwise linear regression, and the
weight assigned to each of the parameters.- In
accordance with equation (9), described hereinabove, to
25 compute stroke volume, the weight of each parameter is
multiplied by the value of the parameter, and the
results for all weights and parameters are summed. A
constant value is then added to the sum to provide the
metric for stroke volume. For the equation with
30 weights and parameters shown in Table 1, the constant,
$C = 55.935091$.

Table 1 - Weights and Parameters for Example Algorithm

	Weight	Parameter	Description
1	-3.4C7786	Z_{Ox}	
2	-2.167552	Z_{Oy}	
3	-1.178316	Z_{Oz}	
4	-3.452352	I_1	
5	2.116957	I_2	
6	1.038714	I_3	
7	-1.217662	I_4	
8	0.267879	I_5	
9	-488.79698	SV_{S3D}	Equation (7)
10	2.734155	$SV_{Diff-3D}$	Equation (8)
11	0.560702	$SV_{Diff-3D}$ (near R wave)	Equation (8) using maximum of the first derivative of DZ within 100 milliseconds of the R wave.
12	-0.082627	$INFLEC_x$	Milliseconds between the max and the min of the first derivative of DZ_x.
13	-733.61	$CONCA_x$	Area in ohms/sec bounded by the DZ_x trace and the line passing through the 0.95*max DZ_x rise point and the 0.40*max DZ_x decay point.
14	-0.069485	$BIN1DZ_x$	Number of samples in the band of 20% of the max DZ_x trace.

15	-0.004758	DECAY$_x$	Milliseconds between the 0.85*max DZ$_x$ rise point and the C.40*max DZ$_x$ decay point (similar to τ_d).
16	739.2874	Z$_x$VOL	Integral of the DZ$_x$ trace (i.e. the x term of equation (7)).
17	-13.339431	MXDZDT$_x$	Max of the first derivative cf DZ$_x$ (i.e. the x term cf equation (8)).
18	-0.084653	MXDZDT$_x$S	Milliseconds between the R wave and the max of the first derivative of DZ$_x$.
19	6.292195	MXDZDTW$_x$	Max of the first derivative of DZ$_x$ within 100 milliseconds of the R wave.
20	-0.036876	MXDZDTW$_x$S	Milliseconds between the R wave and the max of the first derivative of DZ$_x$, within 100 milliseconds of the R wave.
21	7.879514	MNDZDT$_x$	Min of the first derivative of DZ$_x$.
22	0.078928	MNDZDT$_x$E	Milliseconds between the R wave and the min cf the first derivative of DZ$_x$.
23	-3.040184	MNDZDTW$_x$	Min of the first derivative of DZ$_x$ within 350 milliseconds of the R wave.

24	-0.038439	MNDZDTW$_x$E	Milliseconds between the R wave and the min of the first derivative of DZ$_x$, within 350 milliseconds of the R wave.
25	103.84647	MAXDZ$_x$	Max of the DZ$_x$ trace.
26	-0.32096	INFLEC$_y$	See INFLEC$_x$, but for DZ$_y$.
27	1333.1547	CONCA$_y$	See CONCA$_x$, but for DZ$_y$.
28	0.297539	BIN2DZ$_y$	Number of samples in the band bounded by 20% and 40% of max DZy.
29	0.067632	DECAY$_y$	See DECAY$_x$, but for DZ$_y$.
30	578.72077	Z$_y$VOL	See Z$_x$VOL, but for DZ$_y$.
31	-6.133654	MXDZDT$_y$	See MXDZDT$_x$, but for DZ$_y$.
32	-0.324225	MXDZDT$_y$S	See MXDZDT$_x$S, but for DZ$_y$.
33	10.405067	MXDZDTW$_y$	See MXDZDTW$_x$, but for DZ$_y$.
34	-0.223327	MXDZDTW$_y$S	See MXDZDTW$_x$S, but for DZ$_y$.
35	22.520111	MNDZDT$_y$	See MNDZDT$_x$, but for DZ$_y$.
36	0.293328	MNDZDT$_y$E	See MNDZDT$_x$E, but for DZ$_y$.
37	-10.853298	MNDZDTW$_y$	See MNDZDTW$_x$, but for DZ$_y$.
38	0.060624	MNDZDTW$_y$E	See MNDZDTW$_x$E, but for DZ$_y$.
39	13.229832	MXDZ$_y$	Max of the DZ$_y$ trace.
40	-0.219214	INFLEC$_z$	See INFLEC$_x$, but for DZ$_z$.
41	2.146938	CONCA$_z$	See CONCA$_x$, but for DZ$_z$.
42	0.266825	BIN2DZ$_z$	See BIN2DZ$_y$, but for DZ$_z$.
43	0.045675	DECAY$_z$	See DECAY$_x$, but for DZ$_z$.

44	746.7884	Z_zVOL	See Z_xVOL, but for DZ_z.
45	4.463351	$MXDZDT_z$	See $MXDZDT_x$, but for DZ_z.
46	-0.21119	$MXDZDT_zS$	See $MXDZDT_xS$, but for DZ_z.
47	23.561712	$MXDZDTW_z$	See $MXDZDTW_x$, but for DZ_z.
48	-0.126598	$MXDZDTW_zS$	See $MXDZDTW_xS$, but for DZ_z.
49	-2.202599	$MNDZDT_z$	See $MNDZDT_x$, but for DZ_z.
50	0.206271	$MNDZDT_zE$	See $MNDZDT_xE$, but for DZ_z.
51	0.325518	$MNDZDTW_z$	See $MNDZDTW_x$, but for DZ_z.
52	0.007671	$MNDZDTW_zE$	See $MNDZDTW_xE$, but for DZ_z.
53	-203.33016	$MXDZ_z$	Max of the DZ_z trace.

FIG. 7 shows the results of a test of the apparatus and derived algorithm of Table 1 on a group of ten pigs. The axis labeled CO_{ECOM} shows the cardiac output calculated from impedance measurements taken with the apparatus of the present invention by the multi-parameter algorithm with the weights and parameters given in Table 1. The axis labeled CO_{TTFP} shows the cardiac output determined by a transit time flow probe. The data shown in the graph is from 29,657 heart beats recorded during occlusion tests from the ten animals during a 24 hour recording period.

As can be seen, there is a high degree of correlation between the cardiac output as determined by the algorithm, and the cardiac output as measured by a transit time flow probe. Since the cardiovascular system of pigs is commonly used as a model of the human

cardiovascular system, it is expected that an algorithm
having similar or identical independent variables, and
similar weights may be derived using stepwise multiple
linear regression.

5   Although preferred illustrative embodiments
of the invention are described above, it will be
obvious to one skilled in the art that various changes
and modifications may be made therein without departing
from the invention and that the appended claims are
10   intended to cover all such changes and modifications
which fall within the true spirit and scope of the
invention. For example, the shaft electrode and/or the
current electrode could be placed on a separate
inflatable cuff. Additionally, applicant expects that
15   the apparatus and methods of the present invention may
be advantageously applied to animal subjects employed
in clinical studies, as well as humans.

What Is Claimed Is:

1.   Apparatus for computing a metric corresponding to a patient's cardiac output, the apparatus comprising:

a bioelectrical impedance recorder;

a tube having a proximal portion, and a distal portion;

an expandable member disposed on the distal portion;

three orthogonal pairs of sense electrodes disposed on the expandable member and electrically coupled to the bioelectrical impedance recorder;

a current electrode for injecting a current into the patient's thorax; and

a ground electrode;

wherein the three orthogonal pairs of sense electrodes generate signals corresponding to the bioelectrical impedance of blood flow through the aorta and the signals are provided to the bioelectrical impedance recorder.

2.   The apparatus as defined in claim 1 wherein the current electrode is disposed on the expandable member.

3.   The apparatus as defined in claim 1 wherein the ground electrode is disposed on the tube.

4.   The apparatus as defined in claim 1 wherein the expandable member comprises an inflatable cuff, and the apparatus further comprises a lumen for inflating the inflatable cuff.

5.   The apparatus as defined in claim 1 wherein at least one sense electrode belongs to at

least two of the three orthogonal pairs of sense
electrodes.

6.   The apparatus as defined in claim 5
wherein the three orthogonal pairs of sense electrodes
comprise five sense electrodes.

7.   The apparatus as defined in claim 1
wherein the tube is an endotracheal tube, and wherein
the expandable member is adapted to urge the three
orthogonal pairs of sense electrodes into contact with
the patient's tracheal mucosa.

8.   The apparatus as defined in claim 7
wherein the tube is adapted to be inserted in the
trachea of the patient through the mouth, a nasal
passageway, or a tracheotomy port.

9.   The apparatus as defined in claim 1
wherein the tube is an esophageal tube, and wherein the
expandable member is adapted to urge the three
orthogonal pairs of sense electrodes into contact with
an interior of the patient's esophagus.

10.   The apparatus as defined in claim 9
further comprising a stethoscope balloon disposed on
the distal portion, the stethoscope balloon permitting
the apparatus to be used as an esophageal stethoscope.

11.   The apparatus as defined in claim 10
further comprising a thermister disposed in the distal
portion, the thermister providing a signal indicative
of temperature within the esophagus.

12.   The apparatus as defined in claim 1 wherein the apparatus further comprises reference marks on the proximal end of the tube to determine circumferential orientation of the tube.

13.   The apparatus as defined in claim 1 wherein the current electrode is electrically coupled to the impedance recorder, and wherein the impedance recorder injects an alternating current having a predetermined frequency through the current electrode.

14.   The apparatus as defined in claim 1 further comprising a computer coupled to the impedance recorder, the computer receiving a digitized signal generated from the signals corresponding to the bioelectrical impedance of blood flow through the aorta.

15.   The apparatus as defined in claim 14 wherein the computer is programmed to use a multi-parameter algorithm to calculate a metric for ventricular stroke volume from the digitized signal.

16.   The apparatus as defined in claim 15 wherein the computer is further programmed to calculate the metric corresponding to the patient's cardiac output from the metric for ventricular stroke volume.

17.   The apparatus as defined in claim 1 further comprising a fluid administration system for injecting a fluid into the vascular system of the patient, wherein the fluid administration system is responsive to the metric corresponding to the cardiac output.

18.   The apparatus as defined in claim 1 further comprising a drug administration system for injecting a medication into the vascular system of the patient, wherein the drug administration system is responsive to the metric corresponding to the cardiac output.

19.   The apparatus as defined in claim 13 wherein the medication comprises one or more of dobutamine, dopamine, epinephrine, norepinephrine, and nitroprusside.

20.   The apparatus as defined in claim 1 further comprising a pacemaker controlling the heart rate of the patient, wherein the pacemaker is responsive to the metric corresponding to the cardiac output.

21.   A method of measuring the cardiac output of an organism comprising steps of:
        positioning three orthogonal pairs of sense electrodes within the organism in the vicinity of the aorta;
        injecting a current into the thorax of the organism through a current electrode;
        applying a voltage between the current electrode and a ground electrode so that a current flows through the tissues of the organism disposed between the current electrode and the ground electrode; and
        detecting voltages developed across the three orthogonal pairs of sense electrodes caused by the current flowing in the tissues of the organism, the voltages varying in accordance with changes in the bioelectrical impedance of the tissues.

22. The method as defined in claim 21
wherein positioning three orthogonal pairs of sense
electrodes comprises positioning three orthogonal pairs
of sense electrodes within the organism's trachea, so
that the three orthogonal pairs of sense electrodes
contact the organism's tracheal mucosa in a position
near the aorta.

23. The method as defined in claim 21
wherein positioning three orthogonal pairs of sense
electrodes comprises positioning three orthogonal pairs
of sense electrodes within the organism's esophagus, so
that the three orthogonal pairs of sense electrodes
contact an interior surface of the organism's esophagus
at a position near the aorta.

24. The method as defined in claim 21
wherein injecting a current comprises injecting an
alternating current having a predetermined frequency
between the current electrode and the ground electrode.

25. The method as defined in claim 21
wherein the steps of applying a voltage between the
current electrode and the ground electrode and
detecting a voltage developed across the three
orthogonal pairs of sense electrodes are performed
continuously.

26. The method as defined in claim 21
further comprising computing a metric for ventricular
stroke volume from the voltages detected by the three
orthogonal pairs of sense electrodes using a multi-
parameter algorithm.

27.   The method as defined in claim 26
further comprising deriving the multi-parameter
algorithm using a stepwise multiple linear regression
technique.

28.   The method as defined in claim 26
further comprising computing a metric for the cardiac
output of the organism from the metric for ventricular
stroke volume.

29.   The method as defined in claim 21
further comprising steps of:
        providing a fluid administration system for
injecting a fluid intravenously into the organism's
vascular system; and
        periodically actuating the fluid
administration system responsive to the detected
voltage developed across the three orthogonal pairs of
sense electrodes.

30.   The method as defined in claim 21
further comprising steps of:
        providing a drug administration system for
injecting a medication intravenously into the
organism's vascular system; and
        periodically actuating the drug
administration system responsive to the detected
voltage developed across the three orthogonal pairs of
sense electrodes.

31.   The method as defined in claim 21
further comprising steps of:
        providing a pacemaker electrically coupled to
the heart of the organism to control heart rate; and

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adjusting the heart rate responsive to
voltage developed across the three orthogonal pairs of
sense electrodes to optimize cardiac output.

32.   The method as defined in claim 31
wherein the step of adjusting the heart rate comprises
a step of lowering the heart rate to obtain either a
predetermined minimum heart rate or until the cardiac
output is measured to be decreasing.

33.   Apparatus for detecting a three-
dimensional bioimpedance field in the vicinity of a
patient's aorta, the apparatus comprising:
                 a tube having a proximal portion, and a
5   distal portion;
                 an expandable member disposed on the distal
portion;
                 three orthogonal pairs of sense electrodes
disposed on the expandable member;
10   a current electrode for injecting a current
into the patient's thorax; and
                 a ground electrode;
                 wherein the three orthogonal pairs of sense
electrodes generate signals corresponding to the _ _
15   bioelectrical impedance of blood flow through the
aorta.

34.   The apparatus as defined in claim 33
wherein the current electrode is disposed on the
expandable member.

20   35.   The apparatus as defined in claim 33
wherein the ground electrode is disposed on the tube.

36. The apparatus as defined in claim 33 wherein the expandable member comprises an inflatable cuff, and the apparatus further comprises a lumen for inflating the inflatable cuff.

5   37. The apparatus as defined in claim 33 wherein at least one sense electrode belongs to at least two of the three orthogonal pairs of sense electrodes.

38. The apparatus as defined in claim 37
10 wherein the three orthogonal pairs of sense electrodes comprise five sense electrodes.

39. The apparatus as defined in claim 33 wherein the tube is an endotracheal tube, and wherein the expandable member is adapted to urge the three
15 orthogonal pairs of sense electrodes into contact with the patient's tracheal mucosa.

40. The apparatus as defined in claim 39 wherein the tube is adapted to be inserted in the trachea of the patient through the mouth, a nasal
20 passageway, or a tracheotomy port.

41. The apparatus as defined in claim 33 wherein the tube is an esophageal tube, and wherein the expandable member is adapted to urge the three orthogonal pairs of sense electrodes into contact with
25 the interior of the patient's esophagus.

42. The apparatus as defined in claim 41 further comprising a stethoscope balloon disposed on the distal portion, the stethoscope balloon permitting the apparatus to be used as an esophageal stethoscope.

43.   The apparatus as defined in claim 38
further comprising a thermister disposed in the distal
portion, the thermister providing a signal indicative
of temperature within the esophagus.

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$$F(t) \longrightarrow \boxed{T(t)} \longrightarrow I(t)$$

FIG. 1A

$$F_1(t) \longrightarrow \boxed{T_1(t)} \quad W_1$$

$$F_2(t) \longrightarrow \boxed{T_2(t)} \quad W_2$$

$$\vdots$$

$$F_N(t) \longrightarrow \boxed{T_N(t)} \quad W_N$$

$$\longrightarrow \boxed{\Sigma} \longrightarrow I(t)$$

FIG. 1B

FIG. 2A

FIG. 2B

FIG. 3

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                                                      ___ 201
                 ┌─────────────────────┐
                 │                     │
                 │    Collect data.    │
                 │                     │
                 └─────────────────────┘
                            │
                            ▼                         ___ 202
                 ┌─────────────────────┐
                 │  Compute stroke volume │
                 │ using multiple algorithms. │
                 └─────────────────────┘
                            │
                            ▼                         ___ 203
                 ┌─────────────────────┐
                 │ Start stepwise multiple linear │
                 │ regression. Set equation to │
                 │    have no independent  │
                 │       variables.       │
                 └─────────────────────┘
                            │
                            ▼                         ___ 204
                 ┌─────────────────────┐
                 │  Forward selection. Add │
                 │ independent variable with │
                 │  highest F test to equation. │
                 └─────────────────────┘
                            │
                            ▼                         ___ 205
                 ┌─────────────────────┐
                 │   Perform backward   │
                 │ elimination. If redundant │
                 │  independant variable │
                 │ detected, remove it from the │
                 │       equation.       │
                 └─────────────────────┘
                            │
                            ▼
                        ◇─────────◇                   ___ 206
              No ──────◇ All independent ◇
                        ◇ variables processed? ◇
                        ◇─────────◇
                            │
                           Yes
                            ▼
                 ┌─────────────────────┐
                 │ Done. Resulting equation is │
                 │  final multi-parameter │
                 │ algorithm for stroke volume. │
                 └─────────────────────┘
```

FIG. 4

FIG. 5

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FIG. 6A

FIG. 6B

FIG. 7