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Eggers et al.

(54) **SYSTEMS AND METHODS FOR HEMODYNAMIC DETECTION OF CIRCULATORY ANOMALIES**

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(73) Assignee: **CARDIOX CORPORATION**, Columbus, OH (US)

(21) Appl. No.: **14/100,724**

(22) Filed: **Dec. 9, 2013**

Related U.S. Application Data

(63) Continuation of application No. 12/418,866, filed on Apr. 6, 2009.

(60) Provisional application No. 61/156,723, filed on Mar. 2, 2009, provisional application No. 61/080,724, filed on Jul. 15, 2008.

Publication Classification

(51) **Int. Cl.**

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A61B 5/00 (2006.01)

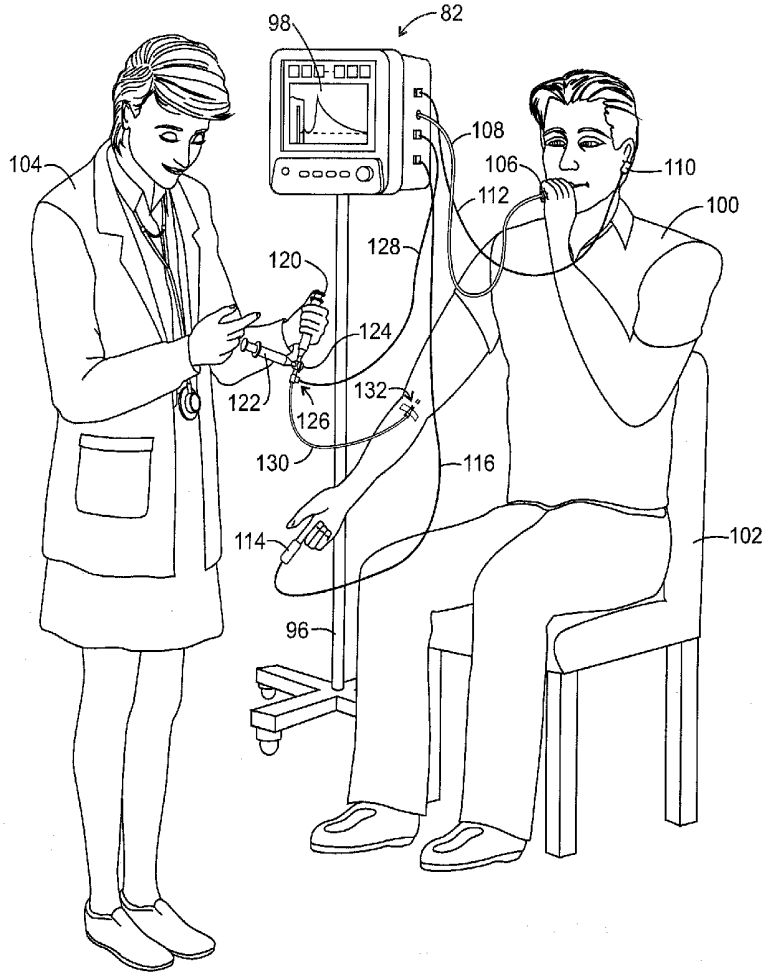
(52) **U.S. Cl.**

CPC ***A61B 5/0275*** (2013.01); ***A61B 5/6815*** (2013.01)

USPC **600/432**; 600/431

(57) **ABSTRACT**

Systems and methods for detecting circulatory anomalies such as, for example, right-to-left cardiac and pulmonary shunts. A fluorescing indicator is injected into the bloodstream of a subject. An optical sensor is used to transcutaneously excite the indicator into fluorescence and to transcutaneously detect the fluorescence, and a relative concentration of the indicator is determined as a function of time. An indicator dilution curve is generated from the relative concentration readings, the curve shape is analyzed for the indication of a shunt and, if a shunt is detected, a ratiometric area under the curve analysis is performed and combined with a calculated cardiac output value to provide a shunt conductance value. A Valsalva maneuver may be performed as a part of the method. System embodiments may include a controller/monitor that monitors, times, cues and/or analyzes various steps of a shunt detection test.



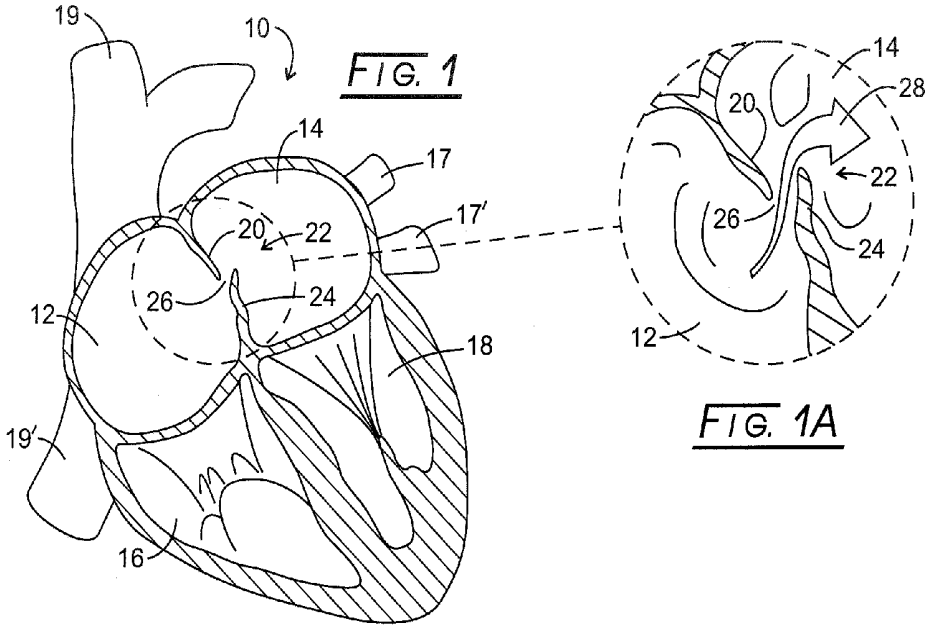


FIG. 1

FIG. 1A

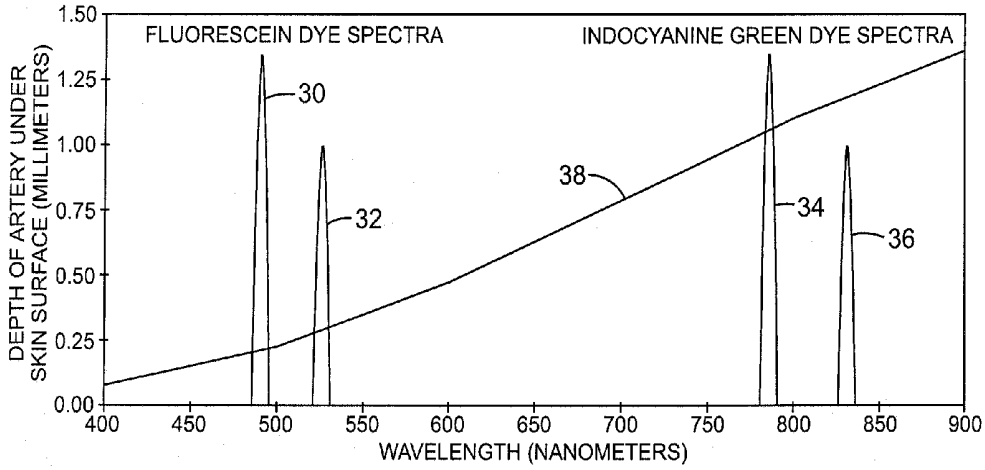


FIG. 2

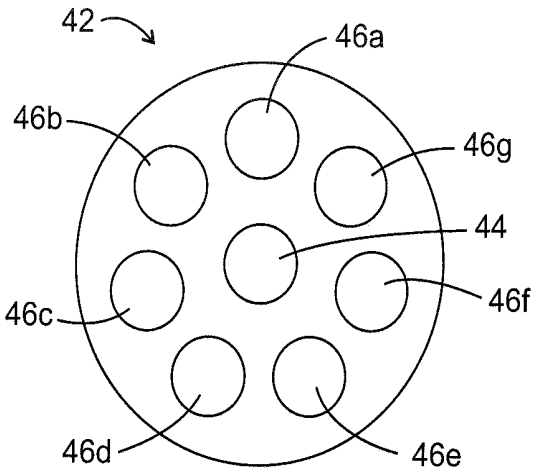
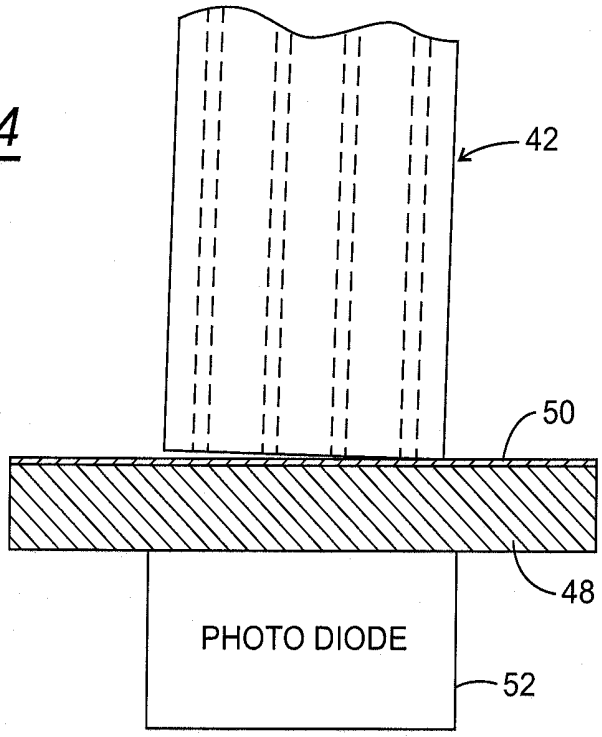


FIG. 3

FIG. 4



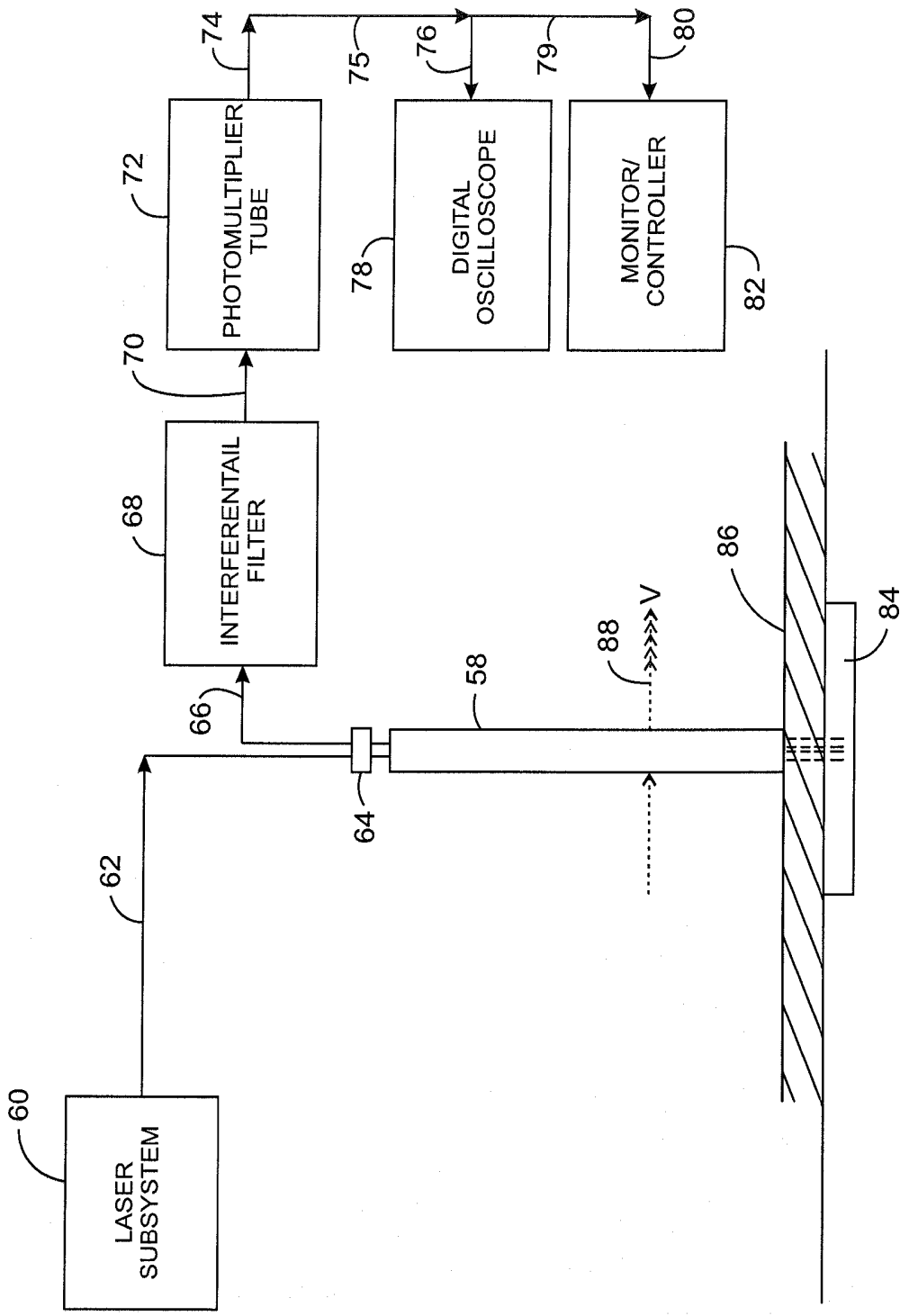

LASER SUBSYSTEM
60
62
64
66
INTERFERENTAIL FILTER
68
70
PHOTOMULTIPLIER TUBE
72
74
75
DIGITAL OSCILLOSCOPE
76
78
79
MONITOR/ CONTROLLER
80
82
58
88
V
86
84

FIG. 5

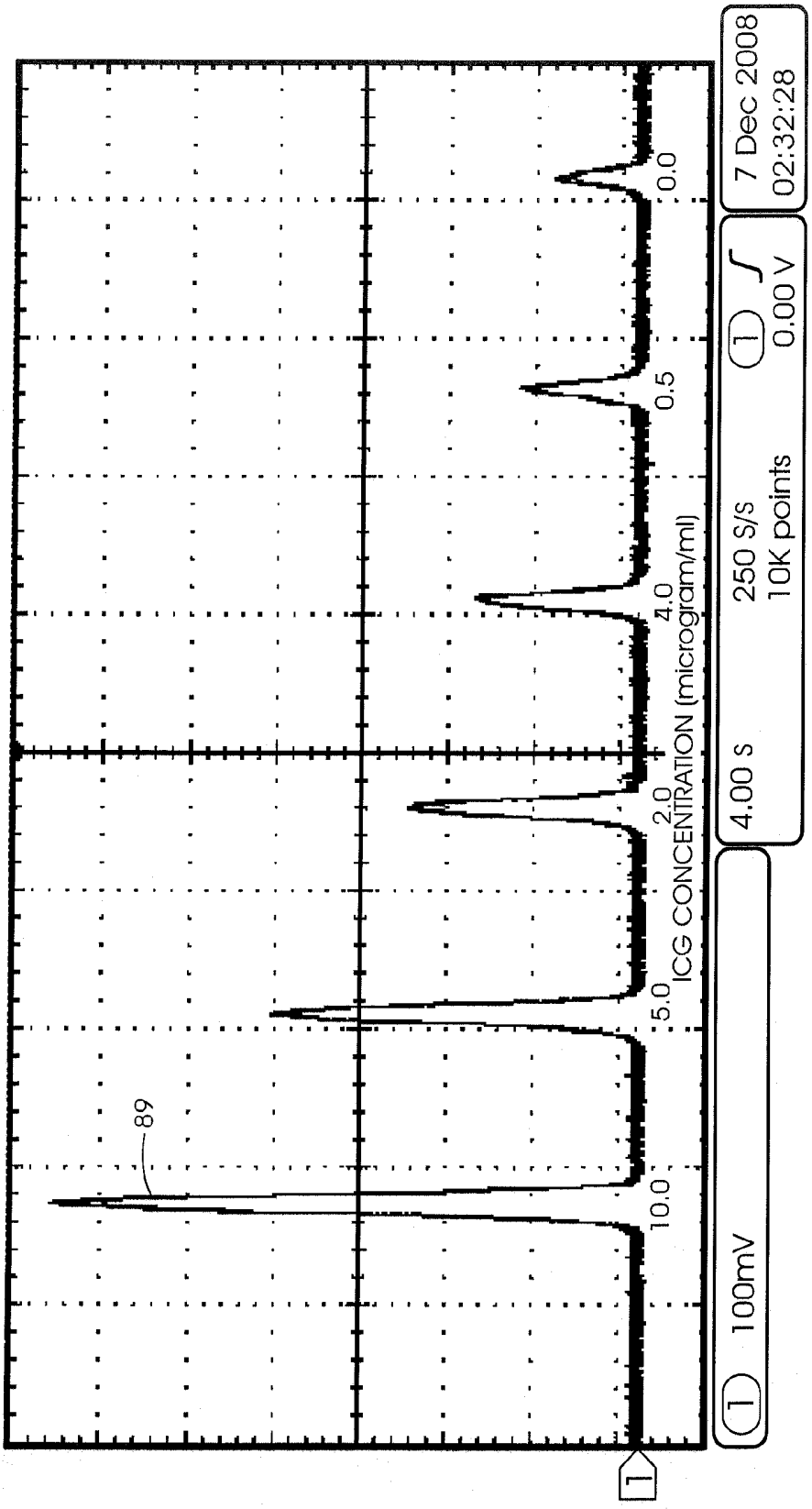

89
10.0
5.0
2.0
4.0
0.5
0.0
ICG CONCENTRATION (microgram/ml)
1 100mV
4.00 s
250 S/s
10K points
1 ∫
0.00 V
7 Dec 2008
02:32:28

FIG. 6

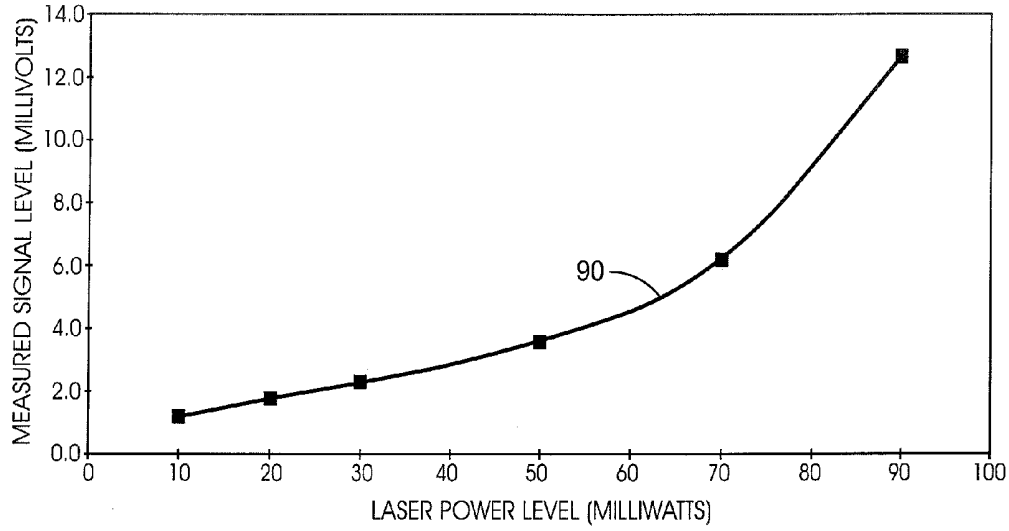

MEASURED SIGNAL LEVEL (MILLIVOLTS)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
10
20
30
40
50
60
70
80
90
100
90
LASER POWER LEVEL (MILLIWATTS)

FIG. 7

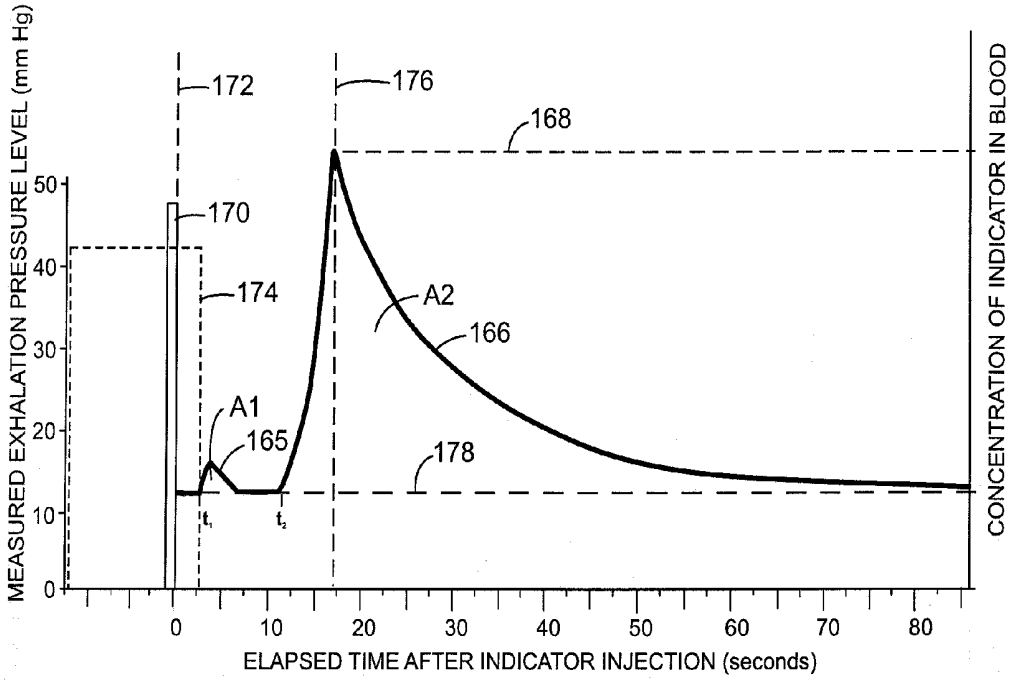

MEASURED EXHALATION PRESSURE LEVEL (mm Hg)
50
40
30
20
10
0
172
176
168
170
174
A2
166
A1
165
178
t_1
t_2
0
10
20
30
40
50
60
70
80
ELAPSED TIME AFTER INDICATOR INJECTION (seconds)
CONCENTRATION OF INDICATOR IN BLOOD

FIG. 10

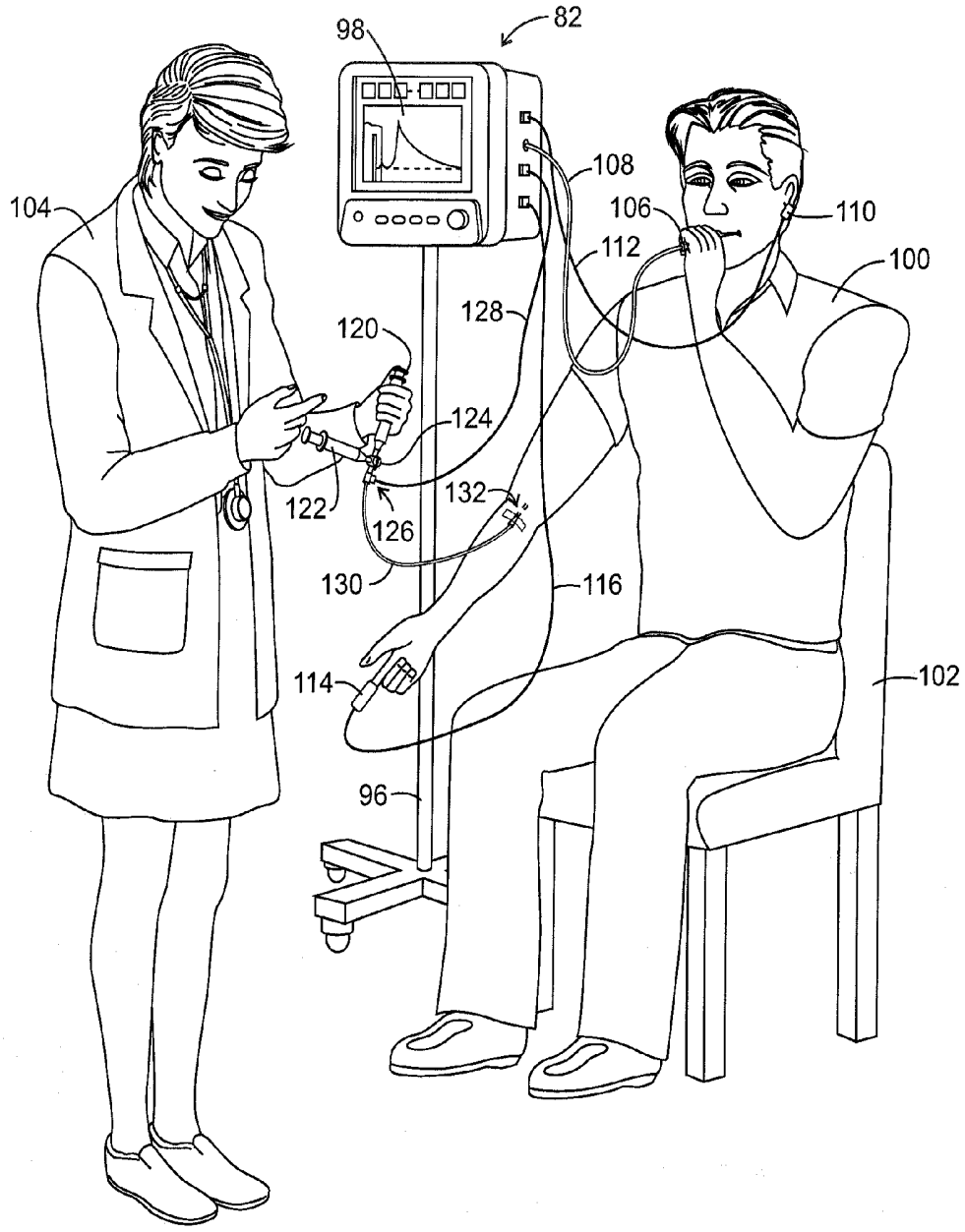

82
98
104
108
106
110
112
100
128
120
124
122
126
132
130
116
114
102
96

FIG. 8

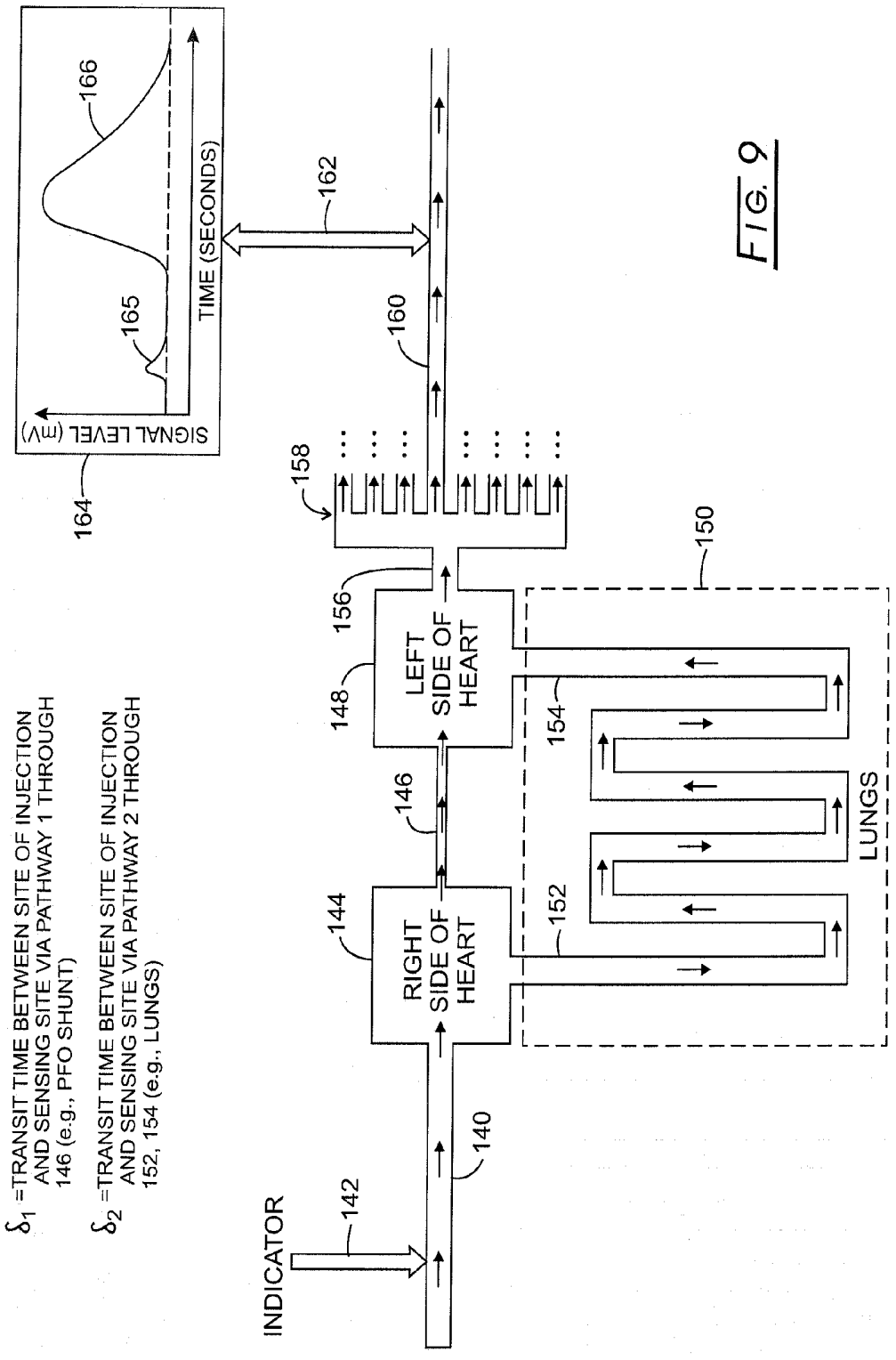

INDICATOR
142
140
RIGHT SIDE OF HEART
144
146
LEFT SIDE OF HEART
148
156
158
160
162
150
152
154
LUNGS
166
165
TIME (SECONDS)
SIGNAL LEVEL (mV)
164
δ_1 =TRANSIT TIME BETWEEN SITE OF INJECTION AND SENSING SITE VIA PATHWAY 1 THROUGH 146 (e.g., PFO SHUNT)
δ_2 =TRANSIT TIME BETWEEN SITE OF INJECTION AND SENSING SITE VIA PATHWAY 2 THROUGH 152, 154 (e.g., LUNGS)

FIG. 9

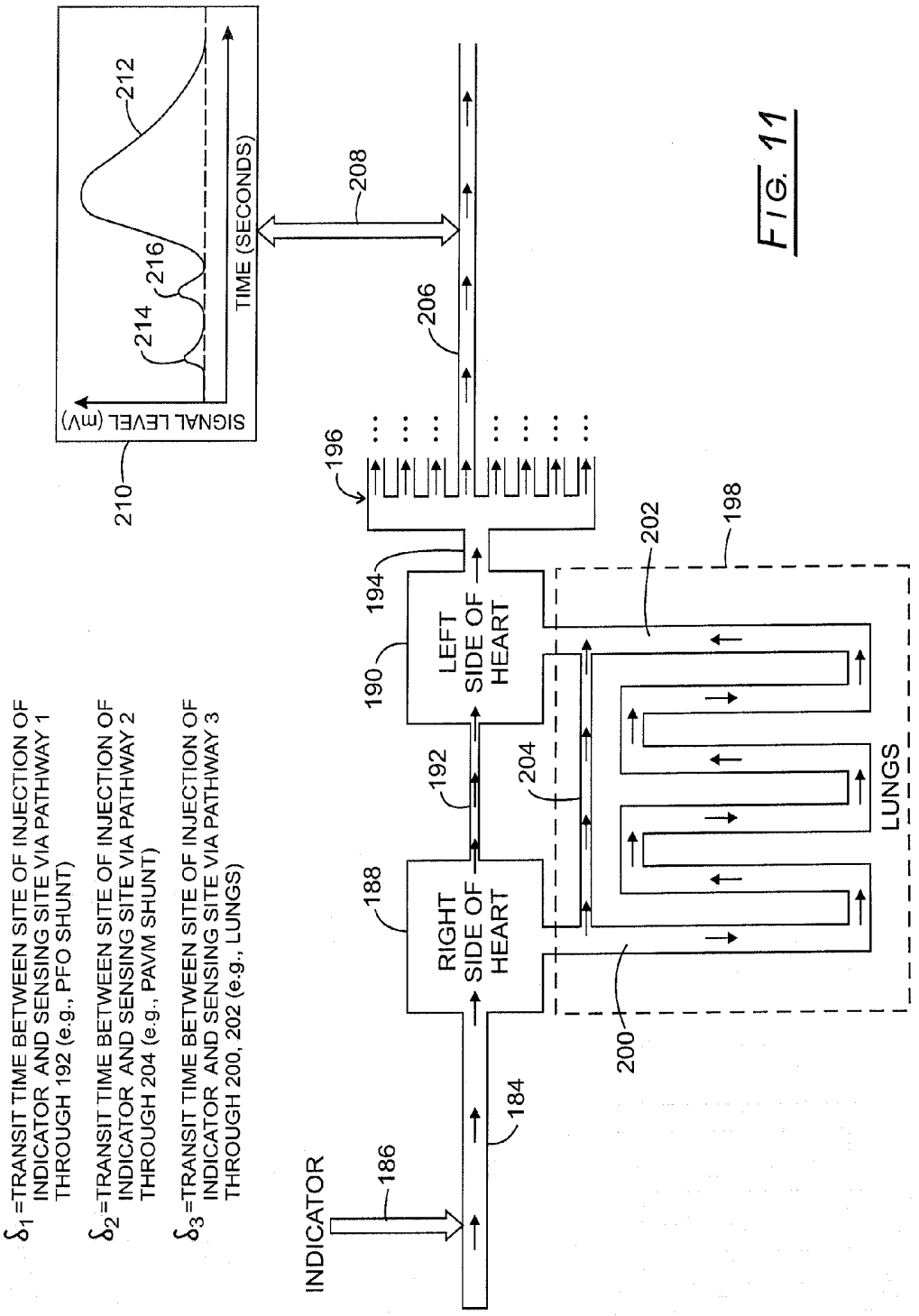

INDICATOR
186
184
RIGHT SIDE OF HEART
188
LEFT SIDE OF HEART
190
192
194
196
LUNGS
198
200
202
204
206
208
210
212
214
216
SIGNAL LEVEL (mV)
TIME (SECONDS)
δ_1=TRANSIT TIME BETWEEN SITE OF INJECTION OF INDICATOR AND SENSING SITE VIA PATHWAY 1 THROUGH 192 (e.g., PFO SHUNT)
δ_2=TRANSIT TIME BETWEEN SITE OF INJECTION OF INDICATOR AND SENSING SITE VIA PATHWAY 2 THROUGH 204 (e.g., PAVM SHUNT)
δ_3=TRANSIT TIME BETWEEN SITE OF INJECTION OF INDICATOR AND SENSING SITE VIA PATHWAY 3 THROUGH 200, 202 (e.g., LUNGS)

FIG. 11

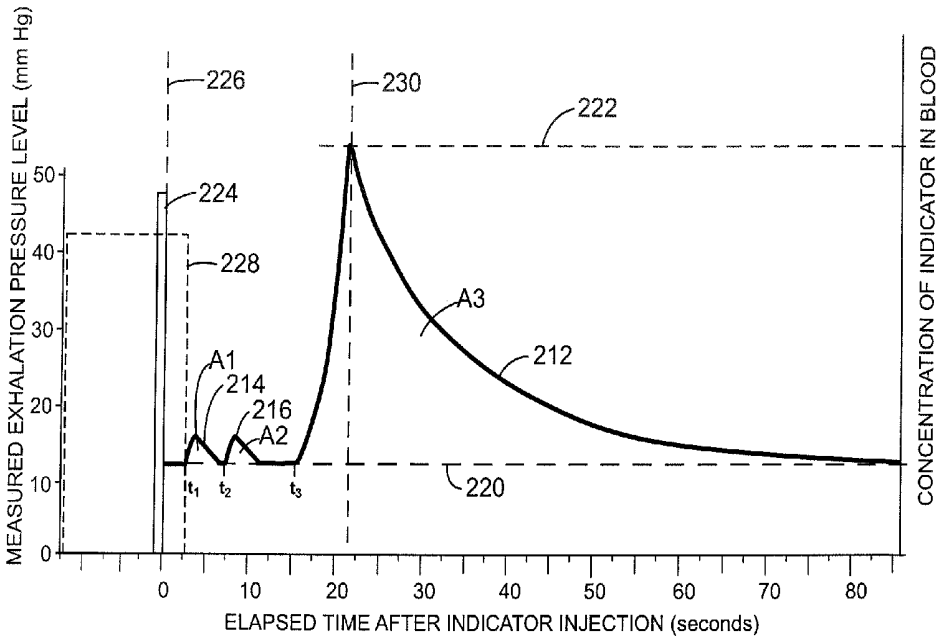

MEASURED EXHALATION PRESSURE LEVEL (mm Hg)
CONCENTRATION OF INDICATOR IN BLOOD
ELAPSED TIME AFTER INDICATOR INJECTION (seconds)
226
230
222
224
228
A3
212
A1
214
216
A2
220
t1
t2
t3
0
10
20
30
40
50
60
70
80

FIG. 12

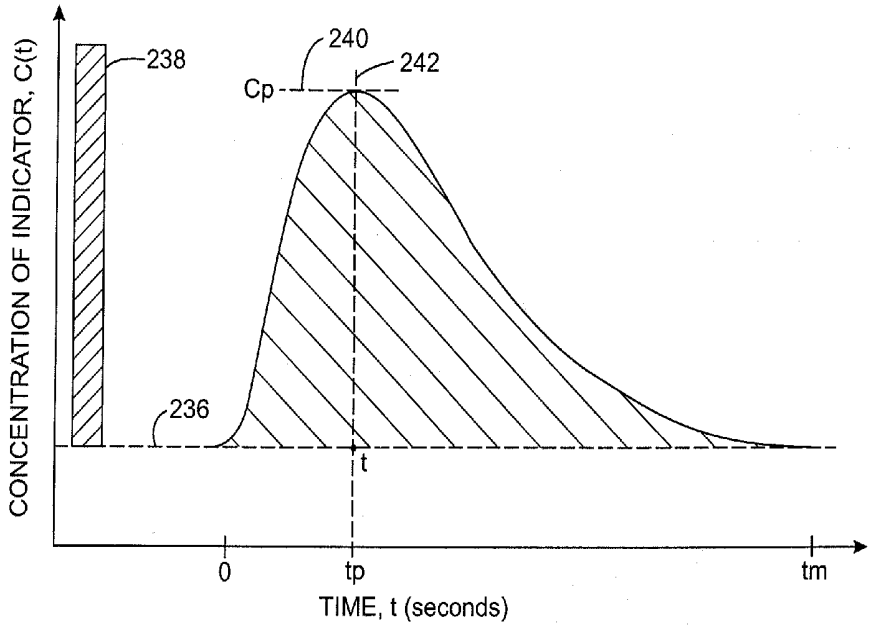

CONCENTRATION OF INDICATOR, C(t)
TIME, t (seconds)
238
240
242
Cp
236
t
0
tp
tm

FIG. 13

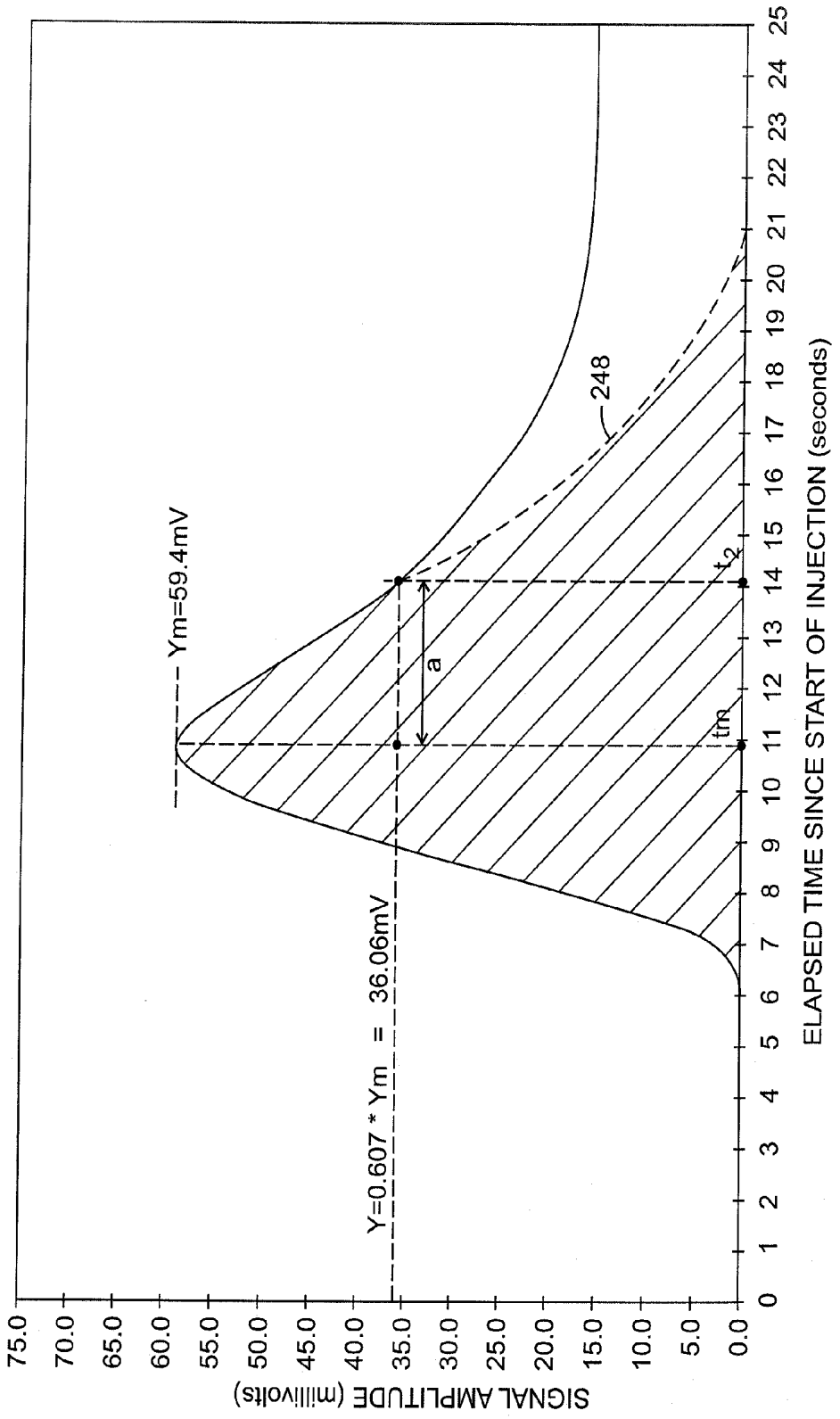

Ym=59.4mV
Y=0.607 * Ym = 36.06mV
248
a
t_2
tm
SIGNAL AMPLITUDE (millivolts)
ELAPSED TIME SINCE START OF INJECTION (seconds)
75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

FIG. 14

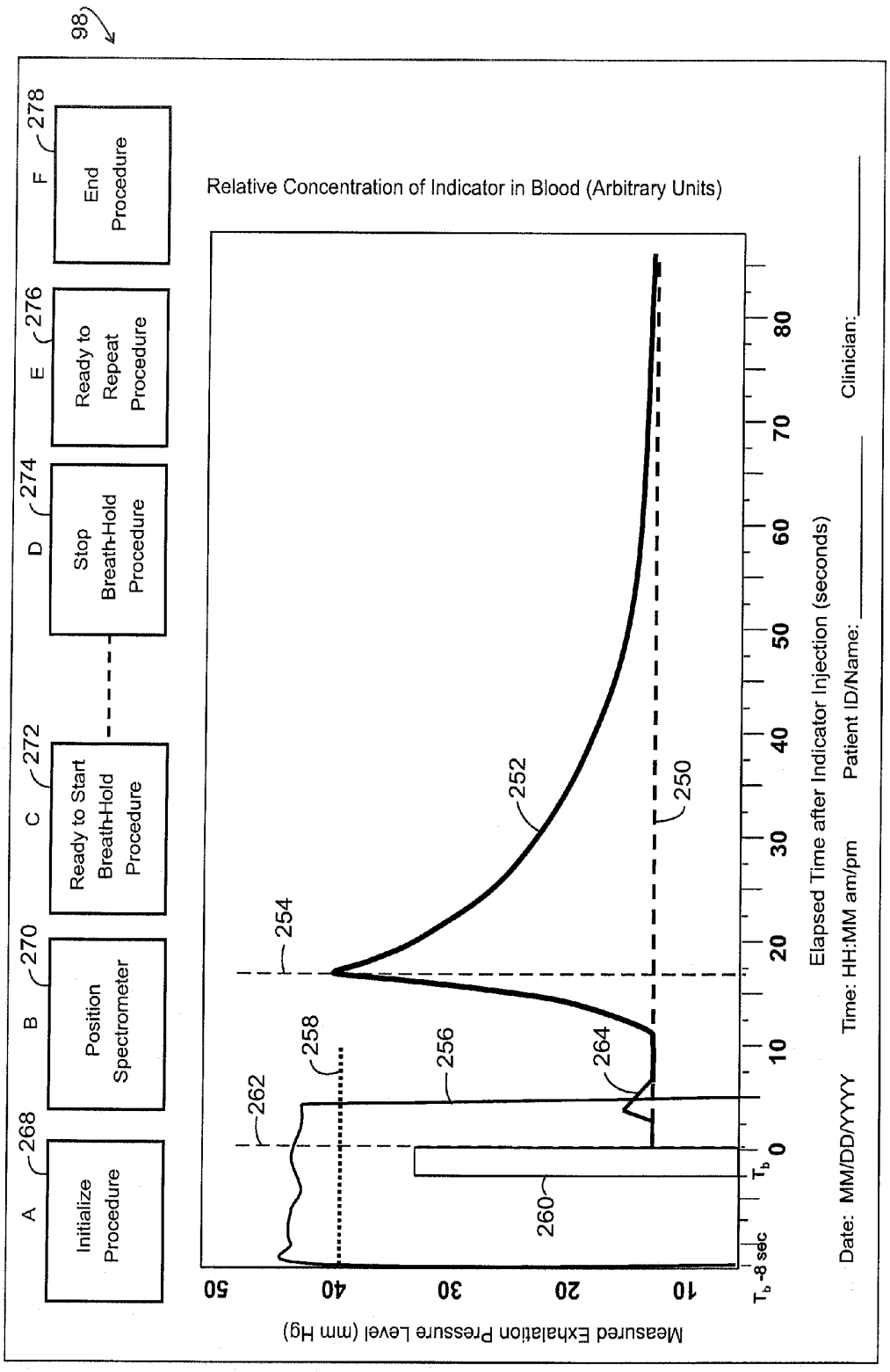

98
A
268
Initialize Procedure
B
270
Position Spectrometer
C
272
Ready to Start Breath-Hold Procedure
D
274
Stop Breath-Hold Procedure
E
276
Ready to Repeat Procedure
F
278
End Procedure
Relative Concentration of Indicator in Blood (Arbitrary Units)
Measured Exhalation Pressure Level (mm Hg)
50
40
30
20
10
T_b -8 sec
T_b
0
10
20
30
40
50
60
70
80
Elapsed Time after Indicator Injection (seconds)
Date: MM/DD/YYYY
Time: HH:MM am/pm
Patient ID/Name:
Clinician:
250
252
254
256
258
260
262
264

FIG. 15

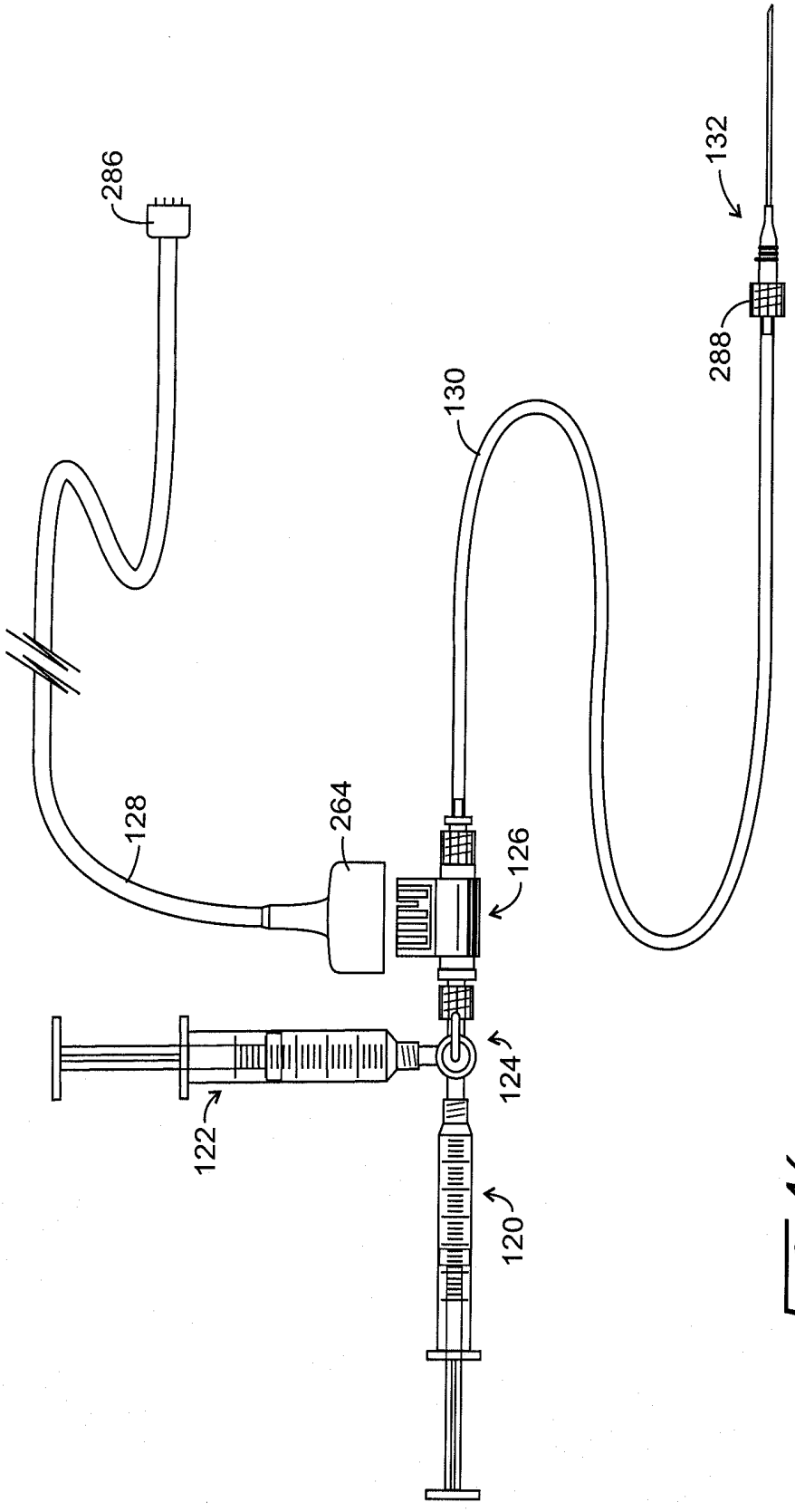


FIG. 16

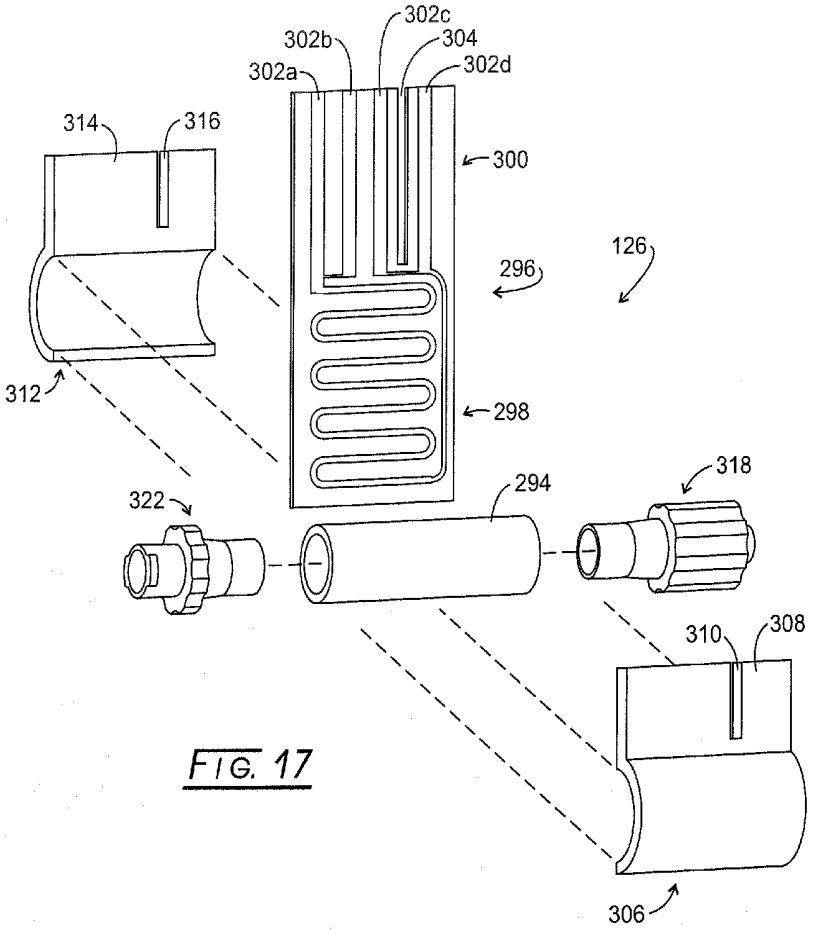

302c
302b
304
302a
302d
314
316
300
126
296
312
298
322
294
318
310
308
306

FIG. 17

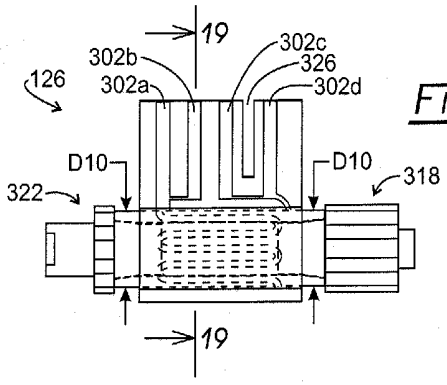

19
302c
302b
326
126
302a
302d
D10
D10
318
322
19

FIG. 18

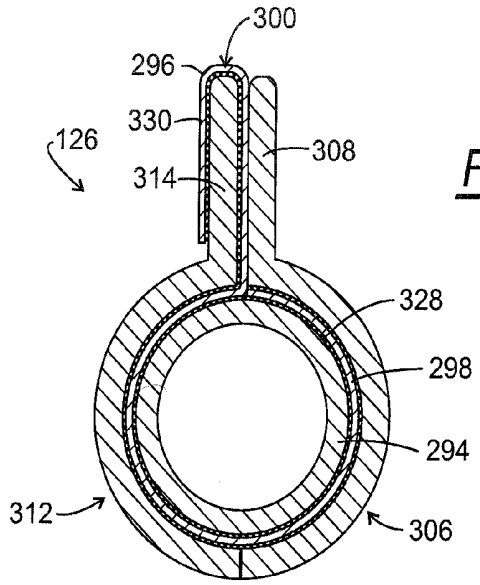


FIG. 19

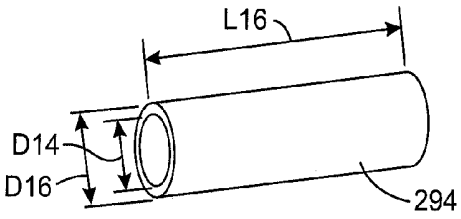


FIG. 21

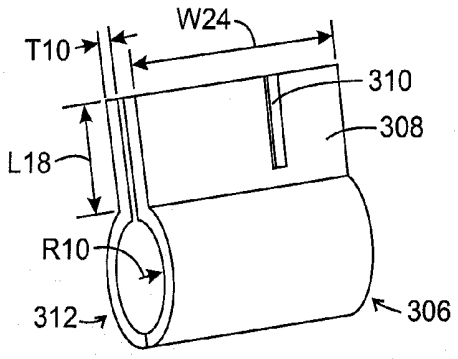


FIG. 22

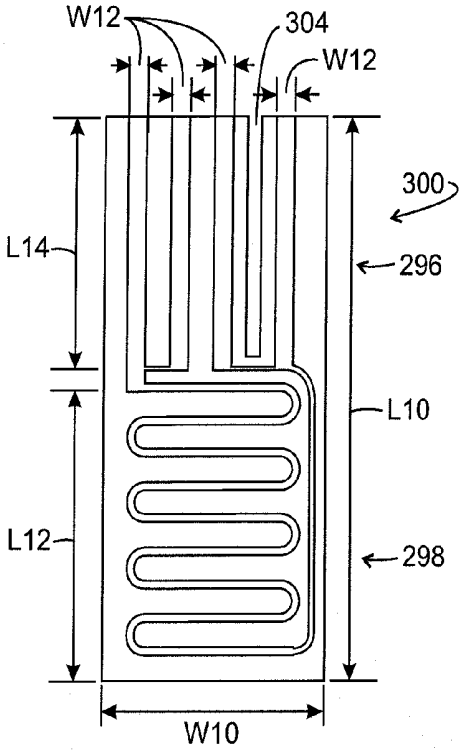


FIG. 20

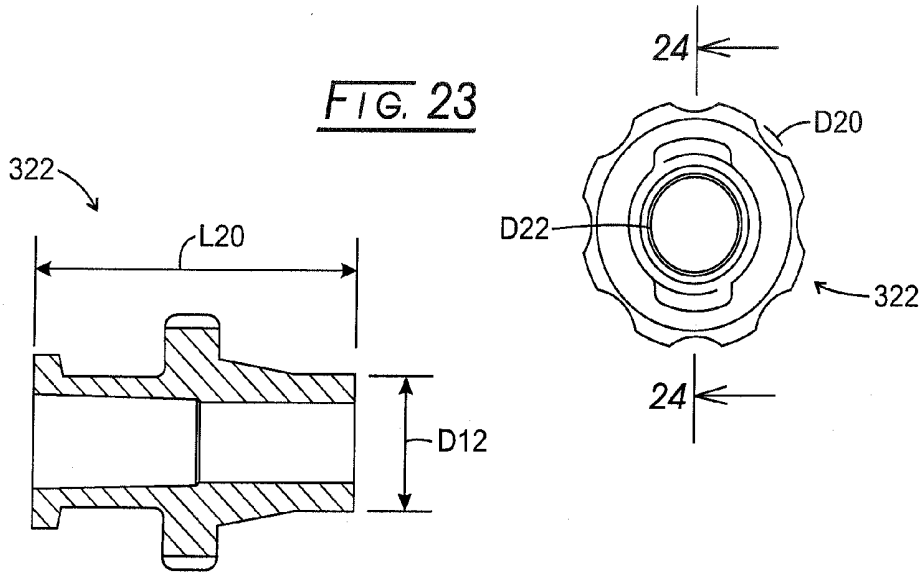


FIG. 23

FIG. 24

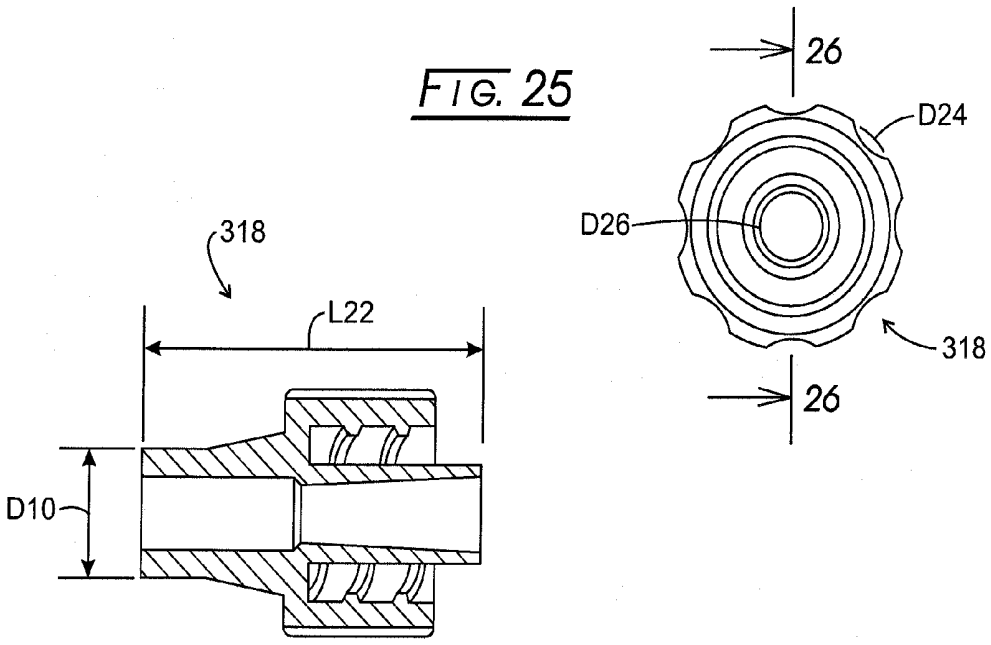
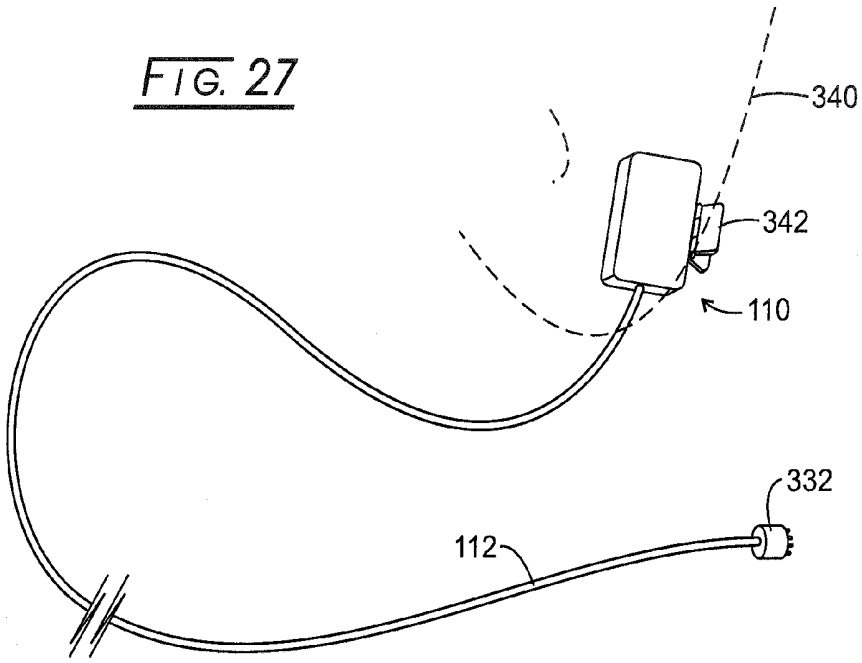


FIG. 25

FIG. 26

FIG. 27


340
342
110
332
112

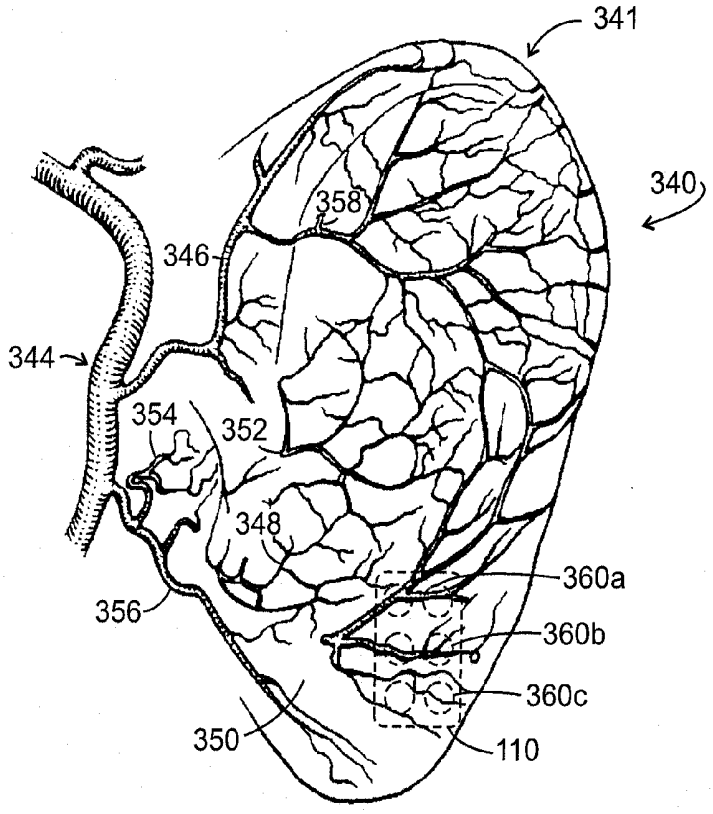

341
340
358
346
344
354
352
348
360a
356
360b
360c
350
110

FIG. 28

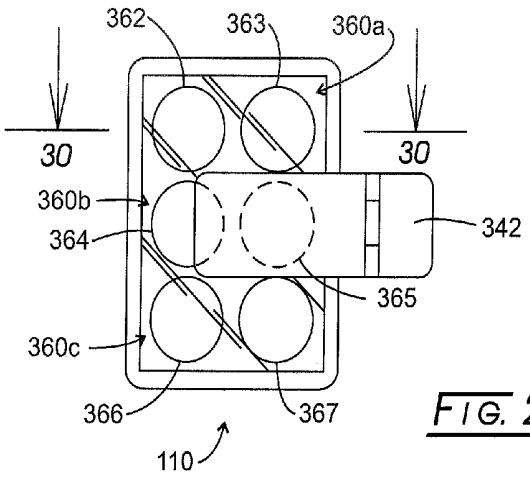

362
363
360a
30
30
360b
364
342
365
360c
366
367
110

FIG. 29

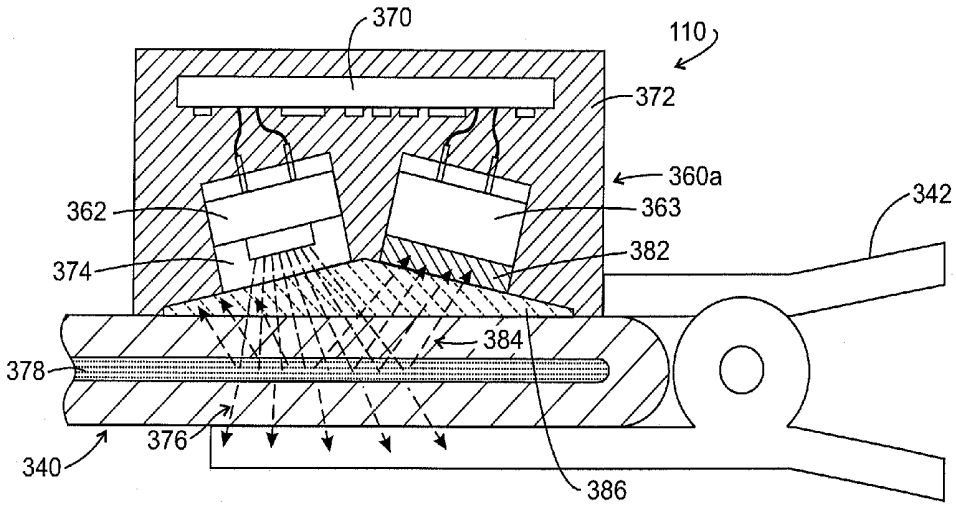

370
110
372
360a
362
363
342
374
382
384
378
376
340
386

FIG. 30

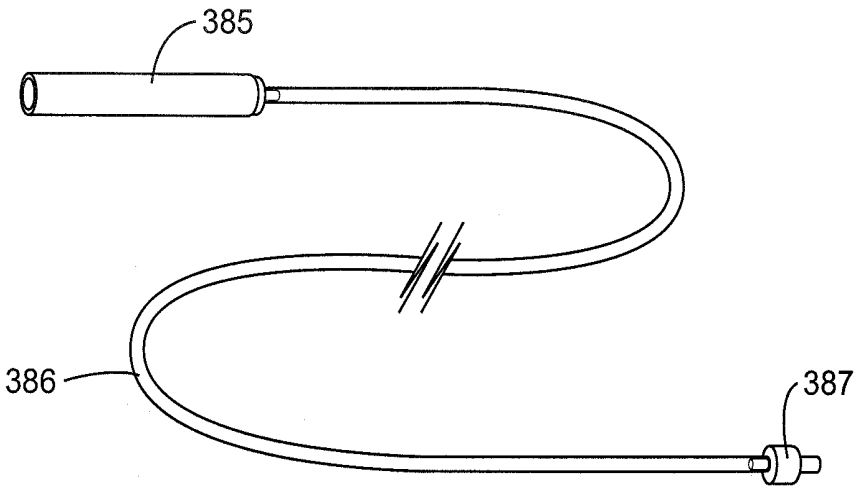


FIG. 31

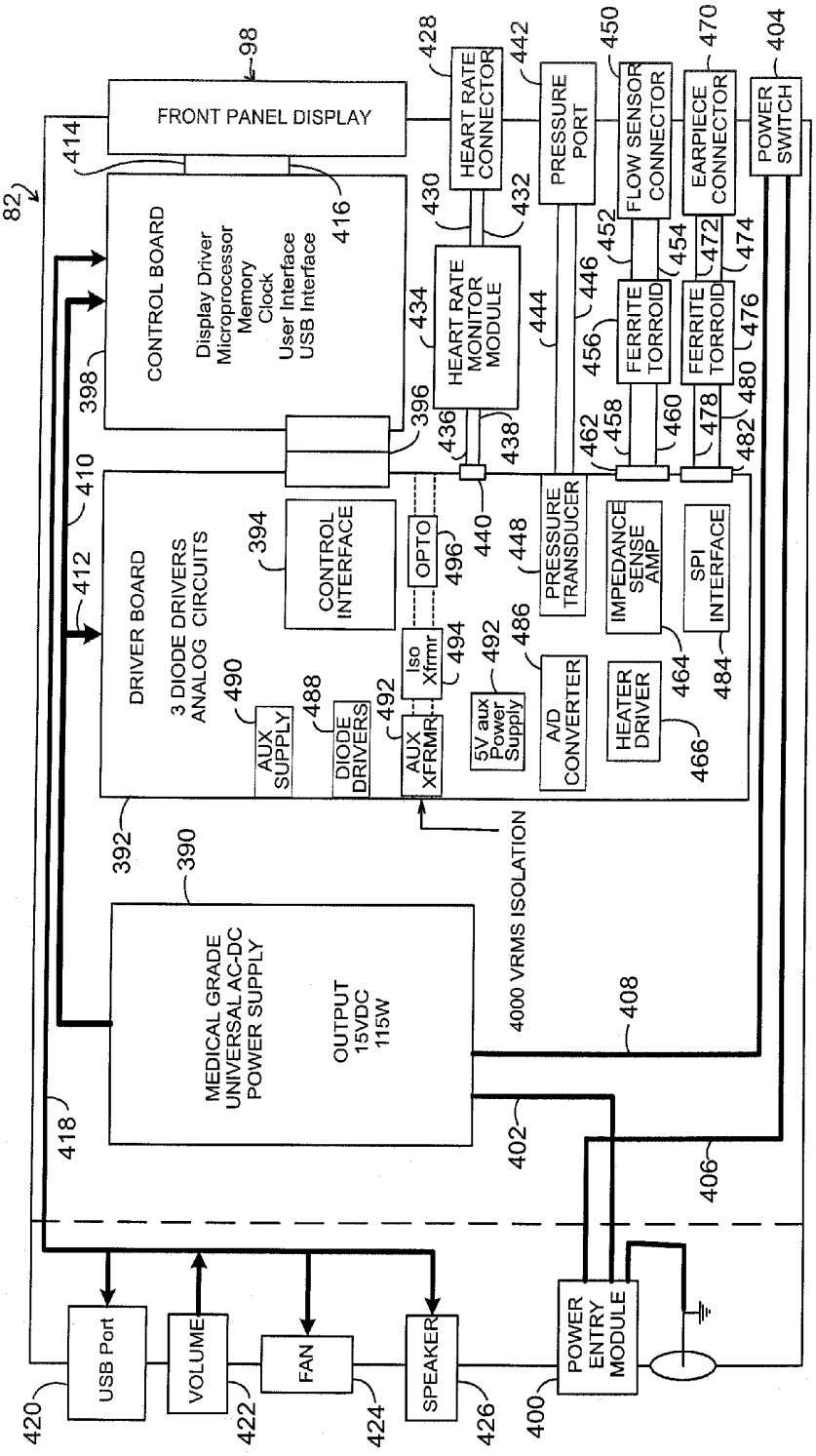
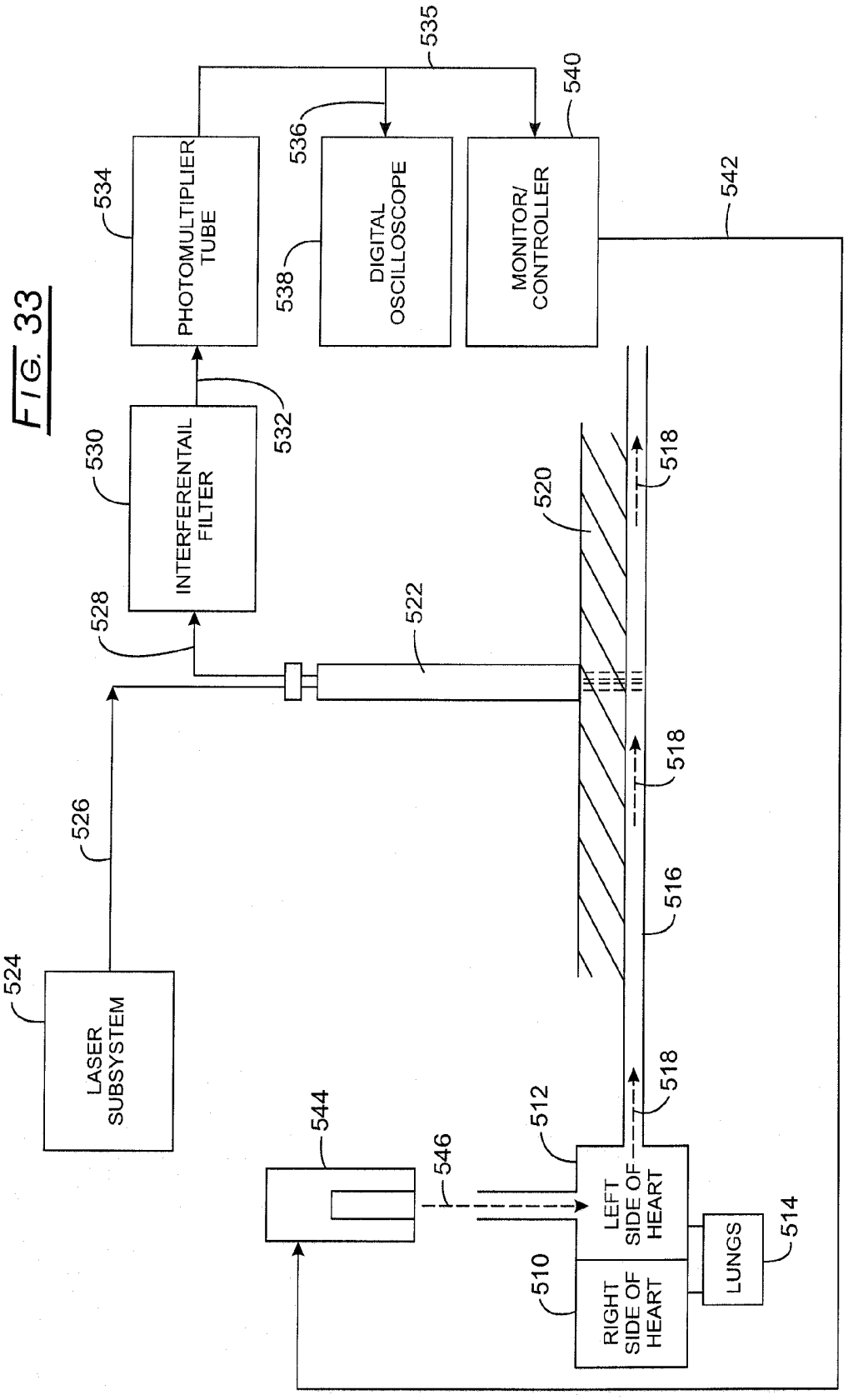

82
98
FRONT PANEL DISPLAY
414
CONTROL BOARD
Display Driver
Microprocessor
Memory
Clock
User Interface
USB Interface
416
398
410
412
DRIVER BOARD
3 DIODE DRIVERS
ANALOG CIRCUITS
394
CONTROL INTERFACE
OPTO
496
Iso Xfrmr
494
AUX SUPPLY
490
DIODE DRIVERS
488
AUX XFRMR
492
5V aux Power Supply
492
A/D CONVERTER
486
PRESSURE TRANSDUCER
448
IMPEDANCE SENSE AMP
SPI INTERFACE
484
HEATER DRIVER
464
466
392
390
MEDICAL GRADE UNIVERSAL AC-DC POWER SUPPLY
OUTPUT 15VDC 115W
4000 VRMS ISOLATION
408
418
402
406
HEART RATE MONITOR MODULE
434
396
436
438
440
444
HEART RATE CONNECTOR
428
430
432
PRESSURE PORT
442
FLOW SENSOR CONNECTOR
450
452
454
FERRITE TORROID
446
456
458
460
462
EARPIECE CONNECTOR
470
472
474
FERRITE TORROID
476
478
480
482
POWER SWITCH
404
USB Port
420
VOLUME
422
FAN
424
SPEAKER
426
POWER ENTRY MODULE
400

FIG. 32

FIG. 33


535
540
536
534
PHOTOMULTIPLIER TUBE
DIGITAL OSCILLOSCOPE
MONITOR/ CONTROLLER
542
538
532
530
INTERFERENTAIL FILTER
520
518
528
522
518
526
516
524
LASER SUBSYSTEM
518
544
512
546
LEFT SIDE OF HEART
LUNGS
514
510
RIGHT SIDE OF HEART

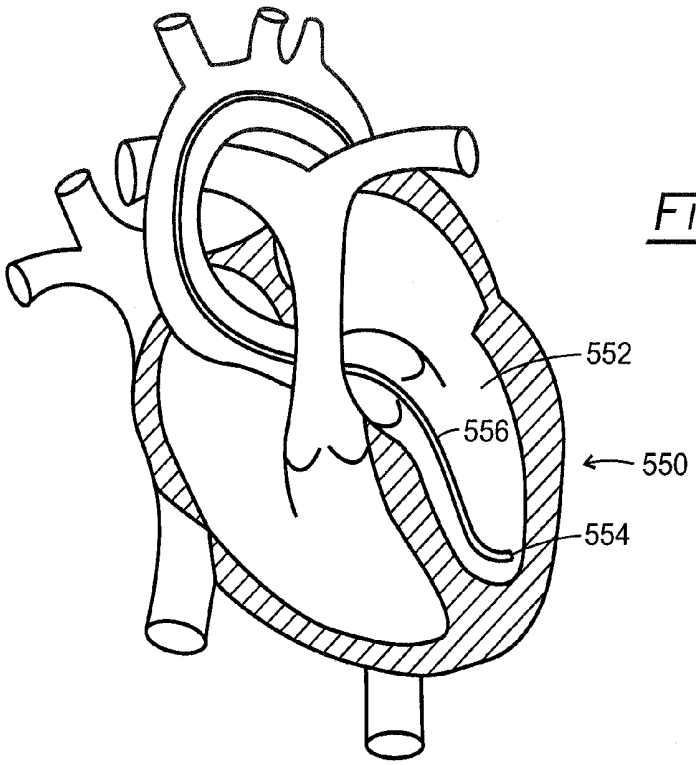

552
556
550
554

FIG. 34

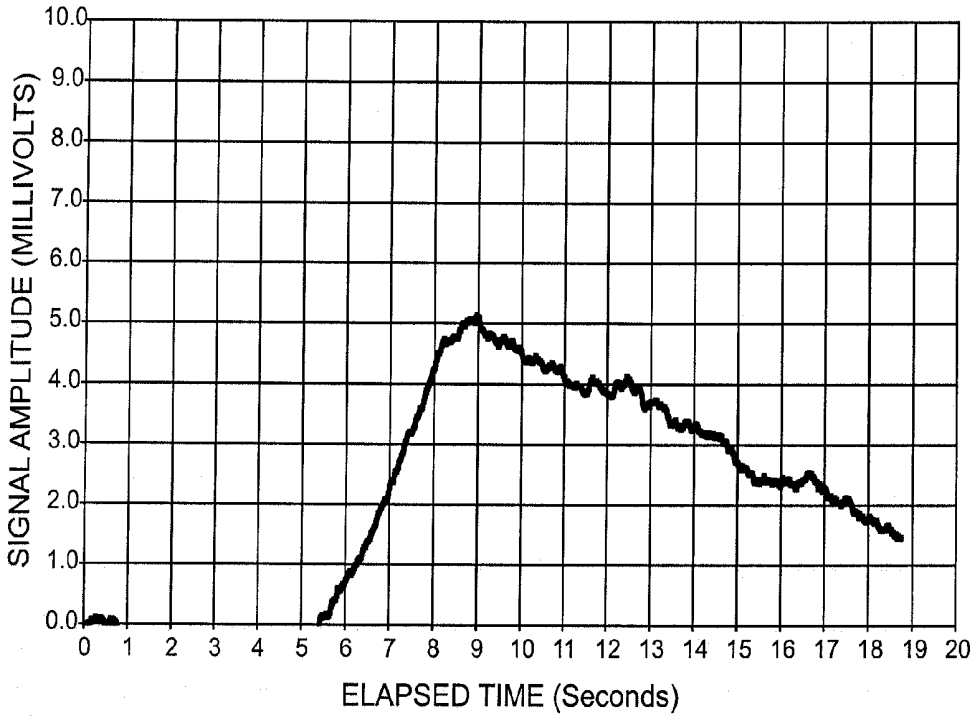

SIGNAL AMPLITUDE (MILLIVOLTS)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
ELAPSED TIME (Seconds)

FIG. 35

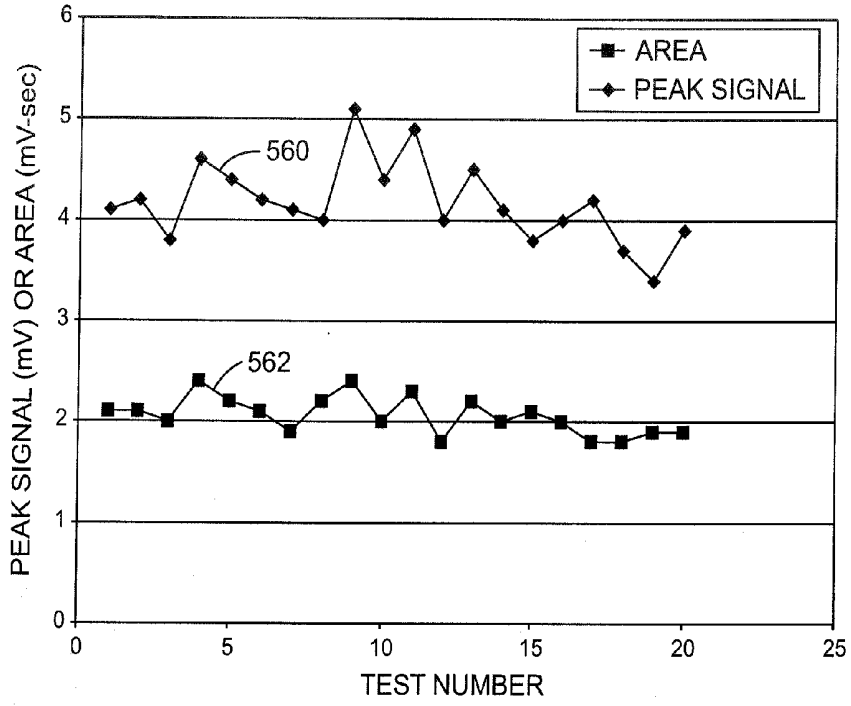

AREA
PEAK SIGNAL
560
562
PEAK SIGNAL (mV) OR AREA (mV-sec)
TEST NUMBER
0
1
2
3
4
5
6
0
5
10
15
20
25

FIG. 36

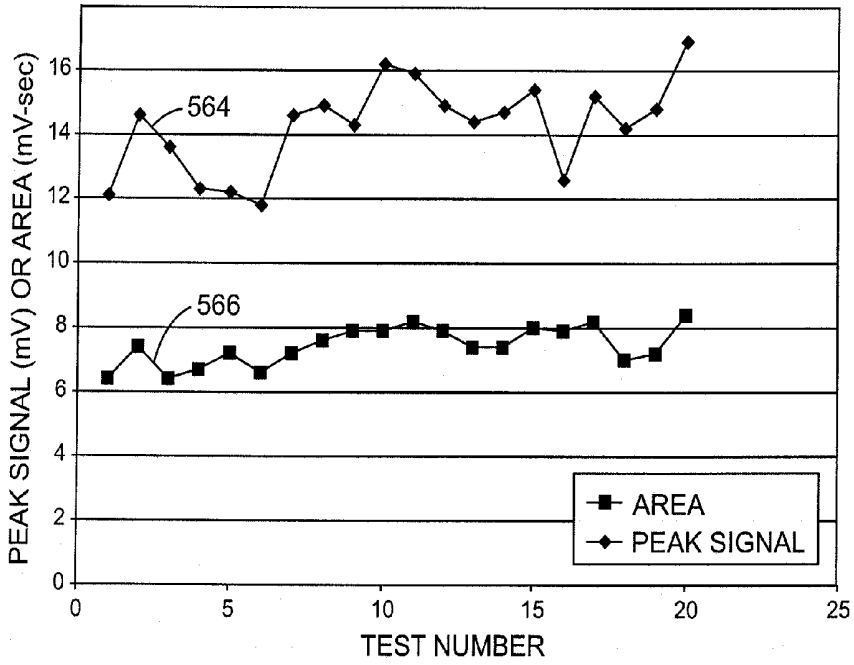

564
566
AREA
PEAK SIGNAL
PEAK SIGNAL (mV) OR AREA (mV-sec)
TEST NUMBER
0
2
4
6
8
10
12
14
16
0
5
10
15
20
25

FIG. 37

FIG. 38A

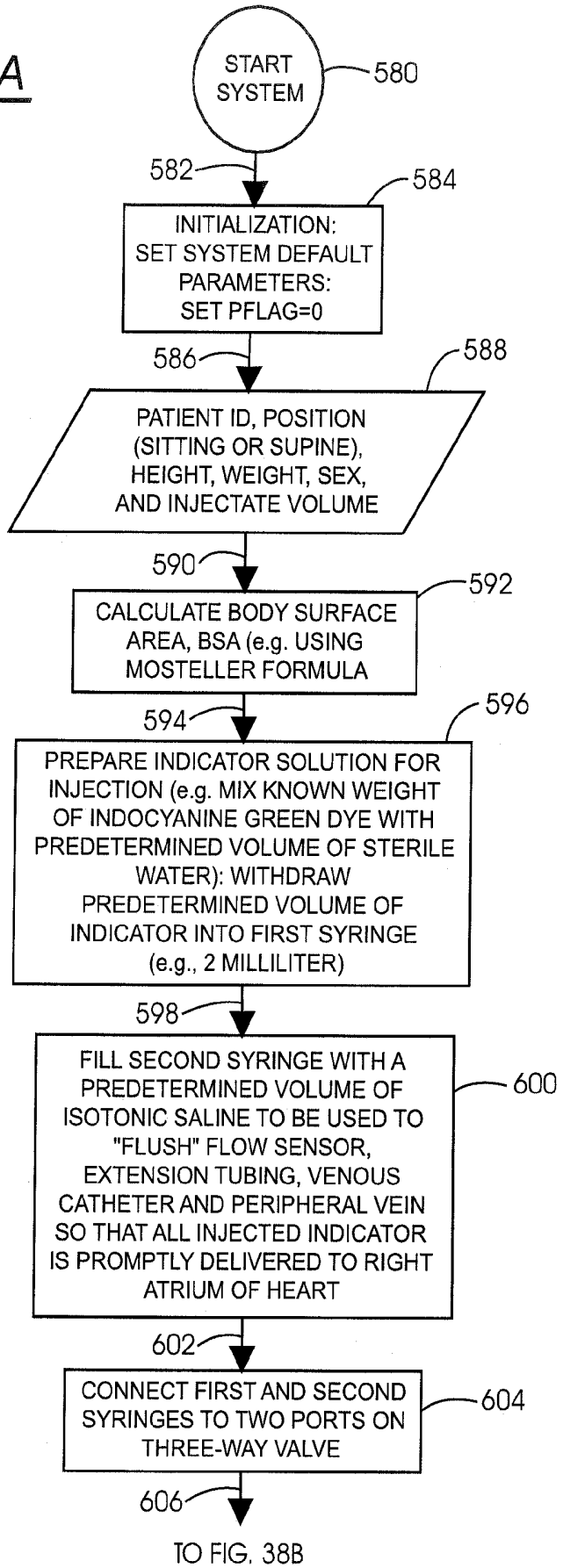

START SYSTEM
580
582
584
INITIALIZATION: SET SYSTEM DEFAULT PARAMETERS: SET PFLAG=0
586
588
PATIENT ID, POSITION (SITTING OR SUPINE), HEIGHT, WEIGHT, SEX, AND INJECTATE VOLUME
590
592
CALCULATE BODY SURFACE AREA, BSA (e.g. USING MOSTELLER FORMULA
594
596
PREPARE INDICATOR SOLUTION FOR INJECTION (e.g. MIX KNOWN WEIGHT OF INDOCYANINE GREEN DYE WITH PREDETERMINED VOLUME OF STERILE WATER): WITHDRAW PREDETERMINED VOLUME OF INDICATOR INTO FIRST SYRINGE (e.g., 2 MILLILITER)
598
FILL SECOND SYRINGE WITH A PREDETERMINED VOLUME OF ISOTONIC SALINE TO BE USED TO "FLUSH" FLOW SENSOR, EXTENSION TUBING, VENOUS CATHETER AND PERIPHERAL VEIN SO THAT ALL INJECTED INDICATOR IS PROMPTLY DELIVERED TO RIGHT ATRIUM OF HEART
600
602
CONNECT FIRST AND SECOND SYRINGES TO TWO PORTS ON THREE-WAY VALVE
604
606
TO FIG. 38B

FIG. 38B

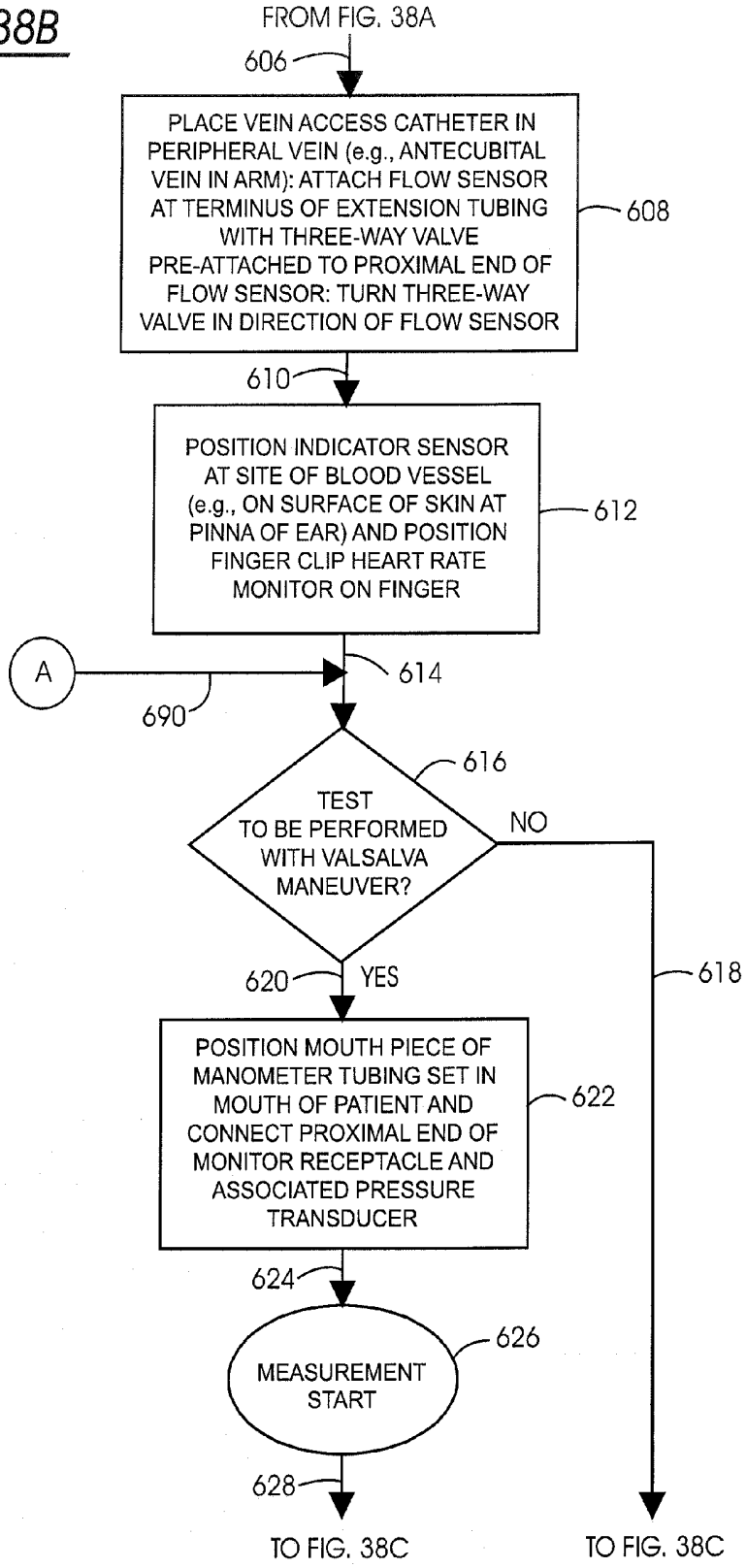

FROM FIG. 38A
606
PLACE VEIN ACCESS CATHETER IN PERIPHERAL VEIN (e.g., ANTECUBITAL VEIN IN ARM): ATTACH FLOW SENSOR AT TERMINUS OF EXTENSION TUBING WITH THREE-WAY VALVE PRE-ATTACHED TO PROXIMAL END OF FLOW SENSOR: TURN THREE-WAY VALVE IN DIRECTION OF FLOW SENSOR
608
610
POSITION INDICATOR SENSOR AT SITE OF BLOOD VESSEL (e.g., ON SURFACE OF SKIN AT PINNA OF EAR) AND POSITION FINGER CLIP HEART RATE MONITOR ON FINGER
612
A
690
614
616
TEST TO BE PERFORMED WITH VALSALVA MANEUVER?
NO
618
620
YES
POSITION MOUTH PIECE OF MANOMETER TUBING SET IN MOUTH OF PATIENT AND CONNECT PROXIMAL END OF MONITOR RECEPTACLE AND ASSOCIATED PRESSURE TRANSDUCER
622
624
MEASUREMENT START
626
628
TO FIG. 38C
TO FIG. 38C

FIG. 38C

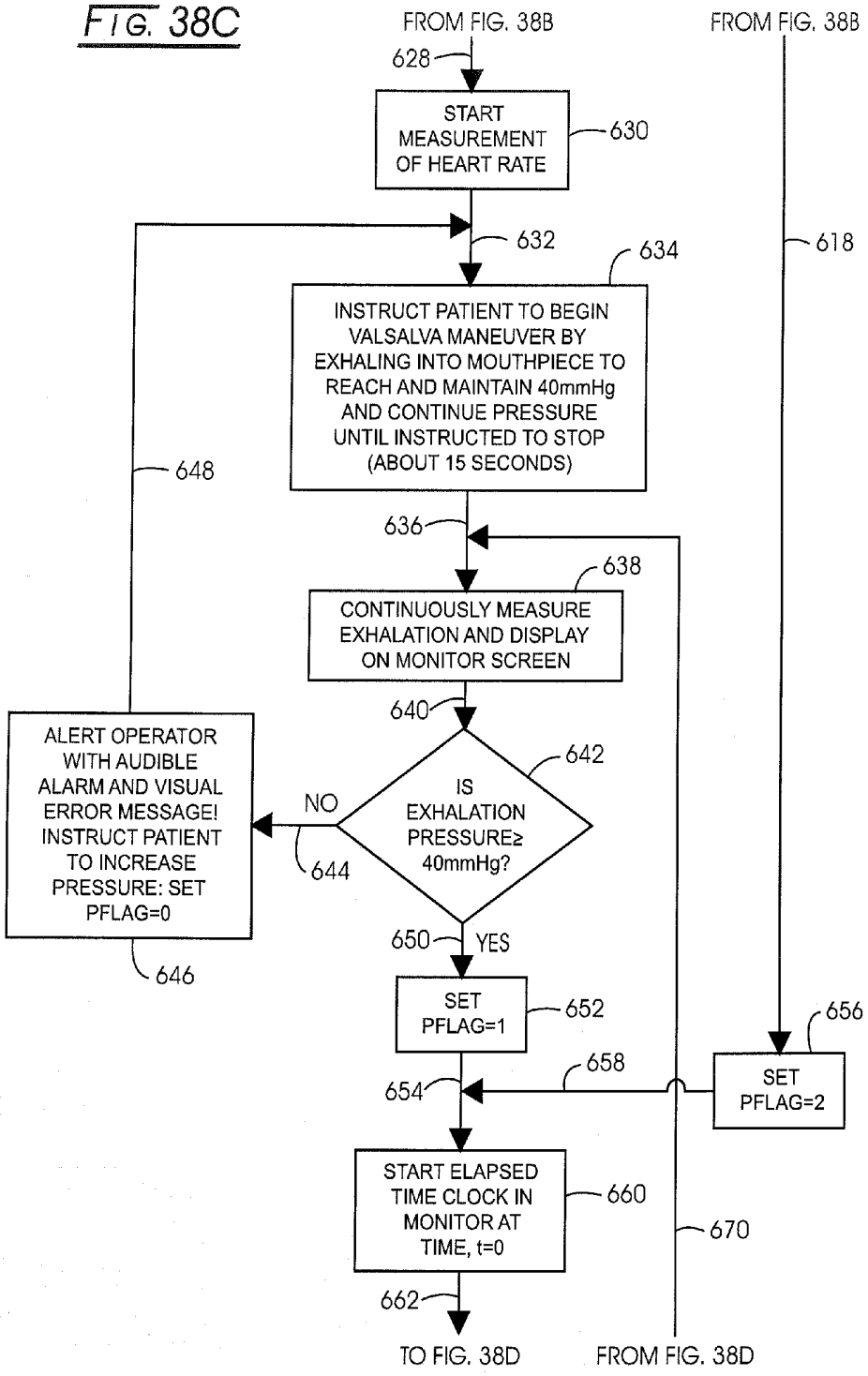

FROM FIG. 38B
FROM FIG. 38B
628
START MEASUREMENT OF HEART RATE
630
632
634
618
INSTRUCT PATIENT TO BEGIN VALSALVA MANEUVER BY EXHALING INTO MOUTHPIECE TO REACH AND MAINTAIN 40mmHg AND CONTINUE PRESSURE UNTIL INSTRUCTED TO STOP (ABOUT 15 SECONDS)
648
636
638
CONTINUOUSLY MEASURE EXHALATION AND DISPLAY ON MONITOR SCREEN
640
642
ALERT OPERATOR WITH AUDIBLE ALARM AND VISUAL ERROR MESSAGE! INSTRUCT PATIENT TO INCREASE PRESSURE: SET PFLAG=0
NO
IS EXHALATION PRESSURE≥ 40mmHg?
644
646
650
YES
SET PFLAG=1
652
656
658
SET PFLAG=2
654
START ELAPSED TIME CLOCK IN MONITOR AT TIME, t=0
660
670
662
TO FIG. 38D
FROM FIG. 38D

FIG. 38D

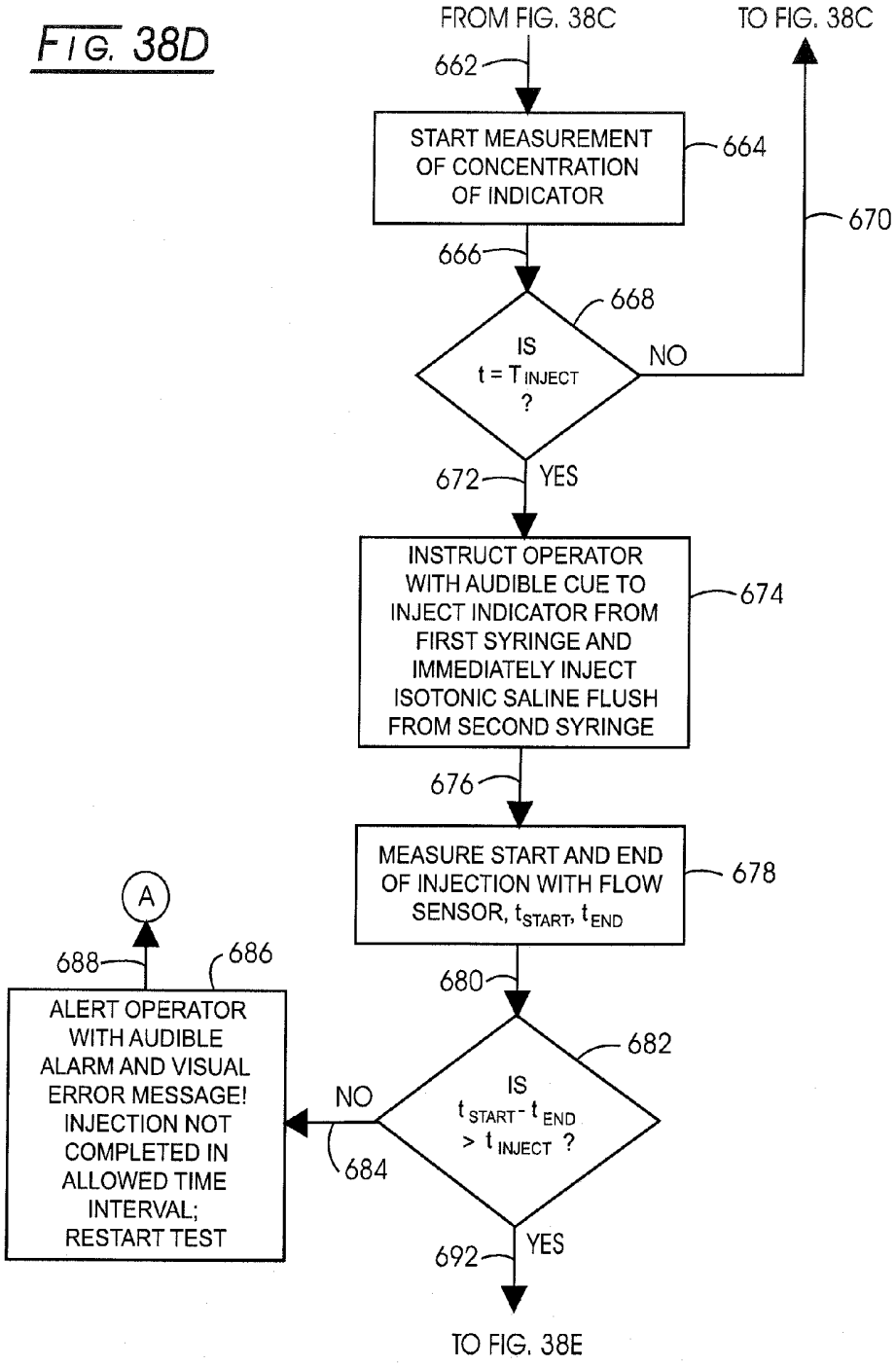

FROM FIG. 38C
TO FIG. 38C
662
START MEASUREMENT OF CONCENTRATION OF INDICATOR
664
666
668
IS t = T INJECT ?
NO
670
672
YES
INSTRUCT OPERATOR WITH AUDIBLE CUE TO INJECT INDICATOR FROM FIRST SYRINGE AND IMMEDIATELY INJECT ISOTONIC SALINE FLUSH FROM SECOND SYRINGE
674
676
MEASURE START AND END OF INJECTION WITH FLOW SENSOR, t START, t END
678
680
IS t START - t END > t INJECT ?
682
NO
684
YES
692
A
688
686
ALERT OPERATOR WITH AUDIBLE ALARM AND VISUAL ERROR MESSAGE! INJECTION NOT COMPLETED IN ALLOWED TIME INTERVAL; RESTART TEST
TO FIG. 38E

FIG. 38E

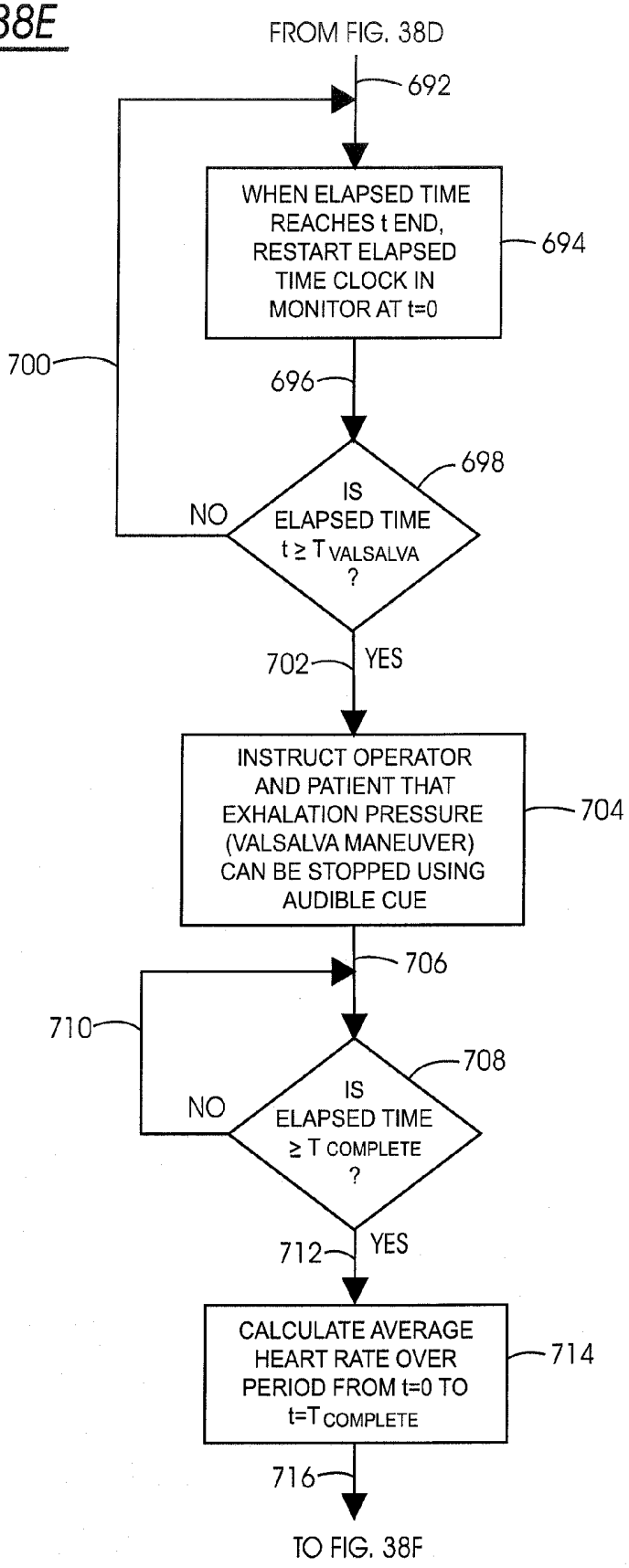
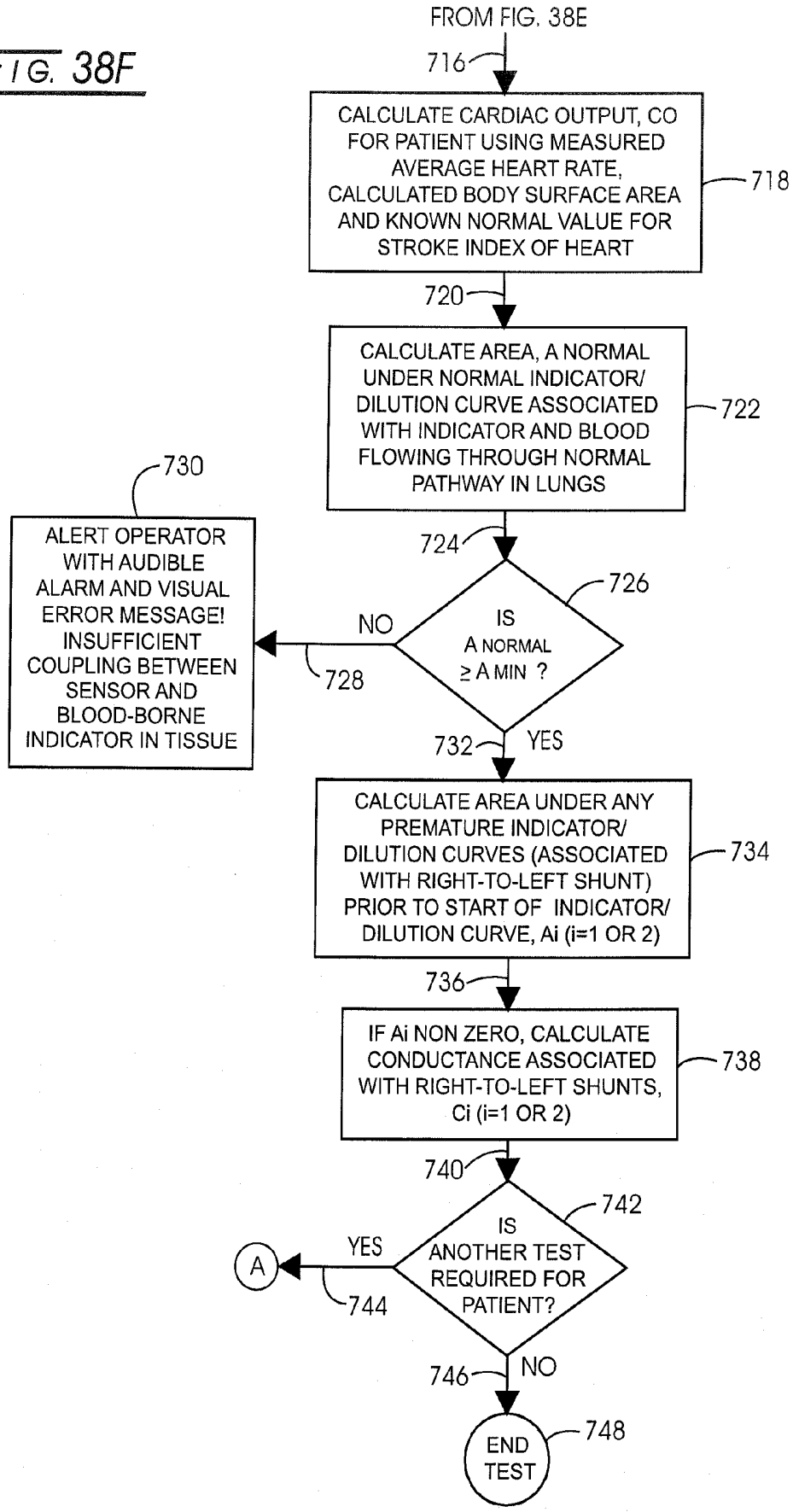

FROM FIG. 38D
692
WHEN ELAPSED TIME REACHES t END, RESTART ELAPSED TIME CLOCK IN MONITOR AT t=0
694
700
696
698
IS ELAPSED TIME t ≥ T VALSALVA ?
NO
702
YES
INSTRUCT OPERATOR AND PATIENT THAT EXHALATION PRESSURE (VALSALVA MANEUVER) CAN BE STOPPED USING AUDIBLE CUE
704
706
710
708
IS ELAPSED TIME ≥ T COMPLETE ?
NO
712
YES
CALCULATE AVERAGE HEART RATE OVER PERIOD FROM t=0 TO t=T COMPLETE
714
716
TO FIG. 38F

FIG. 38F


FROM FIG. 38E
716
CALCULATE CARDIAC OUTPUT, CO FOR PATIENT USING MEASURED AVERAGE HEART RATE, CALCULATED BODY SURFACE AREA AND KNOWN NORMAL VALUE FOR STROKE INDEX OF HEART
718
720
CALCULATE AREA, A NORMAL UNDER NORMAL INDICATOR/ DILUTION CURVE ASSOCIATED WITH INDICATOR AND BLOOD FLOWING THROUGH NORMAL PATHWAY IN LUNGS
722
730
ALERT OPERATOR WITH AUDIBLE ALARM AND VISUAL ERROR MESSAGE! INSUFFICIENT COUPLING BETWEEN SENSOR AND BLOOD-BORNE INDICATOR IN TISSUE
724
726
IS A NORMAL ≥ A MIN ?
NO
728
732
YES
CALCULATE AREA UNDER ANY PREMATURE INDICATOR/ DILUTION CURVES (ASSOCIATED WITH RIGHT-TO-LEFT SHUNT) PRIOR TO START OF INDICATOR/ DILUTION CURVE, Ai (i=1 OR 2)
734
736
IF Ai NON ZERO, CALCULATE CONDUCTANCE ASSOCIATED WITH RIGHT-TO-LEFT SHUNTS, Ci (i=1 OR 2)
738
740
IS ANOTHER TEST REQUIRED FOR PATIENT?
742
YES
A
744
746
NO
END TEST
748

SYSTEMS AND METHODS FOR HEMODYNAMIC DETECTION OF CIRCULATORY ANOMALIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 12/418,866 filed on Apr. 6, 2009, which claims the benefit of Provisional Application No. 61/156,723 filed on Mar. 2, 2009 and Provisional Application No. 61/080,724 filed on Jul. 15, 2008, all of which are hereby incorporated by reference herein.

TECHNICAL FIELD

[0002] The present invention generally relates to a system, method and apparatus for detection of circulatory anomalies in the mammalian body. Important types of such anomalies involve the heart and include anomalies generally referred to as right-to-left cardiac shunts.

BACKGROUND

[0003] An anomaly commonly encountered in humans is an opening between chambers of the heart, particularly an opening between the left and right atria, i.e., an Atrial Septal Defect, creating a right-to-left atrial shunt, or between the left and right ventricles, i.e., a Ventricular Septal Defect (VSD), creating a right-to-left ventricular shunt. A right-to-left shunt may occur as a defect within the vasculature leading to and from the heart, for example a Pulmonary Arteriovenous Malformation (PAVM) may be present, reflecting a direct connection between the pulmonary vein and pulmonary artery. Alternatively, a right-to-left shunt may occur as a defect between great vessels. For example, a Patent Ductus Arteriosus may be present, allowing shunting between the aortic arch and the pulmonary artery.

[0004] Over 780,000 patients suffer strokes each year in the U.S. resulting in 250,000 stroke related deaths. The total cost associated with stroke was reported to be $66 billion in the U.S. in 2007 (Rosamond 2008). Of the patient population presenting with stroke or the early warning sign known as transient ischemic attack (TIA or mini stroke), as many as 260,000 are postulated to be the result of a right-to-left shunt in the heart and/or pulmonary vasculature, allowing paradoxical emboli.

[0005] The most common form of right-to-left shunt is a patent foramen ovale (PFO), which is an opening in the wall of the heart that separates the right side of the heart from the left side of the heart. The right side of the heart receives oxygen-depleted blood from the body and then pumps this blood into the lungs for oxygenation. The lungs not only oxygenate the blood, but also serve as a "filter" for any blood clots or other emboli, as well as to metabolize other agents that naturally reside within the venous blood. During the fetal stage of development, an opening naturally exists between the right and left atria of the heart to enable circulation of the mother's oxygenated blood throughout the vasculature of the fetus. This opening between the right and left side of the fetal heart (known as the foramen ovale) permanently seals shut in consequence of the closure of an overlying tissue flap in approximately 80% of the population within the first eighteen months following birth. The noted flap often remains in a sealing orientation because of a higher pressure at the left side of the heart. However, in the remaining approximate 20% of the population, this opening fails to permanently close and is referred to as a PFO.

[0006] Most of the population with a PFO never experience any symptoms or complications associated with the presence of a PFO, since many PFOs are small enough to remain effectively "closed", or emboli may not form and travel to the right atrium, or they may not pass through a PFO even if it is present and open; thus the paradoxical nature of these emboli. However, for some subjects, this normally closed flap covering the foramen ovale temporarily opens, allowing blood to flow directly from the right side to the left side of the heart. As a consequence, any emboli such as blood clots or other active agents escaping through the PFO bypass the critical filtering functions of the lungs and flow through the temporary open (patent) foramen ovale and directly to the left side of the heart. Once in the left side of the heart, these emboli pass directly into the arterial circulatory system. Since a significant portion of the blood exiting the left side of the heart flows to the brain, any unfiltered blood clots or agents, such as serotonin, may be delivered to the brain. The presence of these now cerebral emboli in the brain arterial flow can produce debilitating and life-threatening consequences. These consequences are known to include stroke, heart attack and are also believed to be one of the causes of certain forms of severe migraine headaches. For further background on circulatory anomalies, see:

[0007] 1) Banas, J., et al. *American Journal of Cardiology* 28: 467-471 (October 1971);

[0008] 2) Castillo, C., et al. *American Journal of Cardiology* 17: 691-694 (May 1966);

[0009] 3) Schwedt, T. J., et al., "Patent Foramen Ovale Migraine—Bringing Closure to the Subject." *Headache* 46(4): 663-671 (2006);

[0010] 4) Spies, C., et al., "Transcatheter Closure of Patent Foramen Ovale in Patients with Migraine Headache." *Journal of Interventional Cardiology* 19(6): 552-557 (2006).

[0011] A relatively large number of patients (approximately three million) have had or may be undergoing sclerotherapy, treating, for instance, varicose veins. This therapy involves an injection of sclerosing solution that in effect creates emboli. If patients undergoing sclerotherapy are among the portion of the population with a PFO, creation of emboli that may bypass the filtering aspect of the lungs creates a significant risk of initiating a TIA, stroke or heart attack. This risk could be avoided by effectively and efficiently screening for a right-to-left shunt and administering appropriate therapy.

[0012] Based on the growing clinical evidence linking strokes, transient ischemic attacks (TIAs) and migraine headaches to right-to-left shunts, at least 16 companies have now entered the field of transcatheter shunt treatment devices for closure of the most common form, viz., a PFO, and certain of these devices are approved for sale in one or more principalities.

[0013] Percutaneous shunt closure devices are expected to soon be widely available in the U.S. for PFO closure, and approximately 20% of the adult population is estimated to have a congenital PFO. Unfortunately, there is currently no available method suitable for widespread screening for the presence of a PFO when the patient experiences early warning signs signaling an ischemic incident, or the patient exhibits or is exposed to an elevated risk of a stroke. Consequently,

the "at risk" fraction of the population with a right-to-left shunt is most often resigned to the possibility of experiencing a stroke before definitive right-to-left shunt testing is performed. Only then are methods such as transesophageal echocardiography (TEE) performed to detect the presence of a right-to-left shunt. If detected, the patient may elect to be treated with anti-clotting agents or elect to undergo transcatheter right-to-left shunt closure or the more conventional open-heart procedure for right-to-left shunt closure.

[0014] TEE in conjunction with the injection of agitated saline contrast "bubbles" is used somewhat as a last resort. While the so-called TEE "bubble study" has not been reviewed by the U.S. Food and Drug Administration and so is performed "off-label", it is still considered the "gold standard" for determining the presence of a right-to-left cardiac shunt. In carrying out this test, microbubble contrasts, produced by the agitation of a saline solution, is injected into a vein leading to the right side of the heart. As this is underway, the somewhat sedated patient is required to bear down with their abdominal muscles (as during defecation) to perform a "Valsalva" maneuver, the release of which will momentarily reverse the pressure differential between the right and left atria and cause a PFO, if present, to open, while an ultrasound transducer, positioned in the esophagus at the level of the heart, is used to record the passage of the microbubbles across the shunt into the left atrium. Because of gagging problems, the patient is partially anesthetized. Typically, patients experience discomfort and the test is hardly suited for screening. The TEE test is also expensive, with an equipment total cost of between $75,000 and $322,000. It additionally requires a physician with a specialized two year fellowship and an anesthesiologist or anesthetist, along with several nurses to assist with operation of the equipment.

[0015] A related test is referred to as transthoracic echocardiography (TTE). Again, a microbubble contrast is injected into a vein leading to the right side of the heart. Since the ultrasound detector is positioned externally over the chest wall in a TTE, the Valsalva maneuver for this procedure is performed by having the patient blow forcefully into a small tube, sometimes connected to a manometer, while ultrasonic echocardiograms are made through the chest wall. The TTE procedure also requires the use of expensive equipment and exhibits relatively poor sensitivity, by some reports as low as 60%.

[0016] A third test, incorporating transcranial Doppler (TCD) technology, also uses microbubbles as a contrast agent along with the Valsalva maneuver. Here, however, ultrasonic sensors located bilaterally on the skull are used to measure embolic signals produced by any microbubbles transiting the mid cerebral artery. This TCD method exhibits a relatively high sensitivity when it can be used. Unfortunately, approximately 20% of the population has a cranial bone that is too thick for sonic transducing to "see" the mid-cerebral artery, and equipment costs range between approximately $30,000 to $45,000. U.S. Patent Publication US2006/0264759 describes such systems and methods for grading microemboli in blood associated with ultrasound contrast agenda (e.g., small air bubbles) within targeted vessels by using Doppler Ultrasound system.

[0017] Additional description of existing methods of analyzing circulation and detecting certain circulatory anomalies are present in the following:

[0018] 5) Swan, H. J. C., et al., "The Presence of Venoarterial Shunts in Patients with Interatrial Communications." *Circulation* 10: 705-713 (November 1954);

[0019] 6) Kaufman, L., et al., "Cardiac Output Determination by Fluorescence Excitation in the Dog." *Investigative Radiology* 7: 365-368 (September-October 1972);

[0020] 7) Karttunen, V., et al. *Acta Neurologica Scandinavica* 97: 231-236 (1998);

[0021] 8) Karttunen, V., et al., "Ear Oximetry: A Noninvasive Method for Detection of Patent Foramen Ovale—A Study Comparing Dye Dilution Method and Oximetry with Contrast Transesophageal Echocardiography." *Stroke* 32(2): 32: 445-453 (2001).

[0022] A continuing difficulty with existing methods is the efficacy of using microbubble contrasts as a circulatory tracking indicator. Microbubbles are created just prior to use, are a transient structure, and decidedly non-uniform in creation and application. It is difficult if not impossible for microbubbles to be used for quantitative measurements, and thus clinicians are forced to rely on a simple binary positive or negative result assessment. In part, the inability to effectively quantify the conductance of a shunt is revealed in the relatively low sensitivity of the existing methods.

[0023] A further problem with existing methods is the difficulty in effectively detecting the circulatory tracking indicator in the form of microbubbles. Each of the existing methods, including the TEE, TTE and TCD methods, suffer from barriers for routine use for screening, whether due to the need for anesthesia or expensive equipment. There is a need for more efficient circulatory tracking reagents, i.e. a reagent that can be reproducibly introduced into the circulatory system, be quantitatively detectable, and utilize relatively straightforward detection systems that are easily tolerated by patients.

[0024] One difficulty with improving the present technology in circulatory tracking reagents is that there heretofore has been no animal model available for screening a variety of different circulatory tracking reagents and their compatible detection systems.

[0025] There exists a growing body of clinical evidence linking the presence of right-to-left shunts to the risk of embolic strokes and occurrence of migraine headaches. In spite of this evidence, there remains a significant unmet need for a high sensitivity, low-cost and non-invasive method to screen those patients at increased risk of stroke in order to detect PFOs or other circulatory anomalies. The ability to screen at-risk patients is a critically unmet need, since shunt-related strokes can only be prevented if the presence of the shunt is detected and closed, or the patient receives anti-clotting therapy, in advance of the occurrence of a stroke. In addition, there is likewise a significant unmet need for a highly sensitive, quantitative low-cost method for evaluating the effectiveness and durability of the shunt closure at three to four time points following the percutaneous closure of the right-to-left shunt. This follow-up testing following shunt closure continues to be essential for the effective titration of the medical therapy administered prior to closure, and for assuring adequacy of the "seal" closing a PFO or other shunt, in order to minimize the risk of future shunt-related strokes.

BRIEF SUMMARY

[0026] The present application is directed to systems, methods and apparatus for detecting and quantifying right-to-left cardiac shunts and/or pulmonary shunts. The preferred indicator, which is employed, is indocyanine green dye (ICG)

that will fluoresce when exposed to an appropriate wavelength of higher energy light, for example, a laser in the red region. The procedure is under the control of a controller/monitor having a visual display and being capable of providing cues to both the operator and the patient.

[0027] A venous access catheter is employed in connection with a peripheral vein such as the antecubital vein in an arm. This delivery system utilizes a unique resistance feedback-controlled heater-type fluid sensor to control injection times for both the indicator and a predetermined volume of isotonic saline used to "flush" flow sensor extension tubing, the venous catheter and peripheral vein so that all injected indicator is promptly delivered to the right atrium of the heart.

[0028] Sensing of the indicator concentration takes place at an arterial vasculature, for example, the pinna or fossa/scapha of the human ear. Additionally, heart rate may be monitored.

[0029] Embodiments of a system may use one or more optical sensors that are positioned along a patient's skin for transcutaneously analyzing the arterial vasculature therein. These optical sensors may include a plurality of laser/photodetector pairs, such as an array of three laser/photodetector pairs, which are directed to the arterial vasculature underlying the skin of the patient at the selected location. As mentioned above, this location may be the fossa/scapha or other portion of the ear pinna, or another location where relatively thin tissue contains an arterial blood network.

[0030] Where a test is to be carried out with a Valsalva maneuver, the mouthpiece of a manometer tubing set or of a Valsalva maneuver pressure sensing unit is positioned in the mouth of the patient and connected to a pressure transducer in the controller/monitor. The patient then performs a Valsalva maneuver by exhaling into the mouthpiece to produce some threshold exhalation pressure for some required period of time.

[0031] A visual readout of instantaneous exhalation pressure is made available both to the operator and the patient as well as the threshold level of pressure which must be achieved and maintained in order to successfully carry out the Valsalva maneuver. Alarms and visual error messages are introduced where the Valsalva maneuver is not carried out properly. The controller/monitor preferably instructs the operator with an audible cue to inject indicator and immediately inject isotonic saline flush. These are generally carried out with two syringes working in conjunction with a three-way valve. If the injection interval is not appropriate, again an audible alarm and error message may be provided to the operator. For the relief of the patient, an audible cue is also given when the Valsalva maneuver can be stopped (released).

[0032] The controller/monitor then calculates average heart rate and cardiac output, using that average heart rate, calculated body surface area, and a known normal value for stroke index of the heart. The system then calculates an area under a normal indicator/dilution curve associated with indicator and blood flow through a normal pathway in the lungs. Additionally, the controller/monitor calculates the area under any premature indicator dilution curve which will be associated with a right-to-left shunt. The controller/monitor further corrects the main indicator/dilution curve for a recirculation phenomenon and quantifies any right-to-left shunt by calculating the conductance associated with such shunts.

[0033] Other aspects and features of the invention will become apparent to those skilled in the art upon review of the following detailed description of exemplary embodiments along with the accompanying drawing figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] In the following descriptions of the drawings and associated exemplary embodiments, like reference numerals across several views refer to identical or equivalent features, and:

[0035] FIG. **1** is a schematic representation of a heart showing a right-to-left heart shunt;

[0036] FIG. **1**A is an enlargement of a portion of the schematically illustrated heart of FIG. **1**;

[0037] FIG. **2** is a chart showing excitation and fluorescence signal attenuation for depth of artery versus wavelength in connection with two regulatory approved dyes;

[0038] FIG. **3** is a schematic end view of a fluorescence probe used for bench-top and animal testing;

[0039] FIG. **4** is a schematic representation of the end geometry utilized with the probe shown in FIG. **3**;

[0040] FIG. **5** is a schematic representation of bench-top test apparatus employed for optimization of a fluorescence detection system;

[0041] FIG. **6** is a representation of the display of a digital oscilloscope used in bench-top testing;

[0042] FIG. **7** is a representation of measured fluorescence peak signal amplitudes with respect to the excitation level of a laser;

[0043] FIG. **8** is a pictorial representation of a test being undertaken under the protocol of the invention;

[0044] FIG. **9** is a schematic representation of a right-to-left shunt test according to the invention;

[0045] FIG. **10** is a representation of a display output showing concentration of indicator in blood, measured exhalation pressure level and interval of injection of indicator;

[0046] FIG. **11** is a schematic representation of the invention showing two shunt conditions;

[0047] FIG. **12** is a display relating concentration of indicator in blood, measured exhalation pressure level and the elapsed time after indicator injection corresponding with the schematic representation of FIG. **11**;

[0048] FIG. **13** is a graph relating concentration of indicator with time;

[0049] FIG. **14** is a graph relating indicator signal amplitude with respect to elapsed time since the start of an injection and further showing a recirculation effect;

[0050] FIG. **15** is a view of a display seen in FIG. **8**;

[0051] FIG. **16** is an assembly view of the indicator injection system of the invention;

[0052] FIG. **17** is an exploded view of a fluid sensor employed with the system of FIG. **16**;

[0053] FIG. **18** is a side view of the fluid sensor employed with the invention;

[0054] FIG. **19** is a sectional view taken through the plane **19-19** in FIG. **18**;

[0055] FIG. **20** is a front view of a printed circuit employed with the fluid sensor of the invention;

[0056] FIG. **21** is a perspective view of a pipe employed with the fluid sensor of the invention;

[0057] FIG. **22** is a perspective view of joined enclosure halves of the fluid sensor of the invention;

[0058] FIG. **23** is a front view of a connector employed with the fluid sensor of the invention;

[0059] FIG. **24** is a sectional view taken through the plane **24-24** in FIG. **23**;

[0060] FIG. **25** is a front view of a connector employed with the fluid sensor of the invention;

[0061] FIG. **26** is a sectional view taken through the plane **26-26** in FIG. **25**;

[0062] FIG. **27** is an assembly view of a sensor employed with the invention;

[0063] FIG. **28** is an anatomical view of a human ear showing arterial vasculature;

[0064] FIG. **29** is a top view of the sensor shown in FIG. **27**;

[0065] FIG. **30** is a sectional view taken through the plane **30-30** shown in FIG. **29**;

[0066] FIG. **31** is an assembly view of a mouthpiece/tubing assembly for use in carrying out a Valsalva maneuver;

[0067] FIG. **32** is a block schematic diagram showing the components of a controller/monitor/data acquisition apparatus according to the invention;

[0068] FIG. **33** is a block schematic view of an animal test arrangement;

[0069] FIG. **34** is a schematic view of a pig heart as employed in exemplary animal tests of the invention;

[0070] FIG. **35** is a graph showing signal amplitude versus elapsed time developed with the animal studies of the invention;

[0071] FIG. **36** is a plot of peak signal and concentration area for an initial twenty tests described in Table 1;

[0072] FIG. **37** is a plot similar to that at FIG. **36** but showing a second twenty tests undertaken as listed in Table 1; and

[0073] FIGS. **38**A-**38**F combine as labeled thereon to form a flow chart illustrating an exemplary method and procedure for detecting a right-to-left cardiac and/or pulmonary shunt.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0074] When a right-to-left shunt is present in the heart or the pulmonary circulation of the human body, a system with two or more alternative blood flow pathways effectively exists. As described above, the most common form of right-to-left shunt in the heart is known as a PFO. During the fetal stage of development, an opening naturally exists between the right and left side of the heart to enable circulation of the mothers oxygenated blood throughout the vasculature of the fetus. This opening between the right and left side of the fetus' heart (known as the Foramen Ovale) permanently seals shut in about 80% of the population within the first eighteen months following birth. This opening fails to permanently close in the remaining about 20% of the population.

[0075] For some individuals, the normally closed overlying tissue flap covering the Foramen Ovale temporarily opens allowing blood to flow directly from the right side to the left side of the heart. As a consequence, any emboli such as blood clots or other metabolically active agents bypass the critical filtering/metabolic functions of the lungs and flow through the temporarily open Foramen Ovale directly to the left side of the heart. Once in the left side of the heart, these emboli pass directly into the circulatory system. Since a portion of the blood exiting the left side of the heart flows to the brain as well as the coronary arteries of the heart, any unfiltered blood clots or agents can produce debilitating and life-threatening consequences. These consequences are known to include stroke, heart attack and are also now believed to be one of the principal causes of certain forms of severe migraine headaches.

[0076] For further discussion, see the following publications:

[0077] 9) Spies C., et al., "Patent Foramen Ovale Closure With the Intrasept Occluder: Complete 6-56 Months Follow-Up of 247 Patients After Presumed Paradoxical Embolism," *Catheterization and Cardiovascular Interventions* 71: 390-395 (2008);

[0078] 10) Wammes-van der Heijden E. A., et al., "Right-to-left shunt and migraine: the strength of the relationship," *Cephalalgia;* 26: 208-213 (2006);

[0079] 11) Schwedt T. J., et al., "Patent Foramen Ovale and Migraine—Bringing Closure to the Subject," *Headache* 2006 46: 663-671 (2006);

[0080] 12) Weinberger J., "Stroke and Migraine," *Current Cardiology Reports* 2007; 9: 13-(2007).

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0081] When a right-to-left shunt is present in the heart or the pulmonary circulation of the human body, a system with two or more alternative blood flow pathways effectively exists. As described above, the most common form of right-to-left shunt in the heart is known as a PFO. During the fetal stage of development, an opening naturally exists between the right and left side of the heart to enable circulation of the mothers oxygenated blood throughout the vasculature of the fetus. This opening between the right and left side of the fetus' heart (known as the Foramen Ovale) permanently seals shut in about 80% of the population within the first eighteen months following birth. This opening fails to permanently close in the remaining about 20% of the population.

[0082] For some individuals, the normally closed overlying tissue flap covering the Foramen Ovale temporarily opens allowing blood to flow directly from the right side to the left side of the heart. As a consequence, any emboli such as blood clots or other metabolically active agents bypass the critical filtering/metabolic functions of the lungs and flow through the temporarily open Foramen Ovale directly to the left side of the heart. Once in the left side of the heart, these emboli pass directly into the circulatory system. Since a portion of the blood exiting the left side of the heart flows to the brain as well as the coronary arteries of the heart, any unfiltered blood clots or agents can produce debilitating and life-threatening consequences. These consequences are known to include stroke, heart attack and are also now believed to be one of the principal causes of certain forms of severe migraine headaches.

[0083] For further discussion, see the following publications:

[0084] 9) Spies C., et al., "Patent Foramen Ovale Closure With the Intrasept Occluder: Complete 6-56 Months Follow-Up of 247 Patients After Presumed Paradoxical Embolism," *Catheterization and Cardiovascular Interventions* 71: 390-395 (2008);

[0085] 10) Wammes-van der Heijden E. A., et al., "Right-to-left shunt and migraine: the strength of the relationship," *Cephalalgia;* 26: 208-213 (2006);

[0086] 11) Schwedt T. J., et al., "Patent Foramen Ovale and Migraine—Bringing Closure to the Subject," *Headache* 2006 46: 663-671 (2006);

[0087] 12) Weinberger J., "Stroke and Migraine," *Current Cardiology Reports* 2007; 9: 13-(2007).

[0088] Embodiments of a method, apparatus, and system are described herein for effectively monitoring subject patients for circulatory anomalies. These methods, apparatus, and systems are useful for determining the magnitude of the

flow rate associated with a right-to-left cardiac shunt and/or within the pulmonary vasculature, for instance.

[0089] In a preferred embodiment, a non-invasive optical sensor is positioned on the surface of the subject's skin at a location (e.g., the auricle of the ear). A biocompatible indicator is next injected at a predetermined rate into a peripheral (e.g., antecubital) vein of the subject while the subject may be directed to engage in a breathing maneuver (i.e., a Valsalva maneuver), such as by exhaling into a manometer mouthpiece. A pressure differential may be thus produced that is effective for causing the opening of a PFO, for instance, allowing blood to flow across a right-to-left cardiac shunt. The non-invasive optical sensor is used to transcutaneously measure the concentration of the injected indicator as a function of time. As seen below in connection with FIG. **10**, if a premature inflection or peak occurs in the indicator concentration level at a point in time t_1 that is prior to the rise and fall of the concentration associated with the majority of the indicator flowing through the normal pathway of the lungs and arriving at the sensor at a point in time t_2, then a right-to-left cardiac shunt (PFO). As described herein, exemplary systems, apparatus and methods provide for calculating and quantifying the extent of circulatory anomalies in a manner superior to any other systems, apparatus and methods available, and are capable of providing diagnostics effective for determining the appropriate clinical treatment of circulatory anomalies.

[0090] In the discourse to follow research activities are somewhat tracked as the invention developed. In this regard, bench tests are described looking to basic studies that lead to subsequent animal (pig) tests. Fundamentals of measuring cardiac output led to the evolution of a method and system wherein right-to-left cardiac shunts could not only be detected but also quantified.

[0091] Effective utilization of the system requires an indicator, i.e., a circulatory tracking reagent, or an analyte capable of passing through the lungs, and which provides information with respect to the left atrium of the heart. Previous systems for detecting PFOs, which relied on ultrasonic detection of microbubbles, are almost completely incapable of providing information on the size of as PFO, and require semi-invasive detection methods such as trans-esophageal ultrasound. The inventors had earlier studied techniques for monitoring total circulating blood volume and cardiac output as described at U.S. Pat. No. 6,299,583 by Eggers, et al., issued Oct. 9, 2001, and incorporated herein by reference.

[0092] Referring initially to FIG. **1**, a mammalian heart is schematically represented and identified in general at **10**. The right atrium is shown at **12** and correspondingly, the left atrium is represented at **14**. Beneath the right atrium **12** is the right ventricle **16** which is located adjacent to the left ventricle **18**. An interauricular septum **20** separates atria **12** and **14** and is shown in FIG. **1**A in enlarged fashion to illustrate a PFO represented generally at **22**. Typically, venous blood enters the heart through the superior vena cava and inferior vena cava, **19** and **19'**, feeding the right atrium **12**, to the right ventricle **16** and pulmonary artery passing to the lungs. From the lungs, the left atrium is supplied with oxygenated blood via the pulmonary veins **17** and **17'**, with that blood then being pumped throughout the arterial system by the left ventricle **18** to the aorta, (not shown in FIG. **1**).

[0093] As illustrated in FIG. **1**, the atypical presence of a PFO **22** results from, for example, the presence of displaceable tissue flap **24**, creating opening **26**. Shunt flow of venous blood from the right to the left atria through opening **26** is represented in FIG. **1**A by the arrow **28**. Shunt flow thus does not pass through the lungs, bypassing the pulmonary circulatory circuit, and potentially allowing detrimental blood components to bypass the filtering capabilities of the lung capillary beds.

[0094] The present disclosure describes exemplary embodiments of a system and method for detecting and quantifying atypical or abnormal blood flow, particularly left to right atrial shunts, and other arterial-venous malformations and disruptions in typical blood circulation. The method relies on effectively quantifying the relative blood flow or blood flow volume passing through normal and aberrant pathways. One example of such aberrant pathways are openings, or shunts between the right and left atria.

[0095] In order to provide for effective quantification of shunts between arterial and venous blood flow, an indicator (circulatory tracking reagent) is used. It was initially determined that a high degree of sensitivity would be achieved in screening capabilities for detecting atypical blood flow through the utilization of a fluorescing moiety as an indicator in a cardiac output (CO) emulating system. Accordingly, fluorescing dyes were examined and, in particular, fluorescing dyes which have been approved for use in humans. Two such exemplary dyes were available, fluorescein and indocyanine green dye (ICG).

[0096] As discussed further below, a number of additional circulatory tracking reagents are available for use with the system, including such indicators as spectrophotometric, densitometric and radiometric indicators. A variety of previous efforts to utilize circulatory tracking indicators is disclosed in, for example: U.S. Pat. No. 3,412,728, which describes a method and apparatus for monitoring blood pressure, utilizing an ear oximeter clamped to the ear to measure blood oxygen saturation using photo cells which respond to red and infrared light; U.S. Pat. No. 3,628,525, which describes an apparatus for transmitting light through body tissue for purposes of measuring blood oxygen level; U.S. Pat. No. 4,006,015, which describes a method and apparatus for measuring oxygen saturation by transmission of light through tissue of the ear or forehead; and U.S. Pat. No. 4,417,588, which describes a method and apparatus for measuring cardiac output using injection of indicator at a known volume and temperature and monitoring temperature of blood downstream. This and similar art suffer from an inability to effectively quantify the magnitude (i.e., functional conductance) of shunts, in part because of the failure and or inability to effectively quantify cardiac output.

[0097] A number of existing patents also describe potential reagent systems that if adapted, could be utilized with present systems, methods and apparatus. For example, U.S. Pat. No. 4,805,623 describes a spectrophotometric method used for quantitatively determining concentration of a dilute component in an environment (e.g., blood) containing the dilute component where the dilute component selected from group including corporeal tissue, tissue components, enzymes, metabolites, substrates, waste products, poisons, glucose, hemoglobin, oxy-hemoglobin, cytochrome. The corporeal environment described includes the head, fingers, hands, toes, feet and earlobes. Electromagnetic radiation is utilized including infrared radiation having a wavelength in the range of 700 to 1,400 nanometers. U.S. Pat. No. 6,526,309 describes an optical method and system for transcranial in vivo examination of brain tissue (e.g., for purpose of detect-

ing bleeding in the brain and changes in intracranial pressure), including the use of a contrast agent to create image data of the examined brain tissue.

[0098] Detailed examination of the desirable properties of fluorescein and ICG dye demonstrate how other indicators can be applied to present systems and methods. Notably, these fluorescing dyes are excited by one wavelength of electromagnetic radiation, and emit a detectable signal at a second wavelength. Looking to FIG. **2** in this regard, the excitation signal for fluorescein dye is represented at curve **30** which is an excitation signal at less than about 500 nanometers (nm). A resultant fluorescence emission from the excitation at **30** is shown at curve **32**, at a wavelength of about 525 nm.

[0099] Looking to the ICG dye spectrum, an excitation curve is shown at **34**, having a peak excitation wavelength at about 785 nanometers. Correspondingly, the fluorescence emission from excitation at curve **34** is represented at curve **36** with a peak emission wavelength of about 830 nanometers. Directed across FIG. **2** is a curve **38** representing the level of constant signal attenuation or absorption of about 37% resulting from passage of signal through tissue. Note that if a blood vessel is about one millimeter beneath the surface of skin, the system would perform at about 37% of the original intensity of the excitation signal and fluorescence signal for the case of ICG dye indicator. In contrast, a 37% decrease in excitation and emission signal level would result for the fluorescein dye indicator at a tissue thickness of only 0.25 mm. Since the blood vessels being targeted are at least 1 mm below the skin surface, the attenuation and associated signal loss would be much larger. Therefore, ICG dye is the preferred indicator.

[0100] Turning again to the ICG dye spectrum, note that the excitation signal **34** for ICG intersects curve **38** at a depth allowing for readily reaching blood vessels, for example within the pinna (e.g., scaphoid fossa) of the ear. Accordingly, ICG dye is usable as a circulatory tracking agent when detecting through skin, and ICG dye was the indicator elected for subsequent study.

[0101] To utilize this fluorescing form of indicator in carrying out cardiac output related procedures, a sensor or probe apparatus having the capability to direct laser excitation illumination to a blood vessel as well as to collect and filter an emitted fluorescent response (i.e., a sensor having both excitation and detection components) was developed utilizing fiber optic technology. Looking to FIG. **3**, one end of such a sensor, **42**, is revealed. At the center of sensor **42** is a fiber optic channel identified at **44** which projects excitation emissions, for example, at **785** nanometers for ICG. Surrounding central fiber **44** are 7 glass fibers identified at **46***a*-**46***g*. All of the glass fibers **46***a*-**46***g* in this exemplary embodiment have an outside diameter of 600 microns.

[0102] When an ICG indicator within the bloodstream reaches the site of irradiation with 785 nm (laser) light, the fluorescent moiety within the ICG indicator is excited as described in connection with FIG. **2** to an elevated energy state for a brief period. As the excited moiety returns to its normal energy state, it emits light at a longer wavelength (viz., 830 nm) and the difference between the excitation wavelength (viz., 785 nm) and the fluorescence emission wavelength (viz., 830 nm) is known as the Stokes Shift. This Stokes Shift of nominally 45 nm allows the fluoresce emission to be extracted by using a interferential or other type of optical filter to reflect or otherwise attenuate all but the wavelength band of interest (viz., 820 to 840 nm).

[0103] It is important that the interface between this interferential filter and the fiber optic sensor be accurately aligned. With alignment at a preferred angle of about 7 degrees, the filter will reflect unwanted wavelengths. Angles of photon incidence of greater than about 45 must be avoided since interferential filters will become ineffective.

[0104] Looking to FIG. **4**, sensor **42** reappears along with filter **48**. Filters, as represented at **48**, typically are coated at their entrance with a metal as represented at **50**. Metal **50** represents an optical coupling agent known to those skilled in the art of optics and multi-coated optical lenses. It was found beneficial to assure that the alignment was about 7 degrees to avoid undue reflections at angles which would pass the filter. Beyond the filter **48** is a photo detector **52**. In general, establishing a quality sensor/filter interface permitted the use of higher laser power levels.

[0105] In the course of investigation, a variety of bench top jigs or the like were developed. One such arrangement is revealed in FIG. **5**. As shown, a laser excitation and fluorescence collecting sensor is represented schematically at **58**. In this regard, a glass fiber laser input to sensor **58** from a source shown at block **60** is coupled with a fiber transmitter **62** extending to a spliced connection **64**. In turn, connection **64** is coupled to the input of sensor **58**. Block **60** incorporates a multi-mode laser subsystem, such as the laser subsystem marketed as a model No. 785-2P-OEM by Ocean Optics, Inc. Splice connection **64** in this exemplary embodiment is a model No. SMA-2FL-ADP.

[0106] A collected fluorescence output is directed from splice **64** via glass fiber **66** to an interferential filter passing generally 830 nanometers and represented at block **68**. Filter **68** was provided as a model No. 679-3230 marketed by OptoSigma, Inc. As represented by line **70**, filter **68** is connected such that it operatively cooperates with a photomultiplier tube **72**. Tube **72** was provided as a model No. H7712-10 marketed by Hamanatsu, Inc.

[0107] During initial testing, signals from photomultiplier tube **72** were directed as represented at arrows **74**-**76** to a phase one digital oscilloscope provided as a model No. DT03054 marketed by Techtronics, Inc. At a later time, such signals would be further directed as represented at arrows **79** and **80** to a phase **2** controller/monitor **82**, comprising a controller/data acquisition system discussed later herein.

[0108] The transmitting and receiving end of sensor **58** performed in conjunction with a sealed glass capillary cylinder sample tube, e.g., **84**, carrying ICG fluorescing dye of given concentrations. In general, such tubes as at **84** have an inside diameter of 1-2 milliliters. To simulate performance transcutaneously, the tube **84** is positioned just below the surface of a human skin phantom material represented at **86**. For many of the tests, sensor **58** was moved along tube **84** or transversely across a plurality of tubes of varying ICG dye concentrations as represented by the motion arrow **88**. The movement was imparted through a DC motor driven apparatus.

[0109] As shown in FIG. **6**, a digital oscilloscope was utilized to monitor a static test carried out utilizing a plurality of sample cylinders as at **84**, each carrying a unique and different ICG concentration as measured in micrograms/milliliter (μg/ml). This test was performed in air as opposed to utilizing the phantom skin **86**. Curve **89** of FIG. **6** demonstrates the fluorescence emissions of samples of a range of ICG concentration. Note that if the concentration of ICG elevates from 0.5 to

10.0 μg/ml, the strength of the fluorescence signal increases dramatically. Noise is represented at the 0.0 μg/ml position.

[0110] Bench top testing also evolved the information set out at curve **90** in FIG. **7**. Curve **90** represents a static test in which sample vials of ICG having a concentration of 2 micrograms per ml were subjected to varying power levels (as measured in milliwatts) of an excitation laser. Note that very high signal levels in millivolts were recognized as the power level reached about 70 milliwatts.

[0111] As the investigation continued, the ability to simply and quickly screen patients for right-to-left cardiac shunts was envisioned. Referring to FIG. **8**, a rendition of an exemplary system for achieving that goal is depicted. In the figure, the controller/monitor/data acquisition system described at block **82** reappears with that device positioned upon a portable stand and providing, inter alia, a display represented generally at **98** and having interactive features as well as showing a dye dilution type curve which may be analyzed for cardiac hemodynamics.

[0112] A patient being screened is shown at **100** sitting on a chair **102**. A nurse or clinician is shown at **104** administering the test under cueing guidance from the logic within controller/monitor **82**. Patient **100** is shown exhaling or blowing into a mouth-piece **106** which, in turn, extends via a delivery tube **108** to a manometer within the controller/monitor **82**. Thus, the hemodynamic testing according to present systems and methods may employ a "Valsalva manuever," wherein the patient **100** blows into mouth-piece **106**, creating backpressure within the lungs of the patient.

[0113] As mentioned previously, the Valsalva maneuver, by inducing a positive pressure difference between the right and left side of the heart, simulates conditions under which transient cardiac shunts (e.g., right-to-left atrial shunts such as a PFO) tend to open and allow a cross-flow of blood between the arterial and venous blood circulation. As maintenance of lung back-pressure is preferable for effectively identifying shunts, controller/monitor **82** may terminate the test during the Valsalva maneuver if pressure is seen to drop below 40 mm of mercury for some period of time.

[0114] A small sensor **110** is shown attached to the ear of patient **100**. Sensor **110**, in a preferred embodiment, incorporates three paired laser excitation components (emitters) and filtered fluorescence pick up (detector) components. These are polled to find the strongest output signal of fluorescence, such control being provided by the cable **112** operating in conjunction with the controller/monitor **82**. The sensor **110** is preferably positioned on the surface of the ear pinna, such as along the scaphoid fossa region thereof. Additionally, during a period of about 60 seconds following the injection of the indicator, the heart rate of patient **100** is monitored using a conventional non-invasive heart rate monitor such as that marketed by Nellcor Pulse Oximeter, Inc. of Boulder Colo. The heart rate monitor is shown at **114** operatively associated with the controller/monitor **82** as represented at cable **116**.

[0115] In FIG. **8**, nurse or clinician **144** is shown to be working with two syringes represented at **120** and **122**. Syringes **120** and **122** are connected to a hand actuated three-way valve shown generally at **124**. Syringe **120** holds a predetermined amount of indicator, while syringe **122** holds isotonic saline. The injection commencement and interval is monitored by a flow sensor represented generally at **126**. From the flow sensor **126**, a delivery tube **130** extends to a relatively short vein access catheter represented generally at **132**. Catheter **132** is placed in a peripheral vein (e.g., the antecubital vein in the arm) of patient **100**. Patient **100** is subsequently instructed to commence the Valsalva maneuver, thereafter maintaining a minimum of 40 mm of mercury pressure.

[0116] The test at hand is temporal in nature, thus proper timing of each aspect of the test is quite important. Accordingly, the controller/monitor **82** both monitors and cues each step in the process. In this regard, the controller/monitor **82** may provide patient **100** with visual feedback that helps the patient regulate his/her exhalation pressure level and may also time the Valsalva maneuver. The Valsalva maneuver should last about 15 seconds, and may be represented as a bar on the display **98** of the controller/monitor **82**.

[0117] At a cued time provided by the controller/monitor **82**, injection of the indicator bolus (e.g., 2 ml of 2.5 mg/ml) ICG dye over about a period of one second is performed by the nurse or clinician **144**, followed immediately by the injection of a clearing bolus of isotonic saline (e.g., 5 ml injected over a period of 2 seconds). The rapid injection of the indicator bolus and the clearing bolus is carried out to assure that all of the injected indicator is rapidly transported from the injection site to the right atrium of the heart. If the indicator and isotonic saline are not injected within a predefined period, for example, 5 seconds before the end of the Valsalva maneuver, then a warning may be provided by the controller/monitor **82**.

[0118] Once the injection of the indicator bolus and isotonic saline clearing bolus have been successfully completed in the prescribed time period, the sensor **110** detects the relative concentration of the ICG indicator as it passes through the vasculature of the ear. Digital filtering of the output signal from the fluorescence detectors of the sensor **110** is performed using, for example, Finite Impulse Response Digital Filtering (see Lyons, R. G., "Understanding digital signal processing", Addison-Wellsley Publishing Company, Reading, Mass. 1997:157-204). The controller/monitor **82** tracks the passage of the indicator bolus from the peripheral vein where injected, through the right atrium and pulmonary circuit to the left atrium and ventricle and subsequent passage to the arterial blood. If any part of the indicator bolus diverges from the typical blood flow pathway, for instance via a right-to-left cardiac shunt, then the system is designed to detect and quantify such aberrations. For instance, if a premature increase in the indicator concentration occurs prior to the main indicator/dilution curve that is associated with that much larger portion of the injected indicator which takes the longer and more time consuming pathway through the lungs, then the premature increase indicates the presence of a right-to-left cardiac shunt.

[0119] In contrast to typical mammalian cardiovascular flow systems involving a single flow pathway between the injection site and the exit of the heart, a method for calculating the total flow rate of a system involving two or more individual flow pathways is described below. These abnormal cardiovascular flow systems comprise two or more indicator/dilution curves corresponding to two or more flow pathways determined at two or more physical locations corresponding to two or more separate pathways. The areas under (1) the premature smaller indication/dilution curve and (2) the much larger indicator/dilution curve can be used to ratiometrically quantify the magnitude of the right-to-left cardiac shunt.

[0120] This indicator bolus premature arrival and the delay by traveling through the lungs can be represented schematically. Looking to FIG. **9**, indicator is shown being introduced

to the venous blood stream **140** as represented at arrow **142**. The indicator in the venous blood at blood stream **140** is directed to the right side of the heart as represented at block **144**. A right-to-left cardiac shunt is represented by the small conduit **146** that is shown extending to the left side of the heart represented at block **148**. Meanwhile, the lungs are represented within the dashed boundary **150**, a circuitous route of filtering and aeration being represented by conduit **152** as it extends from the right side of the heart to conduit **154**. As it exits the lungs following filtering and aeration as represented at conduit portion **154**, the refreshed blood now enters the left side of the heart, whereupon it is distributed as represented at conduit **156** and multiple arterial conduits represented in general at **158**.

[0121] One conduit of the conduit array **158** is depicted at **160** as being analyzed by the sensor **110** and controller/monitor **82**, as collectively represented in FIG. **8** by arrow **162**. Dye dilution curves are the result of said analysis, as shown at display **164**. The principle of the dilution curves at display **164** is that the detection of an indicator bolus resulting from the passage of indicators through the lungs is seen at **166**. However, note the premature and smaller indicator detection peak/dilution curve **165** which results from the passage of indicator along the cardiac shunt (PFO) **146**. The PFO represented by curve **165** can be quantified by a ratiometric analysis with reference to dilution curve **166**. Thus, not only is the presence of a PFO detected but it is quantified. Additionally, any recirculation component will have been removed from the principal curves as at **166**.

[0122] Looking momentarily to FIG. **10**, curve **166** reappears with its peak concentration represented at dashed line **168**. The interval of injection of the indicator bolus is represented as a bar **170**, the termination of injection being represented at dashed line **172**. The interval of carrying out the Valsalva maneuver is represented by dashed block **174**. The timing by the system following indicator injection, in seconds, commences with dashed line **172**. The elapsed time until the peak of curve **166** occurs as represented at dashed line **176** and the base line of the system (noise) is represented by horizontal dashed line **178**. The passage of a portion of the indicator bolus through a cardiac shunt, such as the PFO represented at **146** of FIG. **9**, is revealed by the leading curve **165**, which precedes principal curve **166** with an onset time of t_1.

[0123] It is also possible for the pulmonary system to exhibit both a PFO and a pulmonary arterial venous malformation (PAVM). The ability to distinguish between a PFO and a PAVM is valuable, since the closure device and method for remediating these two types of shunts is distinctly different. Referring to FIG. **11**, a combination of these conditions is schematically portrayed. As is the case of FIG. **9**, circulating venous blood is represented at conduit **184** receiving indicator as represented at arrow **186**. The venous blood is directed to the right side of the heart as represented at block **188**. As described earlier in FIG. **9**, a right-to-left shunt occurs from the right atrium of the heart to the left atrium of the heart represented at block **190**. The cardiac shunt (PFO) is represented in FIG. **11** by conduit **192**. From the left side of the heart indicator bolus is represented as passing to conduit **194** and an arterial conduit array represented in general at **196**.

[0124] The lungs are represented at dashed boundary **198**. Note that venous blood is shown to extend along introductory conduit **200** while filtered blood returns from the lungs to the left side of the heart as represented at conduit **202**. Note, however, that in this case a second right-to-left shunt, as represented by conduit **204**, exists within the pulmonary system. Conduit **204** may, for example, also represent a PAVM from the blood stream arterial conduit array **196**.

[0125] Another conduit is shown extending from arterial array **196** at **206**. Indicator within a conduit as at **206** is subjected to excitation illumination and responds to resultant fluorescence as represented at arrow **206** and **208** and display **210**. Display **210** shows a recirculation corrected principal dye dilution curve **212**, a dye dilution curve **214** representing the cardiac shunt at conduit **192** and a later occurring dye dilution curve **216** representing the pulmonary shunt described in connection with conduit **204**.

[0126] Referring now to FIG. **12**, curves **212**, **214** and **216** reappear extending above baseline concentration dashed line **220**. The peak of curve **212** is represented at dashed line **222** and the interval of injection of the indicator bolus is represented at bar **224**. The termination of injection is represented at vertical dashed line **226**, which commences measurement of elapsed time after indicator injection (in seconds). Like the case of the curve display of FIG. **10**, the interval of carrying out the Valsalva maneuver is represented by dashed bar **228** and the time where the peak of curve **212** occurs is shown at dashed line **230**.

[0127] Method for Estimating Cardiac Output Using Indicator/Dilution Method

[0128] The indicator-dilution method for measuring Cardiac Output was originally developed by Hamilton during the 1920's for use with dyes as the indicator. This work by Hamilton was based on earlier work by Stewart in 1897 and led to the following equation for calculation of the Cardiac Output of the heart, CO_t:

$$CO_t = \frac{D}{\int_0^{tm} C(t)\,dt} \qquad \text{(Eq. 1)}$$

where

[0129] D is the amount of indicator (e.g., grams);

[0130] C(t) is the measured concentration of the indicator at any time t (e.g., grams/ml); and

[0131] $\int_0^{tm} C(t)dt$ represents the area under the concentration vs. time curve as seen in FIG. **13** (e.g., gram-second/ml).

[0132] An exemplary indicator/dilution curve is illustrated in FIG. **13**. In the example shown in FIG. **13**, there is no recirculation of the indicator during the time period of the indicator/dilution from 0 to time t_m. In this idealized case, the decay of the concentration curve following the peak at time t_p is an exponential function once the decay curve is less than 0.70 of the peak concentration value, C_p. In the figure, baseline concentration is represented at dashed line **236**. Indicator injection is shown at bar **238**. Concentration peak C_p is shown at dashed line **240** at time t, represented by dashed line **242**.

[0133] An exemplary measured indicator/dilution curve for an adult pig is shown in FIG. **14**, which illustrates the effect of recirculation of a portion of the indicator back through the heart and its return to the measurement site. In the example shown in FIG. **14**, the indicator, ICG dye, was injected into the left ventricle of a Yorkshire pig. The concentration of the ICG dye was measured transcutaneously at the skin surface of the ear of the pig. The relative concentration level was measured by irradiating the tissue with light at a precise wavelength of 785 nm at a power level of 100 milliwatts through a

600 micron diameter optical fiber in contact with the skin surface of the ear of the pig. The 785 nm light was directed to one or more blood vessels (preferably arterial) underlying the skin surface.

[0134] As the ICG indicator within the blood stream reaches the site of irradiation with 785 nm light, the fluorescent component within the ICG indicator is excited to an elevated energy state for a brief period. As the excited component returns to its normal energy state, it emits light at a longer wavelength (viz., 830 nm). As previously disclosed, the (nominally 45 nm) difference between the excitation wavelength (viz., 785 nm) and the fluorescence emission wavelength (viz., 830 nm) is known as the Stokes Shift, and it allows the fluorescence emission to be extracted by using an interferential or other type of optical filter to reflect or otherwise attenuate all but the wavelength band of interest (viz., 820 to 840 nm). The fluorescence emissions collected in this example by seven 600 micron diameter optical fibers surrounding the excitation fiber (see FIG. **3**) were subjected to an optical filter that causes a significant attenuation of all light wavelengths except those in the near vicinity of the fluorescence wavelength of interest, viz., 830 nm. In this manner, the excitation light at **785** nm is blocked by the optical filter.

[0135] In addition to optical filtering, Fast Fourier Transform filtering methods or Finite Impulse Response (nonrecursive) filtering methods can be used to remove spectral content from the measured fluorescence signal that is outside the frequency band of interest. In the present example, the digital filtering of the fluorescence signal serves as a "low pass" filter allowing only signals with a frequency component in the range from 0 to 0.8 Hz to be included in the digitally filtered form of the measured data.

[0136] Referring again to FIG. **14**, several methods can be used to exclude the recirculation component of the indicator/dilution curve so that the area under the idealized indicator/dilution curve can be obtained (i.e., the indicator/dilution curve without the recirculation component). One method is illustrated in FIG. **14** and involves the assumption that the down slope of the indicator/dilution curve is a log-normal distribution.

[0137] For further discussion of measuring cardiac output and calculating the area under the dye dilution curve, see:

[0138] 13) Moore, J., Kinsman, J., Hamilton, W. and Spurling, R., "Studies on the Circulation **2**. Cardiac Output Determinations: comparison of the Injection Method with the Direct Fick Procedure," *American Journal of Physiology* 89: 331-339 (1929);

[0139] 14) Snoeckx L., et al., "On-Line Computation of Cardiac Output with the Thermodilution Method using a Digital Minicomputer," *Cardiovascular Research,* 10: 556-564, (1976); and

[0140] 15) Lewi P., "Areas under thermal-dilution curves, assuming log-normal distribution," *American Journal of Physiology,* 207(1): 144-148 (1964).

[0141] Utilizing the presently derived method, the area A under the indicator/dilution curve with the recirculation component removed can be calculated as follows:

$$A = Y_m * a * c \quad \text{(Eq. 2)}$$

where

[0142] A=area under indicator/dilution curve without recirculation component (millivolt-seconds);

[0143] Y_m=maximum signal amplitude (millivolts);

[0144] a=width of indicator/dilution curve to right of time, t_m at $Y=0.607*Y_m$ (seconds); and

[0145] c=constant value=2.20.

[0146] As seen in FIG. **14**, the above equation estimates the area under the indicator/dilution curve shown by the dashed line **248**, which represents the shape of the down slope of the indicator/dilution curve without recirculation.

[0147] Another method which can be used to estimate the shape of the down slope curve without the recirculation component involves the use of least mean squares regression for the exponential curve fit to obtain the coefficient, a in the equation.

$$Y = Y_2 e^{-\alpha(t-t2)} \quad \text{(Eq. 3)}$$

where

[0148] Y is the signal amplitude at time, t (millivolts);

[0149] Y_2 is the signal amplitude at time, t_2 (millivolts);

[0150] $t-t_2$ is the elapsed time following time t_2 (seconds);

[0151] α is the exponential coefficient which defines the signal amplitude down-slope curve and is derived by an exponential curve fit to the actual measured signal amplitude values in time interval between t_1 and t_2;

[0152] t_1 is the time at which $Y_1 = *Y_m$;

[0153] t_2 is the time at which $Y_2 = F_2 * Y_m$; and

[0154] F_1 and F_2=0.9 and 0.6, respectively.

Method for Measuring Shunt Conductance

[0155] Referring again to Eq. 1, note that the integral in the denominator of the expression for Cardiac Output, CO_t is in terms of a concentration value, C(t) and it is in the same unit as the amount of the indicator injected D. By way of example, the amount of indicator injected D is in units of micrograms and the concentration of the indicator C(t) is in units of microgram/milliliter or microgram/ml. However, the presently disclosed non-invasive method for measuring the Shunt Conductance, C involves the measurement of a relative concentration value which, by way of example, is in unit of millivolts. Therefore, Eq. 1 can be rewritten in terms of measurement of a signal amplitude, V(t) as a function of time to obtain a volumetric flow rate as follows:

$$CO_t = \frac{D}{CCF * \int_0^t V(t)\,dt} \quad \text{(Eq. 4)}$$

where

[0156] CO_t=volumetric flow rate (milliliter/second);

[0157] D=amount of indicator injected (micrograms);

[0158] V(t)=measured signal level as a function of time which is directly proportional to the concentration of the indicator in the blood stream (millivolts); and

[0159] CCF=indicator concentration conversion factor used to convert measured signal level (in millivolts) into indicator concentration (micrograms/ml) and which has the unit (micrograms/ml-millivolt).

[0160] The indicator concentration conversion factor, CCF is a constant value for a specific set of transcutaneous measurement fluorescence measurement parameters which include (1) excitation light intensity (e.g., laser power in units of milliwatts), (2) thickness of skin between surface of light source/fluorescence detector and blood vessel(s) carrying blood-borne indicator, (3) quantum efficiency of the fluorescing indicator or indicators (4) light scattering characteristics

of the skin and skin type, (5) amplifier gain in fluorescence detection circuit, and (6) attenuation of fluorescence light flux through optical filtering component(s).

[0161] As discussed above related to the calculation of Cardiac Output using indicator/dilution methods, the integral term corresponds to the area under the curve defined by the measured signal level as a function of time. Also, as seen before in FIG. **14**, the recirculation effects must be excluded by extrapolating an exponential down slope curve from data measured briefly after the time at which the peak signal level is measured. Rewriting Eq. 4 in terms of the area under the curve A after recirculation components have been excluded provides:

$$CO_t = \frac{D}{CCF * A} \quad \text{(Eq. 5)}$$

[0162] The new method described is useful for detecting the presence of a right-to-left cardiac shunt as has been shown in FIG. **9** and FIG. **10**. If a right-to-left cardiac shunt is present then a relatively small indicator/dilution curve will precede the much larger indicator/dilution curve. The former relatively small indicator/dilution curve with area A_1, is associated with that amount of the blood-borne indicator originally injected D which passes through a right-to-left cardiac shunt without first passing through the longer and more time-consuming pathway through the lungs. The latter, much larger indicator/dilution curve with area A_2 is associated with that amount of the blood-borne indicator originally injected D which flows along the normal pathway from the right atrium to the right ventricle and through the lungs to then reach the left atrium and proceed on to the arterial circulation. This latter pathway requires a longer transit time which results in a starting time for this latter curve t_2 associated with the normal blood flow pathway occurring later than the starting time for the former curve t_1 associated with the abnormal right-to-left cardiac shunt flow pathway as illustrated at **146** in FIG. **9**.

Calculating Individual Flow Rates for Two or More Indicator/Dilution Curves Separated in Time

[0163] The calculation of the volumetric flow rate in Equations 1, 4 and 5 corresponds to a mammalian circulatory system in which there is only one pathway for the flow of liquid (e.g., blood) and injected indicator from the site of indicator injection (e.g., peripheral vein) to the ascending aorta exiting the left ventricle of the heart. Alternatively, two or more indicator/dilution curves result if there are two or more flow pathways having different transit times within the system which then converge at a single measurement site at a location downstream from the two or more pathways. By way of example, such a system with two pathways in which pathway **146** has a shorter transit time δ_1 and pathway **152-154** has a longer transit time δ_2 is shown in FIG. **9** where transit time δ_1 refers to elapsed time from the time of indicator injection to the time of the onset of the initial rise in indicator/dilution curve.

[0164] As illustrated in FIG. **9** at **164**, two distinct indicator/dilution curves can be measured at a single downstream site where the indicator/dilution curves are separated in time by the difference between the transit times δ_1 and δ_2. As before, the total flow rate, CO_t for this flow system involving two flow components can be calculated.

[0165] As seen in this hypothetical flow system illustrated in FIG. **9**, the flow rate for the total system, CO_t can be calculated by combining the areas under each of the two indicator/dilution curves **165** and **166** in each of the two pathways for the atypical flow of liquid which can be calculated based on Eq. 5 as follows:

$$CO_t = \frac{D}{CCF * A_t} = \frac{D}{CCF * (A_1 + A_2)} \quad \text{(Eq. 6)}$$

where

[0166] CO_t=volumetric flow rate (e.g., milliliter/second);

[0167] D=amount of indicator injected (e.g. micrograms);

[0168] CCF=indicator concentration conversion factor to convert measured signal level (e.g. millivolts) into indicator concentration (e.g., micrograms/ml-millivolts);

[0169] A_t=total area under one or more indicator/dilution curves corresponding to one or more pathways for the flow of liquid in the system (e.g., millivolts-seconds);

[0170] A_1=area under the indicator/dilution curve **165** for flow pathway **146** (e.g., millivolt-second); and

[0171] A_2=area under the indicator/dilution curve **166** for flow pathway **152-154** (e.g., millivolt-second).

[0172] As illustrated in FIG. **9** in a liquid flow system where two flow pathways result in two indicator/dilution curves, the flow rate in pathway **1**, C_i can be calculated ratiometrically as follows:

$$CO_1 = CO_t * \frac{A_1}{A_1 + A_2} \quad \text{(Eq. 7)}$$

where

[0173] CO_1=volumetric flow rate in pathway **146** (e.g., milliliter/second);

[0174] Co_t=total volumetric flow rate for both pathways **146** and **154** (e.g., milliliter/second);

[0175] A_1=area under the indicator/dilution curve **165** for flow through pathway **146** (e.g., millivolt-second); and

[0176] A_2=area under the indicator/dilution curve **166** for flow through pathway **152-154** (e.g., millivolt-second).

[0177] For the case of equal volumetric flow rates in pathways **146** and **152-154**, the areas under the curves A_1 and A_2 will be equal. In this exemplary case, Eq. 7 can be written as follows (where A_1=A_2):

$$CO_1 = CO_t \frac{A_1}{2A_1} = \frac{1}{2} * CO_t \quad \text{(Eq. 8)}$$

[0178] Alternatively, if the volumetric flow rate at pathway **146** is only one-tenth of the flow rate through pathway **154**, then A_2=10*A_1 and Eq. 7 can be written in this exemplary case as follows (where A_2=10*A_1):

$$CO_1 = CO_t \frac{A_1}{A_1 + 10A_1} = \frac{1}{11} * CO_t \quad \text{(Eq. 9)}$$

[0179] As illustrated in FIG. **11** in a case of a flow system with three pathways in which pathway **192** has the shortest transit time δ_1, pathway **204** has a longer transit time δ_2, and pathway **202** has the longest transit time δ_3, is shown in FIG. **12**. As illustrated in FIG. **12**, three distinct indicator/dilution curves can be measured at a single downstream site where the three indicator/dilution curves are separated in time by the differences between the transit times δ_1, δ_2 and δ_3. The total flow rate CO_t for this flow system involving three flow components can be calculated by combining the areas under each of the three indicator/dilution curves corresponding to each of the three pathways for the flow of liquid, which can be calculated based on Eq. 5 as follows:

$$CO_t = \frac{D}{CCF * A_t} = \frac{D}{CFF * (A_1 + A_2 + A_3)} \quad \text{(Eq. 10)}$$

[0180] where

[0181] CO_t=volumetric flow rate (e.g., milliliter/second);

[0182] D=amount of indicator injected (e.g. micrograms);

[0183] CCF=indicator concentration conversion factor to convert measured signal level (e.g. millivolts) into indicator concentration (e.g., micrograms/ml-millivolts);

[0184] A_t=total area under one or more indicator/dilution curves corresponding to one or more pathways for the flow of liquid in the system (e.g., millivolts-seconds);

[0185] A_1=area under the indicator/dilution curve for flow pathway **192**, curve **214** (e.g., millivolt-second);

[0186] A_2=area under the indicator/dilution curve for flow pathway **204**, curve **216**, (e.g., millivolt-second); and

[0187] A_3=area under the indicator/dilution for the primary pathway **200-202** through the lungs, curve **212** (e.g., millivolt-second).

[0188] As illustrated in FIG. **11**, in a liquid flow system where three flow pathways result in three indicator/dilution curves, the flow rate for any single pathway can be calculated ratiometrically as follows for the case of flow rate in pathway **192**:

$$CO_1 = CO_t * \frac{A_1}{A_1 + A_2 + A_3} \quad \text{(Eq. 11)}$$

where

[0189] CO_1=volumetric flow rate in pathway **1** (e.g., milliliter/second);

[0190] Co_t=total volumetric flow rate for both pathways **1** and **2** (e.g., milliliter/second);

[0191] A_1=area under the indicator/dilution curve for flow through pathway **192** (e.g., millivolt-second);

[0192] A_2=area under the indicator/dilution curve for flow through pathway **204** (e.g., millivolt-second); and

[0193] A_3=area under the indicator/dilution curve for flow through the main pathway **200-202** through lungs (e.g., millivolt-second).

[0194] For the case of equal volumetric flow rates in the three pathways, the areas under the curves A_1, A_2 and A_3 will be equal based on the principles of the Steward-Hamilton equation for indicator/dilution based flow rate measurement as discussed with regard to Equations 4 and 5. Hence, Equation 11 can be written in this exemplary case as follows (where A_1=A_2=A_3):

$$CO_1 = CO_t * \frac{A_1}{3A_1} = \frac{1}{3} * CO_t \quad \text{(Eq. 12)}$$

[0195] For the case of a flow system with two flow pathways the flow rate in any single pathway CO_i is giving by the general relationship:

$$CO_i = CO_t\left(\frac{A_i}{A_1 + A_2}\right) \quad \text{(Eq. 13)}$$

where

[0196] CO_i=volumetric flow rate in pathway i (e.g., milliliter/second);

[0197] Co_t=total volumetric flow rate for both pathways **1** and **2** (e.g., milliliter/second);

[0198] A_i=area under the indicator/dilution curve for flow through pathway i (e.g., millivolt-second);

[0199] A_1=area under the indicator/dilution curve for flow through pathway **192** (e.g., millivolt-second);

[0200] A_2=area under the indicator/dilution curve for flow through pathway **204** (e.g., millivolt-second); and

[0201] I=pathways **192** or **204**.

[0202] For the case of a flow system with three flow pathways as illustrated in FIG. **11**, the flow rate in any single pathway, CO_i is giving by the general relationship:

$$CO_i = CO_t\left(\frac{A_i}{A_1 + A_2 + A_3}\right) \quad \text{(Eq. 14)}$$

where

[0203] CO_i=volumetric flow rate in pathway i (e.g., milliliter/second);

[0204] CO_t=total volumetric flow rate for all pathways (e.g., milliliter/second);

[0205] A_i=area under the indicator/dilution curve for flow through pathway i (e.g., millivolt-second);

[0206] A_1=area under the indicator/dilution curve for flow through pathway **192** (e.g., millivolt-second);

[0207] A_2=area under the indicator/dilution curve for flow through pathway **204** (e.g., millivolt-second);

[0208] A_3=area under the principal indicator/dilution (e.g., millivolt-second); and

[0209] i=one of the three pathways.

Identifying the Presence of and Quantifying the Flow Rate Across Right-to-Left Shunts in the Human Body

[0210] The case of a flow system with two flow pathways exists in the human body when a right-to-left cardiac shunt or pulmonary is present. As described above, the most common form of a right-to-left cardiac shunt is known as a PFO.

[0211] Exemplary methods, apparatus and systems capable of determining the magnitude of the flow rate associated with a right-to-left cardiac or pulmonary shunt are hereafter disclosed. As previously described, a non-invasive optical sensor is initially positioned on the surface of a subject's skin at a location (e.g., the scaphoid fossa of the ear). A biocompatible indicator is next injected at a predetermined rate into a peripheral (e.g., antecubital) vein of the subject while the subject is

directed to engage in a Valsalva maneuver that may result in the opening of a PFO and a flow of blood directly from the right atrium to the left atrium of the heart without passing through the longer pathway in the lungs.

[0212] The non-invasive optical sensor transcutaneously measures the concentration of the injected indicator as a function of time. As seen in FIG. **10**, if a premature inflection or peak occurs in the indicator concentration level at a point in time t_1 that is prior to the rise and fall of the concentration associated with the majority of the indicator flowing through the normal pathway of the lungs and arriving at the sensor at a point in time t_2, then a right-to-left cardiac shunt (PFO) is present.

[0213] The situation in the human body where only one right-to-left shunt exists is illustrated schematically in FIG. **9**, in which two flow pathways exist having different transit times δ_1 and δ_2. Alternatively, there may be two types of right-to-left shunts in the human body, which represent two additional pathways for the flow of blood as illustrated in FIG. **11**. As stated above, if a sensor is used to measure the concentration of the injected indicator as a function of time at a location downstream from the left side of the heart (e.g., at the auricle of the ear), then a total of three indicator/dilution curves result as seen in FIG. **12**.

[0214] Still referring to FIG. **12**, the first indicator/dilution curve, having an area A_1 under this curve, is associated with the right-to-left cardiac shunt having the shortest pathway between the right atrium and the left atrium of the heart. An example of such a shorter pathway is a pathway directly across the atrial septum such as a PFO. The second indicator/dilution curve, having an area A_2 under the curve, is associated with a right-to-left shunt having a longer pathway between the right atrium and the left atrium of the heart. An example of such a longer pathway is a particular arteriovenous malformation creating a pathway across the pulmonary vasculature commonly known as a Pulmonary Arteriovenous Malformation (PAVM).

[0215] In the cases where there are either one or two right-to-left shunts, a much larger indicator/dilution curve also occurs and is associated with that amount of blood which normally flows through the much longer pathway in the lungs and back to the left atrium of the heart. This larger indicator/dilution curve is seen in FIG. **10** and has an area under the curve (after excluding any recirculation component as described previously) of A_2 or is seen in FIG. **12** having an area under the curve (after excluding any recirculation component as described previously) of A_3.

[0216] For the case of a human subject with a single right-to-left cardiac shunt as seen in FIG. **10**, the magnitude of the flow rate associated with the shunt may be referred to as the "Shunt Conductance," and is given by Eq. 15 as follows:

$$CO_1 = CO_t * \frac{A_1}{A_1 + A_2} \quad \text{(Eq. 15)}$$

where the terms are the same as those defined for Equations 7 and 13.

[0217] Likewise, for the case of a human subject with two right-to-left shunts detected as seen in FIG. **12**, the magnitude of the flow rate associated with each of the shunts may also be referred to as "Shunt Conductance," and is given by Equations 16 and 17 as follows:

$$\text{First right-to-left shunt} = CO_1 = CO_t * \frac{A_1}{A_1 + A_2 + A_3} \quad \text{(Eq. 16)}$$

$$\text{Second right-to-left shunt} = CO_2 = CO_t * \frac{A_2}{A_1 + A_2 + A_3} \quad \text{(Eq. 17)}$$

where the terms are the same as those defined for Eq. 14.

[0218] As seen in Equations 15, 16 and 17, the areas A_1, A_2 and A_3 are calculated parameters based on the measurement of indicator concentration as a function of time for each of the indicator/dilution curves that corresponds to the presence of a single right-to-left shunt (see A_1 in FIG. **10**) or two right-to-left shunts (see A_1 and A_2 in FIG. **12**). In embodiments of the present invention, indicator/dilution curves are measured in terms of a fluorescence signal level (e.g., millivolts) as a function of time. The concentration conversion factor, CCF appearing in Equations 6 and 10 is cancelled out since it appears in both the numerator and denominator of Equations 7, 11, 13 and 14.

[0219] As seen in Equation 7 and FIG. **10** for the case of a single right-to-left shunt, the total volumetric flow rate for both pathways CO_t is equivalent to the Cardiac Output of the heart. The value for the Cardiac Output can be calculated for the case of a human under normal conditions (e.g., a human that is not concurrently undergoing surgery, post-surgery, recovery from anesthesia, or suffering from shock due to heart failure of trauma-related blood loss). Importantly, subjects to be screened for the presence of one or more right-to-left shunts using the present invention will be tested when their cardiovascular condition can be assumed to be normal. Likewise, the evaluation of the presence and flow rate associated with any residual right-to-left shunt following closure of the shunt will also be performed on human subjects whose cardiovascular condition can be assumed to be normal at the time of the test.

[0220] For the case of an adult human, the normal value of the Stroke Index, SI is known to be 46±5 ml/m^2 (see Shoemaker, W. C., et al., "Textbook of Critical Care," W.B. Saunders Company, Philadelphia 1995: pg. 263). As seen in the Shoemaker reference, Stroke Index, SI is related to Cardiac Index, CI and heart rate, HR as follows:

$$SI = \frac{CI}{HR} \quad \text{(Eq. 18)}$$

where

[0221] SI=Stroke Index (ml/m^2);

[0222] CI=Cardiac Index (ml/second-m^2); and

[0223] HR=heart rate (beats per second) determined by measuring beats per minute and dividing by 60 seconds/minute.

[0224] As seen in the cited Shoemaker reference, the Cardiac Index CI is equal to the Cardiac Output CO divided by the Body Surface Area BSA as follows:

$$CI = \frac{CO}{BSA} \quad \text{(Eq. 19)}$$

where

[0225] CI=Cardiac Index (ml/m^2);

[0226] CO=Cardiac Output (ml/second); and

[0227] BSA=Body Surface Area (square meters or m^2).

[0228] The Body Surface Area (BSA) can be calculated by one of several algorithms incorporating the height and weight of the human subject. One of the recommended algorithms used to calculate the Body Surface Area, BSA is the algorithm known as the Mosteller Formula (see Mosteller, R. D., "Simplified Calculation of Body Surface Area," New England Journal of Medicine 1987; 17[17]: **1098**). The Mosteller Formula for Body Surface Area is given by the following equation:

$$BSA=((H*W)/3131)^{1/2} \quad \text{(Eq. 20)}$$

where

[0229] BSA=Body Surface Area (m^2);

[0230] H=Height of subject (inches); and

[0231] W=Weight of subject (pounds).

[0232] The normal value of the Cardiac Output for a human subject can then be calculated by solving Equations 18 and 19 for Cardiac Output CO as follows. First, rewriting Equation 19 in terms of Cardiac Output CO obtains:

$$CO=CI*BSA \quad \text{(Eq. 21)}$$

[0233] Rewriting Equation 18 in terms of Cardiac Index CI obtains:

$$CI=SI*HR \quad \text{(Eq. 22)}$$

[0234] Substituting formula for Cardiac Index CI (Equation 22) into the formula for Cardiac Output CO in Equation 21 obtains:

$$CO-CI*BSA=SI*HR*BSA \quad \text{(Eq. 23)}$$

where:

[0235] a. the normal value for SI is known to be 46±5 ml/m^2;

[0236] b. HR is measured using a heart rate monitor and averaged over the period of the measurement of the relative concentration of the indicator during the period from the indicator injection to the time of the peak of the normal indicator/dilution curve associated with blood flow through the lungs and back to the left atrium of the heart (beats/second); and

[0237] c. BSA is calculated using Mosteller Formula given in Equation 20 in units of m^2.

[0238] Hence, the normal value of the total Cardiac Output can be estimated within a narrow range based on the known normal value for Stroke Index SI (viz., 46±5 ml/m^2), by measuring the subject's heart rate HR and calculating the Body Surface Area BSA based on the subject's height and weight. This estimated value for Cardiac Output, CO is equivalent to the total flow rate CO_t incorporated into Equations 7, 11, 13 and 14. By way of example and referring to Equation 7, Equation 23 and FIG. **10**, the flow rate or Shunt Conductance CO_1 associated with a single right-to-left shunt can be written:

$$CO_1 = CO_t * \frac{A_1}{A_1 + A_2} = SI * HR * BSA * \frac{A_1}{A_1 + A_2} \quad \text{(Eq. 24)}$$

where:

[0239] CO_1=flow rate or Shunt Conductance through right-to-left shunt (ml/second);

[0240] SI=Stroke Index whose normal value is 46±5 ml/m^2;

[0241] HR=Heart Rate which is measured using a heart rate monitor (beats/second);

[0242] BSA=Body Surface Area calculated using Mosteller Formula (m^2);

[0243] A_1=calculated area under measured indicator/dilution indicator concentration curve associated with right-to-left shunt as seen in FIG. **10** (millivolt-second); and

[0244] A_2=calculated area under measured indicator/dilution indicator concentration curve associated with blood flow through the lungs and back to left atrium of the heart as seen in FIG. **10** (millivolt-second).

[0245] Hence, Eq. 24 allows the equivalent flow rate or Shunt Conductance through a single right-to-left shunt to be calculated within a narrow range (based on normal range of Stroke Index of 46±5 ml/m^2). Likewise, Equation 14 for the case of two co-existing right-to-left shunts can be re-written as follows:

$$CO_1 = CO_t\left(\frac{A_1}{A_1 + A_2 + A_3}\right) = SI * HR * BSA * \frac{A_1}{A_1 + A_2 + A_3} \quad \text{(Eq. 25)}$$

$$CO_2 = CO_t\left(\frac{A_2}{A_1 + A_2 + A_3}\right) = SI * HR * BSA * \frac{A_2}{A_1 + A_2 + A_3} \quad \text{(Eq. 26)}$$

where

[0246] CO_1=flow rate or Shunt Conductance through a first right-to-left shunt (ml/second);

[0247] CO_2=f low rate or Shunt Conductance through a second right-to-left shunt (ml/second);

[0248] SI=Stroke Index whose normal value is 46±5 ml/m^2;

[0249] HR=Heart Rate which is measured using a heart rate monitor (beats/second);

[0250] BSA=Body Surface Area calculated using Mosteller Formula (m^2);

[0251] A_1=calculated area under a first measured indicator/dilution indicator concentration curve associated with right-to-left shunt (millivolt-second);

[0252] A_2=calculated area under a second measured indicator/dilution indicator concentration curve associated with shunt flow through pulmonary arterial pathway (e.g., PAVM) and back to left atrium of the heart (millivolt-second); and

[0253] A_3=calculated area under a third measured indicator/dilution indicator concentration curve associated with blood flow through lungs and back to left atrium of heart (millivolt-second).

Benefits of Ratiometric Analysis Method for Quantifying the Volumetric Flow Rate Associated with Right-to-Left Shunts

[0254] As a result of the ratiometric approach specified in the present invention for calculating the flow rate or Shunt Conductance associated with one or two right-to-left shunts, several terms required for the calculation of the volumetric flow rate of a system are cancelled out and therefore do to have to be determined. Note that Eq. 6 for the case of calculating the flow rate in a system with two flow pathways includes the parameters for (a) the amount of the indicator injected D (e.g., grams) and (b) the factor for converting the measured signal level (in millivolts) into a concentration level CCF (e.g., grams/ml).

[0255] However, due to the ratiometric form of Equation 7 in the present invention, the terms D and CCF cancel out. Also, the units of measure for the fluorescence signal level (e.g., millivolts-seconds) cancel out. As a result, the exact amount of the indicator injected does not have to be accurately known. However, the amount of the indicator injected needs to be sufficiently large so that the much smaller indicator/dilution curves associated with one or two right-to-left shunts can be adequately resolved and their corresponding areas can be accurately calculated. In one embodiment of the present invention involving the use of ICG dye (supplied, for example, by Akorn, Inc., 2500 Millbrook Drive, Buffalo Grove, III. 60089) as the indicator, the preferred amount of ICG dye injected is 2.0 ml at an ICG dye concentration of 2.5 milligram/ml which is equivalent to an injected ICG dose of 5.0 milligrams. The chemical name for Indocyanine Green is 1H-benz(e)indolium, 2-[7-[1,3-dihydro-1,1-dimethyl-3-(4-sulfobutyl)-2H-benz[e]indo-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-hydroxide, inner salt, sodium, or 2-[7-[1,1-dimethyl-3-(4-sulfobutyl)benz[e]indolin-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-1H-benz[e]indolium hydroxide, inner salt, sodium salt.

[0256] A typical right-to-left shunt test procedure might involve a total of 3 to 5 tests which represents a total injected indicator dose of 15 to 25 milligrams. This cumulative dosage amount is well below the manufacturer's specified guideline which recommends a maximum ICG dose per day of 2 milligrams per kilogram of body weight. The recommended ICG dose for a human subject weighting 140 pounds or 63.6 kg is about 127 milligrams, a factor of 5 to 8.5 times higher than the amount of ICG dye required to perform multiple right-to-left shunt measurements on a single human subject weighing 140 pounds. This significant ratio of the actual to recommended dosage limit assures that method embodiments of the present invention can be safely employed.

EXAMPLES

Example 1

Calculation of Flow Rate of Human Subject with Single Right-to-Left Shunt

[0257] This example involves the calculation of the flow rate or Shunt Conductance of a human subject with a single right-to-left shunt, as seen in FIG. **9** using Equation 24 and assuming the following parameters:

[0258] SI=Stroke Index for Normal Subject=46 ml/m^2;

[0259] H=Height of subject=70 inches;

[0260] W=Weight of subject=160 pounds;

[0261] HR=measured average heart rate during period of measurement of indicator concentration as a function of time=1.0 beats/second (i.e., 60 beats/minute);

[0262] A_1=calculated area under indicator/dilution curve derived from measured fluorescence signal level (in units of millivolts) vs. time (in seconds) associated with right-to-left shunt=40.5 millivolts-seconds; and

[0263] A_2=calculated area under indicator/dilution curve derived from measured fluorescence signal level (in units of millivolts) vs. time (in seconds) associated with blood flow through lungs and back to left atrium of heart=3000 millivolts-seconds.

Using subject's actual height and weight, the Body Surface Area BSA is calculated using Eq. 20 as follows:

$$BSA=((H*W)/3131)^{1/2}=((70\text{ inches}*160\text{ pounds})/3131)^{1/2}=1.89\text{ m}^2 \quad \text{(Eq. 27)}$$

Substituting the measured and calculated parameters A_1, A_2 and heart rate as well as the normal Stroke Index value into Equation 24 provides the calculated value for the flow rate or Shunt Conductance, CO_1 as follows:

$$CO_1 = SI * HR * BSA * \frac{A_1}{A_1 + A_2}$$

$$CO_1 = (46\text{ ml/m}^2) * (1.0\text{ beats/sec}) * (1.89\text{ m}^2) * \frac{40.5\text{ mV-secs}}{40.5\text{ mV-secs} + 3000\text{ mV-secs}}$$

$$CO_1 = 1.16\text{ ml/sec}$$

Example 2

Calculation of Flow Rate of Human Subject with Two Right-to-Left Shunts

[0264] This example involves the calculation of the flow rate or Shunt Conductance of a human subject with two right-to-left shunts, as seen in FIG. **11**, using Equations 25 and 26 and assuming the following parameters:

[0265] SI=Stroke Index for Normal Subject=46 ml/m^2;

[0266] H=Height of subject=72 inches;

[0267] W=Weight of subject=185 pounds;

[0268] HR=measured average heart rate during period of measurement of indicator concentration as a function of time=1.2 beats/second (i.e., 60 beats/minute);

[0269] A_1=calculated area under indicator/dilution curve derived from measured fluorescence signal level (in units of millivolts) vs. time (in seconds) associated with a first right-to-left shunt=45.0 millivolts-seconds;

[0270] A_2=calculated area under indicator/dilution curve derived from measured fluorescence signal level (in units of millivolts) vs. time (in seconds) associated with right-to-left shunt=65.7 millivolts-seconds;

[0271] A_3=calculated area under indicator/dilution curve derived from measured fluorescence signal level (in units of millivolts) vs. time (in seconds) associated with blood flow through lungs and back to left atrium of heart=3100 millivolts-seconds;

Using subject's actual height and weight, the Body Surface Area, BSA is calculated using Eq. 20 as follows:

$$BSA=((H*W)/3131)^{1/2}=((72\text{ inches}*185\text{ pounds})/3131)^{1/2}=2.06\text{ m}^2 \quad \text{(Eq. 28)}$$

Substituting the measured and calculated parameters A_1, A_2, A_3 and heart rate as well as the normal Stroke Index value into Equation 25 provides the calculated value for the flow rate or Shunt Conductance for the first right-to-left shunt CO_1 as follows:

$$CO_1 = SI * HR * BSA * \frac{A_1}{A_1 + A_2 + A_3}$$

$$CO_1 = (46\text{ ml/m}^2) * (1.2\text{ beats/sec}) * (2.06\text{ m}^2) * \frac{40.5\text{ mV-secs}}{(45.0 + 65.7 + 3100)\text{ mV-secs}}$$

$$CO_1 = 1.6\text{ ml/sec}$$

[0272] Likewise, substituting the measured, calculated and assumed normal Stroke Index into Eq. 26 provides the calculated value for the flow rate or Shunt Conductance for the second right-to-left shunt, CO_2 as follows:

$$CO_2 = SI * HR * BSA * \frac{A_2}{A_1 + A_2 + A_3}$$

$$CO_2 = (46\ \text{ml/m}^2) * (1.2\ \text{beats/sec}) * (2.06\ \text{m}^2) * \frac{65.7\ \text{mV-secs}}{(45.0 + 65.7 + 3100)\ \text{mV-secs}}$$

$$CO_2 = 2.3\ \text{ml/sec}$$

[0273] In regard to FIG. **8**, the components employed in carrying out an embodiment of a system and method of the invention were generally identified. In the description to follow, the components will be described in more detail, as will relevant animal studies, in particular pig, and the highly desirable repeatable results of such studies.

[0274] Referring now to FIG. **15**, the exemplary display **98** of controller/monitor and data acquisition device **82** is reproduced at a higher level of detail. In FIG. **15**, a baseline concentration dashed line is represented at **250**. Above baseline concentration **250** is a filtered principal dilution curve **252**. Curve **252** has been corrected for recirculation and has a peak time represented by dashed line **254**. The Valsalva maneuver is represented by a dynamic bar graph **256**. Graph **256** is associated with measured exhalation pressure level in millimeters of mercury, the minimum value for that level being at 40 mm as represented at dotted line **258**. Within graph **256** is bar **260** representing the commencement and continuation of the injection of indicator until the termination of injection as represented at dashed line **262**. A premature inflection peak at **264** is present.

[0275] Along the exemplary display **98** are touch screen positions as well as visual cueing indicators. Region **268** is pressed by the nurse or clinician to initialize the overall procedure. Block **270** provides a cue to properly position the sensor described at **110** in FIG. **8**. Block **272** cues that the system is ready for a start of the Valsalva maneuver and corresponding block **274** indicates that the Valsalva maneuver may be ended. A visual cue at block **276** indicates that the procedure can be repeated. In general, several tests will be run with injections from the two syringes **120** and **122**. Where the clinician or nurse desires to end the procedure then touch screen **278** may be pressed. Note the date, time, patient's name and clinician is present along the bottom of this exemplary display.

[0276] Referring to FIG. **16**, an assembly view of the indicator injection assembly is presented. In the figure, first syringe **120** intended for injection of indicator reappears with that identifying numeration and similarly, the second syringe **122** intended for injection of isotonic saline flush again is identified by that same numeration. Syringes **120** and **122** are seen to be coupled to a three way stop-cock valve control represented generally again at **124** which allows the operator to select which syringe is to be used to inject indicator or isotonic saline flush.

[0277] The injected circulatory tracking reagent indicator passes through the earlier described flow sensor **126** which is controllably heated to 30° C., plus or minus 2° C., using resistance feedback control of serpentine copper adhesive material supported on a polyamide substrate, which is sometimes referred to as a "copper-on-Kapton". When an injection of a liquid at room temperature occurs, the cooling effect causes an immediate decrease in the temperature of the heater component. This sudden decrease in temperature is used by the controller/monitor sensing circuitry to detect the precise time at which the injection has been initiated. This allows the monitoring unit to determine if the injections of the indicator from syringe **120** and isotonic saline flush from syringe **122** are initiated within a predetermined time period after the start and before the end of the Valsalva maneuver or test initiation. Flow sensor **126** is removably connected to a multi-lead connector **264** which in turn, is connected to earlier described cable **128** that extends to the controller/monitor **82**. In regard to the former, an additional connector **286**, compatible with the cable connector on controller/monitor **82** may be used.

[0278] Delivery tube **130** extends to connection with a relatively short catheter arrangement **132**. Connection between delivery tube **130** and catheter arrangement **132** being made at a fitment **288**. This relatively shorter catheter is employed to assure that there is no disturbance at the injected vein as a consequence of the manipulation of syringes **120** and **122** or the three way valve **124**.

[0279] Referring to FIG. **17**, an exploded view of the flow sensor **126** is set forth. The innermost component of the flow sensor **126** is a thin-walled metal tube **294**, for example, a tube formed of type **304** stainless steel. Along the outside surface of tube **294** there is attached a flexible heater/lead circuit assembly represented generally at **296**. Assembly **296** is comprised of a polyamide substrate referred to in the trade as "Kapton" upon which is deposited a serpentine thin copper layer represented generally at **298** and a sequence of leads represented generally at **300** and identified individually at **302***a*-**302***d*. A registration slot **304** extends between leads **302***c* and **302***b* (slot **304** was intended for registration cooperation with connector **264**). Of the leads within region **300**, leads **302***a* and **302***d* supply current to the serpentine region **298** to derive the noted heat output. Inner leads **302***b* and **302***c* measure the voltage differential across the serpentine thin copper layer **298**. The measured current flowing through said serpentine layer **298** and measured voltage differential can be used to derive resistance of serpentine layer **298**.

[0280] Accordingly, region **298** is physically and thermally coupled to the outer surface of tube **294** to carry this out by employing a high thermal conductance, electrically insulative, transfer tape adhesive. One such transfer tape adhesive is 8805 manufactured by 3M of Minneapolis Minn.

[0281] Additionally shown in the figure is an enclosure half **306** having a tongue component **308** carrying a connector registration slot **310**. A corresponding enclosure half is shown in general at **312** having a tongue **314** and registration slot **316**. A back end connector represented generally at **318** is inserted and adhesively connected to one end of tube **294**, while an oppositely disposed connector represented generally at **322** is adhesively coupled to the opposite end of tube **294**. When assembled, the upper region **300** of the circuit **296** is glued over tongue **314** to result in the arrangement shown in FIG. **18**. Slots **310**, **316** and **304** combine to define a registration slot **326** as seen in that figure. According to the sectional view of FIG. **19**, the thermally conductive glue layer bonding circuit **296** to tube **294** is shown at **328**, while the glue layer bonding the outside of circuit **296** to enclosure halves **306** and **312** as well as tongue **314** is shown at **330**. For the latter coupling, cyanoacrylate adhesive may be employed.

[0282] FIGS. **20-26** identify dimensions for the components of the flow sensor **126**. The following are preferred dimensions for that component:

[0283] L_{10}=0.8" to 1.6"

[0284] L_{12}=0.4" to 0.7"

[0285] L_{14}=0.4" to 1.2

[0286] L_{16}=0.3" to 1.0"

[0287] L_{18}=0.2" to 0.5"

[0288] L_{20}=0.6" to 1.4"

[0289] L_{22}=0.6" to 1.4"

[0290] D_{10}=0.10" to 0.25"

[0291] D_{12}=0.10" to 0.25"

[0292] D_{14}=0.100" to 0.250"

[0293] D_{16}=0.106" to 0.260"

[0294] D_{20}=0.35" to 0.60"

[0295] D_{22}=0.080" to 0.120"

[0296] D_{24}=0.35" to 0.60"

[0297] D_{26}=0.080" to 0.120"

[0298] R_{10}=0.110" to 0.265"

[0299] W_{10}=0.3" to 1.0"

[0300] W_{12}=0.030" to 0.060"

[0301] W_{24}=0.3" to 1.0"

Width of heater serpentines=0.003" to 0.010"; thickness of Kapton in flexible heater/lead circuit=0.001" to 0.002"; thickness of copper in flexible heater/lead circuit=0.0003" to 0.0010"; and thickness of high thermal conductance, electrically resistive transfer tape adhesives=0.002" to 0.005".

[0302] It may be recalled from FIG. **8** that the fluorescing indicator was arterially detected with a combined laser and filter photodetector arrangement attached to the pinna (e.g. scaphoid fossa) of the human ear. That detector was identified generally at **110** as it performed with controller/monitor **82** via cable **112**. Detector **110** as well as cable **112** are reproduced at a higher scale in FIG. **27**. Looking to that figure, the phantom outline of a human ear may be observed as represented generally at **340**. To the ear **340** the sensor or detector **110** is clipped by a clipping mechanism **342**. Cable **112** also is seen to be coupled with a connector **332**.

[0303] Ear **340** reappears in FIG. **28** in conjunction with an arterial map of the ear **341**. In the latter regard, the superficial temporal artery is represented in general at **344** having an upper branch represented in general at **346**, a cymbia conchae at **348**, lobe at **350**, middle branch **354** and lower branch **356**. The triangular fossa/scapha network is represented at **358**.

[0304] In the lower region, the sensor **110** appears in phantom. In the phantom view, the sensor is seen to incorporate three paired laser/photodetectors **360***a*-**360***c*. Turning to FIG. **29**, of the pairs of emitters and detectors, pair **360***a* is seen to incorporate emitter laser **362** and photodetector/filter **363**; pair **360***b* incorporates emitter laser **364** and photodetector/filter **365**; and pair **360***c* incorporates emitter laser **366** and photodetector **367**.

[0305] Laser **362** reappears in FIG. **30** being controllably energized from the components of a printed circuit board **370** within support housing **372**. The laser is within a circular cavity **374** and is illustrated as being energized to create laser light represented by arrow array **376** penetrating the flesh and arteries at ear **340**. One or more arteries are represented at **378**. Adjacent to laser **362** is photodetector **363** and forwardly disposed interferential filter **382** which receives and passes fluorescing photons as represented at arrow array **384**. Printed circuit board **370** may incorporate such features as amplification stages and analog-to-digital conversion functions. Devices **362** and **363** perform in conjunction with a triangular lens **386**. Practitioners generally will apply an optical coupling agent, such as an optical gel, between the ear and lens **386**.

[0306] Referring now to the exemplary embodiment shown in FIG. **28**, three laser/photodetector pairs **360***a*-**360***c* are positioned at the surface of the skin overlying blood vessels within the ear. Said blood vessels are not visible at the skin surface due to the intervening thickness of tissue between the skin surface and the blood vessels within the ear.

[0307] In the exemplary embodiment shown in FIGS. **28**, **29** and **30**, the use of multiple laser/photodetector pairs allows laser light **376** and resulting fluorescence photons **384** from each pair to be sequentially emitted and received, respectively thereby obtaining a measurement of indicator concentration at three distinct locations as seen in FIG. **28**. By way of example, a first laser/photodetector pair **360***a* comprising laser **362** and photodetector/filter **363** as seen in FIGS. **28**, **29** and **30** is sequentially interrogated by energizing laser **362** to generate laser light **376** for a fixed time period ranging from 1 to 20 milliseconds while measuring the emitted fluorescence photons **384** with photodetector/filter **363** during the same fixed time period. Immediately following this first time period, a second laser/photodetector pair **360***b* comprising laser **364** and photodetector/filter **365** as seen in FIGS. **28**, **29** and **30** is sequentially interrogated by energizing laser **364** to generate laser light for a fixed time period ranging from 1 to 20 milliseconds while measuring the emitted fluorescence photons with photodetector/filter **365** during the same fixed time period. Immediately following this second time period, a third laser/photodetector pair **360***c* comprising laser **366** and photodetector/filter **367** as seen in FIGS. **28**, **29** and **30** is sequentially interrogated by energizing laser **366** to generate laser light for a fixed time period ranging from 1 to 20 milliseconds while measuring the emitted fluorescence photons with photodetector/filter **367** during the same fixed time period.

[0308] This sequential energizing of the laser and measuring the emitted fluorescence photons with the photodetector/filter in each pair of this three-pair array is repeated continuously throughout the 30 to 60 second period of measuring the concentration of the fluorescing indicator within the blood vessels within the ear in the region of the laser/photodetector pairs **360***a*-**360***c*. The laser/photodetector pair which yields the highest measured peak fluorescence photon level during the 30 to 60 second measurement period will be selected to display the relative indicator concentration level as a function of time, as seen in FIG. **15**.

[0309] According to this method, the present invention allows the selection of that laser/photodetector pair which is in the closest proximity to the largest blood vessel or blood vessel array even though the blood vessels cannot be visually observed during the placement of the sensor or detector **110** at a fixed position at the skin surface of the patient (e.g., the pinna of the ear). As a result, the emitted photon signal level obtained from the fluorescing indicator within the blood stream can be maximized, thereby increasing the sensitivity of the method to detect smaller right-to-left shunts as well as increasing the accuracy of the quantification of the Shunt Conductance.

[0310] This use of an array of two or more sensors or detectors can also be applied to the detection of the concentration of indicators in the blood stream other than fluorescing indicators. For example, this same arrangement of two or more sensors or detectors can be applied to relative indicator

concentration measurement methods involving (a) infrared spectroscopy, (b) radiation detection for the case of radio-labeled indicators, (c) radiographic detection of radio-opaque indicators, (d) magnetic resonance based detection involving magnetic resonance imaging contrast agents and/or (e) ultrasound detection methods involving ultrasound contrast agents.

[0311] In addition and still referring to FIG. **28**, the blood vessels in the region of the placement of the detector or sensor **110** may be dilated to increase blood flow and thereby to increase signal level of detectable indicator within the blood stream. This process is widely known as vasodilation and can be accomplished by one or a combination of several methods including (a) pre-heating the tissue at the location of sensor or detector **110** to about 40° C. to 42° C. for a period of several minutes up to 10 minutes prior to the start of the injection of the indicator and/or (b) application of pharmacologic agents such as capsaicin which induce the dilation of blood vessels without the application of an external source of heat.

[0312] The sensor is embodied in a sensor apparatus comprising (a) an emitter-detector pair for monitoring the fluorescence of a fluorescing circulatory tracking reagent; b) an emitter providing a light source emitting a first wavelength for the transcutaneous excitation of an indicator within the bloodstream; and (c) a detector for measuring the intensity of the light emitted at a second wavelength from an indicator within the blood stream. The apparatus typically will be embodied with a plurality of emitter and detector pairs as disposed in a sensor array. The plurality of emitter and detector pairs allows the sensors to be sequentially queried in order to determine the emitter and detector pair providing a preferred sensor from the sensor array. Particularly, it is expected that one emitter/detector pair will be in a preferred proximity to the arterial blood flow of the sensor location. The sensor is a normally utilized as a transcutaneous sensor and the preferred sensor is determined by identifying the sensor in closest relationship a subcutaneous blood vessel in order to maximize the sensitivity of said sensor. The preferred sensor may be determined by one or more of signal to noise ratio, absolute signal level, and minimum background signal. As shown, the sensor apparatus is preferably utilized with an optical coupling agent at the skin/instrument interface. Moreover, the sensor apparatus can be queried for the reflectance of the emitter signal from the skin surface, and thereby used to determine the background radiation level and the absence of reflected signal from the skin triggers a no signal fault indication.

[0313] Referring to FIG. **31**, an exemplary Valsalva maneuver mouthpiece/tubing assembly may be observed. The assembly includes a mouthpiece **385** which, in this example, is formed of rigid polypropylene tubing having an outside diameter of 0.375 inch, an inside diameter of 0.250 inch and an overall length of 1.50 inch. A section of extension tubing **386** is connected to the mouthpiece **385**. Extension tubing **386** is, in this example, vinyl tubing having an outside diameter of 0.250 inch and inside diameter of 0.125 inch with an overall length of 72 inches.

[0314] The mouthpiece **385** is attached to a distal end of the tubing **386** with a fitment (not shown), such as a fitment employing a barbed mechanical attachment and/or gas-tight adhesive attachment. The proximal end of extension tubing **386** terminates at a quick-disconnect fitment **387**, such as a Quick-Disconnect Insert Fitting with Hose Barb fitting for securing to extension tubing as supplied by Cole Parmer, Chicago, Ill., catalog No. K-06360-42. This quick-disconnect fitment **387** attaches to a mating quick disconnect port of controller/monitor **82** which, in turn, is connected to a pressure transducer within the controller/monitor to continuously measure exhalation pressure exerted by a patient into mouthpiece **385** during a Valsalva maneuver.

[0315] With respect to the Valsalva maneuver, it is noted that the display **98** as described in connection with FIG. **15** includes a dynamic bar graph that shows the appropriate level for 40 mmHg of pressure during the 15-20 second period of the described Valsalva maneuver. An audible and/or other warning may be issued by the controller/monitor **82** should the pressure exerted by a patient fall below the minimum pressure during such maneuver.

[0316] Referring now to FIG. **32**, a block schematic representation of the controller/monitor/data acquisition system is presented and again identified by the general numeration **82**. In general, this exemplary controller/monitor **82** includes a medical grade universal AC-DC power supply **390** having a 15 v D.C. output at **115** watts. Adjacent the power supply **390** is a driver board **392**. Driver board **392** is operatively associated through a control interface **394** and coupled **396** with a control board **398**.

[0317] Power supply **390** receives input power via entry module **400**, cable **402**; an input power switch **404** is represented at cable **406**. The opposite input from power switch **404** is at cable **408** which is directed to power supply **390**. The output from power supply **390** is present at cables **410** and **412** extending respectively to control board **398** and driver board **392**. Control board **328** is seen to incorporate a display driver; microprocessor; memory; clock; user interface; and USB interface. It is associated with the front panel display **98** as represented at lines **414** and **416**. The control board **398** also is operationally associated via bi-directional bus **418** with a USB port **420**, a volume control **422**, a fan **424** and a speaker **426**.

[0318] The heart rate monitor shown in FIG. **8** at **114** is coupled to a heart rate connector shown in the instant figure at **428**. Connector **428** is coupled as represented at lines **430** and **432** with a heart rate monitor module **434** which in turn is coupled with the driver board as represented by lines **436** and **438** and by connector **440**.

[0319] Tubing for carrying out the Valsalva maneuver has been described in FIG. **8** at **106** and **108**. The tubing is coupled to a pressure port **442** of the controller/monitor **82** and is operationally associated with a manometer or pressure transducer **448** located upon driver board **392**, as represented by lines **444** and **446**. Next, leads from the flow sensor **126** extend to a flow sensor connector represented at **450**. Flow sensor connector **450** extends through a ferrite torroid **456**, as represented at lines **452** and **454**, and thence via lines **458** and **460** and connector **462** to an impedance sense amplification stage **464** and a heater driver **466**. It may be recalled that the temperature of the heater in the fluid sensor is monitored in a resistance manner owing to the high temperature coefficient of resistance of the copper serpentine heater **298**.

[0320] Cable **112** from optical sensor **110** couples with an earpiece connector as represented at block **470**. Connector **470** is directed through a ferrite torroid **476** as represented at lines **472** and **474** and, as represented by lines **478** and **480**, coupled to connector **482** which is associated with signal processing interface **484**. It may be recalled that the analog signals from the photodetector are filtered and subjected to fast Fourier transform activity that involves A/D conversion

as represented at block **486**. Additionally, the laser diodes are driven by diode drivers represented at block **488**, which perform in conjunction with such details as an auxiliary power supply **490** and auxiliary transformer **492**. Also shown at the driver board **392** is an auxiliary transformer function **492**, an isolation transformer function **494** and an opto-coupling function **496**.

Example 3

System and Method for Testing Circulatory Tracking Indicators and Detectors

[0321] The present disclosure also describes exemplary methods for testing systems for monitoring cardiac output, circulatory behavior of blood fluids, and blood circulation, including circulation within peripheral tissues of a human body and organs, such as the heart, brain or liver. For example, a method is described for utilizing an experimental animal body for determining the efficacy of circulatory tracking systems by emplacing an injection catheter into the circulatory system or a chamber of the heart in a test animal with a functioning circulatory system and heart. Once the injection catheter is emplaced, a number of variables in a circulatory tracking system to be tested may be altered. For instance, a series of circulatory tracking reagents being tested with the method may be injected into the circulatory system of the test animal, and detector systems compatible with the circulatory tracking reagent can be activated at given locations on the body of the test animal. Then, the monitoring of the efficacy of a combination of given detectors, detector locations and circulatory tracking reagents to detect the presence of given circulatory tracking agents at a particular location on the test animal body allows the optimization of a given circulatory tracking system.

[0322] In a specific example directed to determining the efficacy of indicator dyes, a bolus of circulatory tracking reagent is injected into the circulatory system or chamber of the animal heart and the detector is emplaced on the body of the test animal such that the transit of the indicator dye may be traced.

[0323] With respect to animal testing, it should be understood that developing systems, apparatus and methods utilizable with an animal model to test the efficacy of the conceived shunt detection systems, apparatus and methods was not a trivial undertaking. For example, producing a right-to-left shunt within the cardiopulmonary system of a test animal was not practical, and emulating a Valsalva maneuver would not be effective on an animal (e.g., pig) maintained on or under general anesthesia.

[0324] Looking to FIG. **33**, a schematic sketch of one developed animal testing technique is presented. In the figure, the right and left sides of an animal heart are represented respectively at blocks **510** and **512**. Blocks **510** and **512** are depicted as being associated with the lungs of the animal, which are represented at block **514**. Arterial vascularity extending from the left side of the heart is represented by conduit **516** and the movement therethrough of injected indicator and blood is represented at arrow **518**. Tissue overlying blood vessel conduit **516** is represented at **520** and a combination laser exciter and fluorescing photodetection component is represented at **522** with end view of component **522** shown in FIG. **3**. A source of laser excitation into component **522** is represented at block **524** and laser excitation energy by arrow **526**. The fluorescence output of the indicator is shown directed from component **522** at arrow **528**, whereupon it is filtered at interferential filter **530**, the filtered output of which is shown at arrow **532** as being directed to photodetection as represented at block **534**. The photodetected output is alternately directed as represented at arrow **536** to a digital oscilloscope represented at block **538** or, as represented at arrow **535**, to a controller/monitor **540**.

[0325] As represented at arrow **542**, block **544** and arrow **546**, a dosage indicator was controllably injected into the left ventricle of the animal heart during testing with a concentration and dosage that emulates a right-to-left cardiac shunt. To make this injection, a pigtail catheter **556** was utilized.

[0326] A pig heart is schematically illustrated and identified generally at **550** of FIG. **34**. The left ventricle is shown at **552** and the outlet or tip **554** of catheter **556** is shown within left ventricle **552**.

[0327] The general protocol for the in vivo animal experiments was as follows. Four female swine (pig), weighing 80-100 pounds were selected. Preoperative sedation was either telazol or xylazine, 1 g IM. Following sedation the animal was anesthetized via inhalation anesthesia (isoflurane 0.7-3%, initially) in oxygen via nose cone. Flurane was titrated to maintain a surgical plane of anesthesia (abolition of the lateral canthal reflex and lack of hypertension or tachycardia) throughout the procedure. A tracheostomy was performed and the animal was ventilated. Fluid filled catheters for pressure tracings and blood gases were placed by cutdown in the carotid artery and jugular vein to aid in maintaining homeostasis and monitoring adequacy of anesthesia and volume administration. Intravenous anesthesia such as fentanyl and/or pentothal was used as necessary.

[0328] Percutaneous access was established in a femoral artery using a 5 French, 90 cm pig-tail catheter (Cook Royal Flush Plus) fed retrograde into the left ventricle of the heart. Confirmation of catheter placement in the left ventricle was performed with fluoroscopic method and monitoring of pressure waveforms. Once left ventricle placement was confirmed, a transcutaneous fluoroscopic sensor unit was placed in contact with the skin surface at the ear. A syringe pump was used to deliver a range of doses of ICG ranging from approximately 0.016 ml to 2 ml of volume per injection at concentrations ranging from 0.4 to 1.6 mg/ml to allow for measurement of peak fluorescence signal as a function of injected ICG dose. This range of ICG dose levels was selected to simulate the range of magnitudes of right-to-left shunt "leakage rates" or fluid conductances.

[0329] A number of parameters were maintained at constant levels during the in vivo pig experiments. As a fluorescence detection system was utilized, excitation laser power level was at **100** milliwatts. The injection duration was approximately 1.1 seconds, and the ICG dye concentration: 400 micrograms/ml (or μg/ml), while the fluorescence probe was positioned proximal to either a blood vessel in the left ear or blood vessel in the right ear. An optical coupling agent, Aquasonic Gel, was utilized at the probe/skin interface.

[0330] Initially, measurements were taken following introduction of an ICG bolus of peak fluorescence signal amplitude compared with dose levels in order to determine proper positioning of the sensor probe. Peak signal amplitude was measured with a 100 μg dose delivered with a with 10 ml volume via syringe. Once it was determined that an operable sensor site was located, 20 repetitions at a 25 μg dose (0.063 ml injection volume) were performed at intervals of about 1 minute between injections. The injection and monitoring was

repeated utilizing a 12.5 μg dose (0.0315 ml injection volume), and utilizing a 6.4 μg dose (0.0160 ml injection volume).

[0331] Next the effect of injection volume was investigated, by determining peak fluorescence signal amplitude with a fixed dose, and variable bolus volumes. Two different doses were repeatedly delivered in either a 1 ml volume or a 10 ml volume.

[0332] Following the animal testing protocol, euthanasia was performed with 40 mEq of potassium chloride via a central venous line.

[0333] Looking now to FIG. **35**, an animal (pig) test indicator dye dilution curve carried out with respect to a 6.4 μg dose, an injection period of 1.1 seconds, and an ICG concentration of 400 micrograms per millimeter with an injection volume of 0.016 milliliters, is set forth. In particular, the area under such curves in mV seconds and consistent doses of ICG were recorded. Laser power was held at **100** milliwatts.

[0334] A parametric analysis of the test results was used to determine the ICG dose required for the high sensitivity detection of simulated right-to-left shunts of various sizes using the transcutaneous fluoroscopic sensor unit. Looking at Table 1 below, test data or test numbers 091 to 130 are set forth. Also shown in the table for each test is, for example, the area under the shunt curve in millivolt-seconds, as well as the ICG dose.

[0335] In Table 1, the column headings are abbreviated as follows: "Test" represents the individual test number; "Peak [mV]" is the measured peak amplitude in millivolts; "AUC [mVs]" represents the integrated area under the curve in millivolt-seconds; "ICG Dose [mg]" is the indocyanine green dose in milligrams; "Target Location" represents the location of detector placement (right ear at either a distal or proximal location); "Volume Injected [ml]" represents the volume of indicator injected in ml of 400 μg/ml ICG; "Inj. Rate ml/min" represents the measured injection rate of the indicator solution in milliliters/minute; "Inj. Dur. (s)" represents the measured duration of the injection in seconds; "Mean BP mm Hg" represents the mean diastolic blood pressure in millimeters of mercury; and "Heart Rate (BPM)" represents the measured heart rate in beats per minute.

TABLE 1

Sample data for in vivo animal testing

Test	Peak [mV]	AUC [mVs]	ICG Dose [mg]	Target Location	Volume Injected [ml]	Inject. Rate [ml/min]	Inject. Dur. [s]	Mean BP mm Hg	Heart Rate BPM
091	4.1	2.1	0.006	REV distal	0.016	0.87	1.1034	62	93
092	4.2	2.1	0.006	REV distal	0.016	0.87	1.1034	62	93
093	3.8	2.0	0.006	REV distal	0.016	0.87	1.1034	62	93
094	4.6	2.4	0.006	REV distal	0.016	0.87	1.1034	62	93
095	4.4	2.2	0.006	REV distal	0.016	0.87	1.1034	62	93
096	4.2	2.1	0.006	REV distal	0.016	0.87	1.1034	62	93
097	4.1	1.9	0.006	REV distal	0.016	0.87	1.1034	61	94
098	4.0	2.2	0.006	REV distal	0.016	0.87	1.1034	61	94
099	5.1	2.4	0.006	REV distal	0.016	0.87	1.1034	61	94
100	4.4	2.0	0.006	REV distal	0.016	0.87	1.1034	61	94
101	4.9	2.3	0.006	REV distal	0.016	0.87	1.1034	61	94
102	4.0	1.8	0.006	REV distal	0.016	0.87	1.1034	61	94
103	4.5	2.2	0.006	REV distal	0.016	0.87	1.1034	61	94
104	4.1	2.0	0.006	REV distal	0.016	0.87	1.1034	61	94
105	3.8	2.1	0.006	REV prox	0.016	0.87	1.1034	61	94
106	4.0	2.0	0.006	REV prox	0.016	0.87	1.1034	61	94
107	4.2	1.8	0.006	REV prox	0.016	0.87	1.1034	61	94
108	3.7	1.8	0.006	REV prox	0.016	0.87	1.1034	60	95
109	3.4	1.9	0.006	REV prox	0.016	0.87	1.1034	60	95
110	3.9	1.9	0.006	REV prox	0.016	0.87	1.1034	60	95
111	12.1	6.4	0.012	REV prox	0.0315	1.72	1.0988	60	95
112	14.6	7.4	0.012	REV prox	0.0315	1.72	1.0988	60	95
113	13.6	6.4	0.012	REV prox	0.0315	1.72	1.0988	60	95
114	12.3	6.7	0.012	REV prox	0.0315	1.72	1.0988	60	95
115	12.2	7.2	0.012	REV prox	0.0315	1.72	1.0988	60	95
116	11.8	6.6	0.012	REV prox	0.0315	1.72	1.0988	62	172
117	14.6	7.2	0.012	REV prox	0.0315	1.72	1.0988	62	172
118	14.9	7.6	0.012	REV prox	0.0315	1.72	1.0988	62	172
119	14.3	7.9	0.012	REV prox	0.0315	1.72	1.0988	62	188
120	16.2	7.9	0.012	REV prox	0.0315	1.72	1.0988	62	188
121	15.9	8.2	0.012	REV prox	0.0315	1.72	1.0988	62	188
122	14.9	7.9	0.012	REV prox	0.0315	1.72	1.0988	60	100
123	14.4	7.4	0.012	REV prox	0.0315	1.72	1.0988	60	100
124	14.7	7.4	0.012	REV prox	0.0315	1.72	1.0988	60	100
125	15.4	8.0	0.012	REV prox	0.0315	1.72	1.0988	60	100
126	12.6	7.9	0.012	REV prox	0.0315	1.72	1.0988	60	100
127	15.2	8.2	0.012	REV prox	0.0315	1.72	1.0988	60	100
128	14.2	7.0	0.012	REV prox	0.0315	1.72	1.0988	60	100
129	14.8	7.2	0.012	REV prox	0.0315	1.72	1.0988	61	102
130	16.9	8.4	0.012	REV prox	0.0315	1.72	1.0988	61	102

[0336] The area under the dye dilution curve as well as peak signals were plotted for tests 091-110 and 111-130. The peak signals of test numbers 091-110 are plotted in FIG. **36** as curve **560**, while the corresponding areas under the dye dilution curve are provided as curve **562**.

[0337] Looking now to FIG. **37**, the same form of data is plotted for test 111-130. In this regard, curve **564** plots peak signal for those tests and curve **566** plots the area under the dye dilution curve for those tests. The test numbers 091-110 and 111-130 as set forth at Table 1 are replaced with the numbers 1-20 in FIG. **36** and FIG. **37**, respectively.

[0338] As the data in Table 1 and associated FIGS. **36** and **37** demonstrate, various dye combinations may be injected directly into the porcine heart, and the ability to detect the injected indicator may be tested using a variety of detector combinations. Although fluorescent indicators and in particular ICG in combination with a fluorescence excitation and detection systems are described in detail herein, the invention is embodied in a method of testing various additional combinations utilizing a animal model as described.

[0339] For example, additional fluorescent circulatory tracking reagents may be tested utilizing similar sensors to those shown in FIGS. **3-5** and **29-30**, with appropriate emitters and detectors. Moreover, the efficacy of various locations of placement of the sensor apparatus may be readily tested using the animal model and a controlled introduction of circulatory tracking reagent.

[0340] Additional non-fluorescent circulatory tracking reagents may also be tested utilizing the described animal model. Spectrophotometric and or densitometric indicators may similarly be tested simply by altering the emitter and detector frequencies to utilize the known properties of such agents in blood. Radioactive isotopes, for instance, are also amenable for use as a circulatory tracking reagent, and effective use would rely on alteration of the sensor apparatus in order to detect such agents. A variety of radioactive detectors are known to those skilled in the art of radiology, as are rapidly metabolizable radioactive reagents that could be utilized with the disclosed systems, methods and apparatus. Previously, the ability to utilize the wide variety of potential circulatory tracking reagents has been severely limited by the inability to reproducibly invoke the opening of shunts, and even to perform such testing in humans at all.

[0341] A number of different animals in addition to pig may readily be utilized using the animal testing model demonstrated herein. Any mammal potentially could be utilized, although mammals with a heart of the approximate size of a human heart are preferred (e.g., primates such as the rhesus monkey and chimpanzee, as well as canines and felines). Large rodents are additionally predicted to be amenable to the testing technique, yet in the typical laboratory rodent, the small size of veins, heart and circulating blood volume may limit the ease of use of the technique for testing circulatory tracking reagents and compatible sensors.

[0342] FIGS. **38**A-**38**F combine with labels thereon to provide a flow chart illustrating an exemplary method and system for detecting a right-to-left cardiac and/or pulmonary shunt. Referring initially to FIG. **38**A, the exemplary system and method of use starts at node **580** and continues as represented at arrow **582** to block **584**. Block **584** is concerned with initialization, for example, setting the system default parameters and setting the PFLAG equal to zero. Next, as represented at arrow **586** and block **588**, patient identification is recorded, patient position as either sitting or supine is determined, the height of the patient, the weight of the patient, the patient's sex and recommended injectate volume for circulatory indicator reagent is compiled. As represented at arrow **590** and block **592**, from the information at block **588**, body surface area, BSA, is calculated using the above-described Mosteller formula.

[0343] The indicator ICG typically is provided to the practitioner in solid or particulate form. Accordingly, it is necessary to mix it with sterile water as represented at arrow **594** and block **596**. The indicator solution is prepared by mixing a known weight of ICG dye with a predetermined volume of diluents such as sterile water or phosphate buffered saline. A predetermined volume of that indicator, for example, 2 ml is drawn into a first syringe as described at **120** in FIG. **8**. Additionally, as represented at arrow **598** and block **600** a second syringe as described at **122** in FIG. **8** is filled with a predetermined volume of isotonic saline to be used to "flush" the introducing tubing, venous catheter and peripheral vein so that all injected indicators are promptly delivered to the right atrium of the heart.

[0344] The thus filled two syringes are connected to two ports on the three-way valve as identified at **124** in FIG. **8**. In this regard, arrow **602** extends to block **604** setting forth this valve connection. The procedure then continues as represented at arrow **606** which reappears in FIG. **38**B extending to block **608** where the relatively short vein access catheter **132** (FIG. **8**) is placed in a peripheral vein (e.g., antecubital vein in an arm). Additionally, flow sensor **126** is attached at the terminus of the extension tubing with three-way valve **124** pre-attached to the proximal end of the flow sensor. The three-way valve is turned in the direction of the flow sensor. Additionally, as represented at arrow **610** and block **612** an indicator sensor is positioned at the site of a blood vessel, for example, on the surface of skin at the pinna of the ear. That device is shown at **110** in FIG. **8**. Practitioners generally will wish to apply an optical gel between the surface of the ear and the sensor to improve photonic transfer. Additionally, the fingerclip heart rate monitor is applied to the finger of the patient as shown at **114** in FIG. **8**.

[0345] The invention is embodied also in a kit providing a clinician with the disposable materials utilized when practicing the new method. A kit supplying consumable materials necessary for quantifying a circulatory anomaly typically would include a dose of circulatory indicator reagent as a shelf stable material; a diluent for preparing the dose of circulatory indicator reagent for injection; a syringe and needle apparatus for mixing the dose of circulatory indicator reagent and the diluent and for injecting the dose into an injection port; and a dose of nonreactive blood compatible clearing reagent for completing the injection.

[0346] As represented at arrow **614** and block **616**, a determination is made as to whether the test at hand will be performed with a Valsalva maneuver. In the event that such maneuver will not be used, then the method diverts as represented at arrow **618**. Where the Valsalva maneuver is to be used, then as represented at arrow **620** and block **622**, the mouthpiece of the pressure transducer or manometer is set in the mouth of the patient as shown at **106** in FIG. **8** and is further connected to the receptacle at controller/monitor **82**. As represented at arrow **624** and symbol **626**, the measurement start is at hand and the method continues as represented at arrow **628**. Arrow **628** reappears in FIG. **38**C extending to block **630** providing for the start of heart rate measurement.

[0347] Next, the patient as represented at arrow **632** and block **634**, is instructed to begin the Valsalva maneuver by exhaling into the mouthpiece to reach and continue a minimum level of 40 mmHg of pressure. The patient will have

been instructed that this breathing maneuver will be continuous for about 15-20 seconds. Meanwhile, the patient as well as the practitioner may observe the dynamic bar graph at the display of the controller/monitor **82**. This continuous measurement is represented at arrow **636** and block **638**.

[0348] The system carries out this continuous monitoring looking for the noted minimum exhalation pressure as represented at arrow **640** and block **642**. In the event that minimum pressure falls below the threshold, that event is then represented at arrow **644** and block **646**. An audible alarm is sounded and a visual error message published instructing the patient to increase pressure. PFLAG is set to zero and the program reverts as represented at arrow **648** to arrow **632** where the system responds leading to the recommencement of the timing of the Valsalva maneuver.

[0349] Where the exhalation pressure is maintained at an appropriate level, then as represented at arrow **650** and block **652** PFLAG is set to one and the program continues as represented at arrow **654**. Returning momentarily to FIG. **38**B, and the query posed at block **616**, where the test is not to be performed with a Valsalva maneuver, the program reverts to arrow **618** which reappears in FIG. **38**C extending to block **656** which sets PFLAG at two and reverts to arrow **654** as represented at arrow **658**. Next, as represented at block **660** the elapsed time clock is started at time, t=0, and the program continues as represented at arrow **662**.

[0350] Arrow **662** reappears in FIG. **38**D extending to block **664** providing for the start of measurement of concentration of indicator. Next, as represented at arrow **666** and block **668**, a query is posed as to whether t is at the time T_{inject}. In the event it is not, then the system dwells as represented at arrow **670** extending to arrow **636**. However, where the time to inject is at hand, then as represented at arrow **672** and block **674**, the operator is instructed with an audible cue to inject an indicator bolus from the first syringe and immediately inject isotonic saline flush bolus from the second syringe.

[0351] The three-way valve will be manipulated during these injections. Also during the injections, the fluid flow sensor **126** will be active as represented at arrow **676** and block **678**. The start and end of injection is measured with the flow sensor.

[0352] A check is made as represented at arrow **680** and block **682** determining whether the start time less the end time is greater than the time of injection. Where it is not, then as represented at arrow **684** and block **686**, a negative response causes the operator to be audibly alarmed and presented with a visual error message indicating that the injection was not completed in the allowed time interval. It is restarted as represented at arrow **688** leading to node A. Node A reappears in FIG. **38**B along with arrow **690** extending to line **613** leading to a query as to whether the test is to be performed with a Valsalva maneuver.

[0353] Where the determination at block **682** is that the injection took place in a proper time frame, the program continues as represented at arrow **692**. Arrow **692** reappears in FIG. **38**E extending to block **694**. When the elapsed time is extended the elapsed time clock is restarted at t=0. As represented at arrow **696** query is posed as to whether the elapsed time is greater than or equal to the time for Valsalva maneuver continuation. Where the answer to this query is in the negative, then the program dwells as represented at arrow **700** extending to arrow **692**. Where the determination made with respect to the query posed at block **698** is in the affirmative, then as represented at arrow **702** and block **704**, the operator and patient are audibly cued that the Valsalva maneuver can be stopped.

[0354] Next, as represented at arrow **706** and block **708**, a determination is made as to whether the elapsed time is greater than or equal to the completion time. In the event it is not, then the program dwells as represented at arrow **710** extending to arrow **706**. Where the elapsed time has reached the time of completion, then as represented at arrow **712** and block **714**, average heart rate over the elapsed time is computed and the program continues as represented at arrow **716**. Arrow **716** reappears in FIG. **38**F extending to block **718**. Block **718** calls for calculating cardiac output using the measured average heart rate, calculated body surface area and known normal value for stroke index of the heart.

[0355] Next, as represented at arrow **720** and block **722**, the area A under the normal indicator dilution curve is calculated (AUC). This is the curve representing blood and indicator flowing through the lungs. Next, as represented at arrow **724** and block **726**, a query posed at block **726** determines whether the calculated normal area is greater than or equal to a minimum under curve area. In the event that it is not, then as represented at arrow **728** and block **730**, the operator is alerted with an audible alarm and visual error message that insufficient coupling exists between the sensor and blood-borne indicator in tissue. Where a query at block **726** results in an affirmative determination, then the area under any premature indicator/dilution curve or curves associated with a right-to-left shunt is/are calculated. The parameter Ai is the area under premature indicator dilution/curve i, where i is either one or two.

[0356] Next, as represented at arrow **736** and block **738**, if Ai is non-zero, then the conductance associated with right-to-left shunts is calculated as described herein. Then, as represented at arrow **740** and block **742**, a query is made as to whether another test is required for this patient. In the event of an affirmative determination, then as represented at arrow **744**, node A reappearing in FIG. **38**B is reassessed. In the event of a negative determination to the query posed at block **742** then is represented at arrow **746** and symbol **748**, the test is ended.

[0357] While exemplary embodiments of the invention have been described herein, those skilled in the art will understand that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof. Since certain changes may be made in the above compositions and methods without departing from the scope of the invention herein involved, it is intended that all matter contained in the above descriptions and examples or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

[0358] In this application all units are in the metric system or English system for the case of dimensions of the flow sensor **126** and its components and all amounts and percentages are by weight, unless otherwise expressly indicated. Also, all citations referred herein are expressly incorporated herein by reference. All terms not specifically defined herein are considered to be defined according to Dorland's Medical Dictionary, and if not defined therein according to Webster's New Twentieth Century Dictionary Unabridged, Second Edi-

tion. The disclosures of all of the citations provided are being expressly incorporated herein by reference.

What is claimed is:

1. A method for detecting and quantifying a right-to-left cardiac and/or pulmonary shunt in a mammalian body, comprising:

calculating the surface area of the body;

calculating cardiac output using, among other things, the calculated surface area of the body;

determining, as a function of time, the relative concentration of a fluorescing indicator introduced to and circulating within the blood stream of the body, by analyzing indicator fluorescence readings provided by a non-invasive sensor that is located along the skin surface of the body and both transcutaneously excites the indicator into fluorescence and transcutaneously detects said fluorescence;

generating, using the determined indicator concentrations, an indicator dilution curve with a recirculation component excluded therefrom;

calculating the area under a normal portion of the dilution curve;

calculating the area under a premature peak in the dilution curve if such a peak exists;

identifying the existence of a right-to-left shunt if the area under a premature peak in the dilution curve is determined to be non-zero; and

if a shunt is identified, calculating the shunt flow rate (shunt conductance) by performing a ratiometric analysis of the area under the premature peak in the dilution curve to the area under the normal portion of the dilution curve, and multiplying the result of said analysis by the calculated cardiac output value.

2. The method of claim **1**, wherein when a shunt is identified, indicating to a user the presence of a shunt along with a corresponding shunt conductance value.

3. The method of claim **1**, wherein the surface area of the body (BSA) is calculated using the formula $BSA=((H*W)/3131)^{1/2}$, and where H=the height of the body and W=the weight of the body.

4. The method of claim **3**, wherein cardiac output (CO) is calculated using the formula CO=SI*HR*BSA, and where SI=a known Stroke Index value, and HR=a measured heart rate of the body.

5. The method of claim **1**, wherein the sensor is an optical sensor having two or more photon sources independently paired with a like number of corresponding photon detectors.

6. The method of claim **5**, wherein the source/detector pairs are serially activated.

7. The method of claim **5**, wherein the sensor is placed on an auricle portion of the ear of the body, with the photon sources located on one side of the ear and the corresponding photon detectors located on an opposite side of the ear.

8. The method of claim **1**, further comprising causing, subsequent to the introduction of the fluorescent indicator into the blood stream, a temporary reversal of a normal pressure differential that exists between the right and left atria of a heart of the body.

9. The method of claim **1**, further comprising detecting and quantifying multiple right-to-left shunts by identifying multiple premature peaks in the dilution curve, performing a ratiometric analysis of the area under each premature peak in the dilution curve to the area under the entire remainder of the dilution curve, and multiplying the result of each ratiometric analysis by the calculated cardiac output value to obtain a shunt conductance value for each detected shunt.

10. A method for detecting and quantifying a right-to-left cardiac and/or pulmonary shunt in a human subject, comprising:

causing the subject to perform a Valsalva maneuver at some predetermined pressure level for some predetermined length of time;

at a point prior to termination of the Valsalva maneuver, injecting a bolus of a fluorescing indicator into the bloodstream of the subject at a peripheral venous location, and subsequently injecting a bolus of an isotonic flushing material behind the indicator from the same location;

providing a non-invasive, optical sensor adapted to excite the indicator into fluorescence upon exposure to photon energy emitted therefrom, the sensor further adapted to detect said fluorescence;

locating the optical sensor along the skin surface of the subject in an area of underlying vasculature, and using the sensor to transcutaneously excite the indicator and to transcutaneously detect the resulting fluorescence of the indicator as the indicator passes through the vasculature;

calculating the body surface area of the subject;

calculating the cardiac output of the subject using, among other things, the calculated body surface area;

repeatedly determining the relative concentration of the indicator as a function of time using indicator fluorescence readings received from the sensor;

generating an indicator dilution curve using the determined indicator concentrations, while excluding a recirculation component from the indicator dilution curve;

calculating the area under a normal portion of the dilution curve;

calculating the area under a premature peak in the dilution curve, if such a peak exists;

identifying the existence of a right-to-left shunt if the area under a premature peak in the dilution curve is determined to be non-zero;

if a shunt is identified, calculating the shunt flow rate (shunt conductance) by performing a ratiometric analysis of the area under the premature peak in the dilution curve to the area under the normal portion of the dilution curve, and multiplying the result of said analysis by the calculated cardiac output value; and

indicating any identified shunt, along with a corresponding shunt conductance value.

11. The method of claim **10**, wherein the body surface area (BSA) of the subject is calculated using the formula $BSA=((H*W)/3131)^{1/2}$, and where H=the height of the subject and W=the weight of the subject.

12. The method of claim **11**, wherein cardiac output (CO) is calculated using the formula CO=SI*HR*BSA, and where SI=a known Stroke Index value, and HR=a measured heart rate of the subject.

13. The method of claim **9**, wherein the sensor includes two or more laser emitters paired with a like number of corresponding photodetectors, the laser emitters adapted to emit light energy at a first wavelength and the photodetectors adapted to detect fluorescing energy at a second wavelength.

14. The method of claim **13**, wherein the emitter/detector pairs are serially activated.

15. The method of claim **10**, wherein the sensor is placed on an auricle portion of the ear of the subject, with the laser

emitters thereof located on one side of the ear and the corresponding photodetectors thereof located on an opposite side of the ear.

16. The method of claim **10**, further comprising providing a controller/monitor that includes a microprocessor and associated programming and is in communication with the optical sensor, and using the controller/monitor to calculate the body surface area, to calculate the cardiac output, to determine the concentration of the indicator, to generate the dilution curve, to calculate the area under the normal portion of the dilution curve, to calculate the area under any premature peak in the dilution curve, and to calculate the shunt conductance value if a shunt is found to exist.

17. The method of claim **16**, further comprising using the controller/monitor to monitor and time the Valsalva maneuver, and to cue an operator at least to inject the bolus of indicator.

18. The method of claim **16**, further comprising placing a flow sensor in the path of the injected indicator and flushing material, and using the flow sensor to detect the injection thereof, the flow sensor reporting injection detection to the controller/monitor such that the controller/monitor may determine whether the injections were initiated within a predetermined time period after the start of and before the end of the Valsalva maneuver.

19. The method of claim **10**, further comprising detecting and quantifying multiple right-to-left shunts by identifying multiple premature peaks in the dilution curve, performing a ratiometric analysis of the area under each premature peak in the dilution curve to the area under the entire remainder of the dilution curve, and multiplying the result of each ratiometric analysis by the calculated cardiac output value to obtain a shunt conductance value for each detected shunt.

20. A system for detecting and quantifying a right-to-left cardiac and/or pulmonary shunt in a human subject, comprising:

a controller/monitor that includes a microprocessor and associated programming that are together operative to provide a function(s) selected from the group consisting of one or more of monitoring, cueing, timing and analyzing various steps of a shunt detection test;

a pressure sensor located within the controller/monitor;

a Valsalva maneuver device comprising a mouthpiece and tubing assembly, the mouthpiece located at one end of the tubing, an opposite end of the tubing in fluid communication with the pressure sensor;

a first syringe for injecting a bolus of a fluorescing indicator into the bloodstream of the subject at a peripheral venous location, and a second syringe for subsequently injecting a bolus of an isotonic flushing material behind the indicator from the same location;

a flow sensor in communication with the controller/monitor for detecting and reporting injection of the indicator and the flushing material; and

a non-invasive, optical sensor in communication with the controller/monitor, the sensor having at least two serially activatable and paired laser emitters and photodetectors, the sensor adapted to transcutaneously excite the indicator and to transcutaneously detect the resulting fluorescence of the indicator from the skin surface of the subject as the indicator passes through underlying vasculature thereof.

21. The system of claim **20**, wherein the pressure sensor is a manometer or pressure transducer.

22. The system of claim **20**, wherein the controller/monitor is adapted to display visual feedback in response to subject exhalation into the mouthpiece of the Valsalva maneuver device, the visual feedback used to guide the subject through a Valsalva maneuver.

23. The system of claim **22**, wherein the visual feedback is in the form of at least a dynamic pressure graph.

24. The system of claim **20**, wherein the controller/monitor is adapted to terminate a Valsalva maneuver if the exhalation pressure exerted by the subject falls below a predetermined pressure for some predetermined period of time.

25. The system of claim **20**, wherein the controller/monitor is adapted to time a Valsalva maneuver performed by the subject and, based on the timing of the Valsalva maneuver, to display a cue at the appropriate time to inject the fluorescing indicator.

26. The system of claim **20**, wherein the optical sensor is adapted to fit over and be retained on an auricle portion of a subject's ear, with the laser emitters of the sensor on one side of the ear and the corresponding photodetectors on an opposite side of the ear.

27. A system for detecting and quantifying a right-to-left cardiac and/or pulmonary shunt in a human subject, comprising:

a controller/monitor that includes a microprocessor and associated programming that are together operative to provide a function(s) selected from the group consisting of one or more of monitoring, cueing, timing and analyzing various steps of a shunt detection test;

a pressure sensor located within the controller/monitor;

a Valsalva maneuver device comprising a mouthpiece and tubing assembly, the mouthpiece located at one end of the tubing and the other end of the tubing in fluid communication with the pressure sensor;

a first syringe for injecting a bolus of a fluorescing indicator into the bloodstream of the subject at a peripheral venous location, and a second syringe for subsequently injecting a bolus of an isotonic flushing material behind the indicator from the same location; and

a non-invasive, optical sensor adapted to be located along the skin of the subject, and to transcutaneously excite the indicator and to transcutaneously detect the resulting fluorescence of the indicator as the indicator passes through underlying vasculature of the subject;

wherein the programming in the controller/monitor is adapted to, in some order:

(a) calculate the body surface area of the subject,

(b) calculate the cardiac output of the subject,

(c) repeatedly determine the relative concentration of the indicator as a function of time using indicator fluorescence readings received from the optical sensor,

(d) generate an indicator dilution curve using the determined indicator concentrations, while excluding a recirculation component from the indicator dilution curve,

(e) calculate the area under a normal portion of the dilution curve,

(f) calculate the area under a premature peak in the dilution curve, if such a peak exists,

(g) identify the existence of a right-to-left shunt if the area under a premature peak in the dilution curve is determined to be non-zero,

(h) calculate the shunt flow rate (shunt conductance), if a shunt is identified, by performing a ratiometric

analysis of the area under the premature peak in the dilution curve to the area under the normal portion of the dilution curve, and multiplying the result of said analysis by the calculated cardiac output value, and

(i) indicate the presence of a detected right-to-left shunt, along with a corresponding shunt conductance value.

28. The system of claim **27**, wherein the pressure sensor is a manometer or pressure transducer.

29. The system of claim **27**, wherein the controller/monitor is adapted to display visual feedback in response to subject exhalation into the mouthpiece of the Valsalva maneuver device, the visual feedback used to guide the subject through a Valsalva maneuver.

30. The system of claim **29**, wherein the visual feedback is in the form of at least a dynamic pressure graph.

31. The system of claim **27**, wherein the controller/monitor is adapted to terminate a Valsalva maneuver if the exhalation pressure exerted by the subject falls below a predetermined pressure for some predetermined period of time.

32. The system of claim **27**, wherein the controller/monitor is adapted to time a Valsalva maneuver performed by the subject and, based on the timing of the Valsalva maneuver, to display a cue at the appropriate time to inject the fluorescing indicator.

33. The system of claim **27**, wherein the optical sensor is adapted to fit over and be retained on an auricle portion of a subject's ear, with the emitters of the sensor on one side of the ear and the corresponding detectors on an opposite side of the ear.

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专利名称(译)	用于血液动力学检测循环异常的系统和方法		
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摘要(译)

用于检测循环异常的系统和方法，例如，从右到左的心脏和肺分流。将荧光指示剂注射到受试者的血流中。使用光学传感器将指示剂经皮激发成荧光并经皮检测荧光，并确定指示剂的相对浓度作为时间的函数。从相对浓度读数生成指示剂稀释曲线，分析曲线形状用于分流的指示，并且如果检测到分流，则执行曲线分析下的比率区域并且与计算的心输出值组合以提供分流电导值。可以执行Valsalva操纵作为该方法的一部分。系统实施例可以包括控制器/监视器，其监视，计时，提示和/或分析分流检测测试的各个步骤。