

SYSTEM FOR IMPROVED HEMODYNAMIC DETECTION OF CIRCULATORY ANOMALIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of pending U.S. Patent Application Serial No. 12/754,888, filed April 6, 2010, entitled "Hemodynamic Detection of Circulatory Anomalies," and of U.S. Patent Application Serial No. 5 12/418,866, filed April 6, 2009 and entitled "Hemodynamic Detection of Circulatory Anomalies," the disclosures of which are incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

Not applicable.

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BACKGROUND

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 15 generally referred to as cardiac right-to-left shunts.

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. a right-left atrial shunt, or between the left and right ventricles, i.e. a right-left ventricular shunt. The shunt may occur as a defect within the vasculature leading 20 to and from the heart, for example a Pulmonary Arteriovenous Malformation (PAVM) may be present as an open hole shunting between vein and artery. 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 is reported to be \$66 billion in the U.S. in 2007 (Rosamond 2008). Of the patient population presenting with 25 stroke or the early warning sign known as transient ischemic attack (TIA or mini stroke), as many as 260,000 are reported to be the result of a right-to-left shunt in the heart and/or pulmonary vasculature.

The most common form of right-to-left shunt is the patent foramen ovale (PFO) which is an opening in the wall of the heart which separates the right side 30 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 reoxygenation. The lungs not only reoxygenate the blood, but also serve as a "filter" for any blood clots and also serve 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 side of the heart to enable circulation of the mother's oxygen-rich 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 consequence of the closure of a tissue flap in about 80% of the population within the first year 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 20% of the population, this opening fails to permanently close and is referred to as a patent foramen ovale or PFO.

Most of the population exhibiting 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." However, for some subjects, this normally closed flap (i.e., foramen ovale) temporarily opens allowing blood to flow directly from the right side to the left side of the heart. As a consequence, any blood clots or other active agents escaping through the PFO bypass the critical filtering functions of the lungs and flow through the brief opening in this flap and directly to the left side of the heart. Once in the left side of the heart, any unfiltered blood clots or metabolically active agents 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 substances in the brain arterial flow 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 causes of certain forms of severe migraine headaches. For further background on circulatory anomalies, see:

- 1) Banas, J., et al. American Journal of Cardiology 28: 467-471 (October 1971);
- 2) Castillo, C., et al. American Journal of Cardiology 17: 691-694 (May 1966);
- 3) Schwedt, T.J., et al., "Patent Foramen Ovale Migraine – Bringing Closure to the Subject." Headache 46(4): 663-671 (2006).
- 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).

A relatively large number of patients (three million) have or may be undergoing sclerotherapy treating, for instance, varicose veins. This therapy involves an injection of sclerosing solution which in effect creates emboli. If patients undergoing sclerotherapy are among the proportion 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.

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 transvascular shunt treatment devices for closure of the most common form, viz., a patent foramen ovale (PFO), and certain of these devices are approved for sale in one or more principalities.

Percutaneous closure devices are expected to soon be widely available in the U.S. for PFO closure, and over 10% of the adult population is estimated to have a congenital patent foramen ovale (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 possible presence of a right-to-left shunt. If detected, the patient may elect one of a growing number of transcatheter right-to-left shunt closure procedures or the more conventional open-heart procedure for right-to-left shunt closure.

Transesophageal echocardiography (TEE) is resorted to somewhat as a last resort. It is considered the "gold standard" of determining the presence of a right-to-left shunt. In carrying out this test, microbubbles are injected into a vein leading to the right side of the heart. As this is underway, the patient is required to blow into a manometer to at least a pressure of 40 mm of mercury (Valsalva Maneuver). Simultaneously, a sonic detector is held down the throat to record the passage of the microbubbles across the shunt. Because of gagging problems, the patient is partially anesthetized. Typically, patients will refuse to repeat the painful test and it is hardly suited for screening. The TEE test is 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.

Another test is referred to as transthoracic echocardiography (TTE). Again, microbubbles are injected into a vein leading to the right side of the heart.

5 The Valsalva Maneuver is carried out and ultrasonic echograms are made at the chest wall. The procedure requires the use of expensive equipment and exhibits about a 60% sensitivity.

A third test again uses microbubbles as a contrast agent along with the Valsalva Maneuver. Here, however, the ultrasonic sensors perform in
10 conjunction with the temporal artery usually at both sides of the head. This transcranial doppler method (TCD) exhibits a high sensitivity and costs between about \$30,000 to \$40,000 for equipment. Unfortunately, over 20% of the population has a cranial bone that's too thick for sonic transducing. U.S. Patent Publication US2006/0264759 describes such systems and methods for grading
15 microemboli in blood associated with ultrasound contrast agenda (e.g., small air bubbles) within targeted vessels by using Doppler Ultrasound system.

Additional description of existing methods of analyzing circulation and detecting certain circulatory anomalies are present in the following.

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

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

7) Karttunen, V., et al. Acta Neurologica Scandinavica 97: 231-236
25 (1998);

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).

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A continuing difficulty with existing methods is the efficacy of using microbubbles 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
35 quantitative measurements, and thus clinicians are forced to rely on a 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.

5 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 transesophageal echocardiography, transthoracic echocardiography, and the transcranial doppler method, 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
10 quantitatively detectable, and utilize relatively straightforward detection systems that are easily tolerated by patients.

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
15 detection systems.

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.
20 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 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 closure at 3 to 4 time points
25 following the percutaneous closure of the right-to-left shunt. This follow-up testing following shunt closure continues to be essential for assuring adequacy of the "seal" closing a PFO or other shunt, in order to minimize the risk of future shunt-related strokes.

30 In application for United States Patent Serial No. 12/418,866, a generally non-invasive technique for screening for circulatory anomalies such as patent ovale foramen is disclosed. With the system and method, a fluorescing indicator (indocyanine green dye) is injected within the venous system and a resultant dilution curve is detected at the arterial vasculature in the pinna of the ear. In
35 general, a red region laser beam is applied at the ear surface in a reflection operational mode and the indicator photons emitted in fluorescence are filtered

and measured for intensity. This results in one or more intensity curves, an initial one being in response to a shunt condition and the subsequent curve representing a larger concentration resulting from passage of the indicator through the lungs and back through the heart. In this regard, if a shunt condition
5 is present, the intensity read-out will generate a lower intensity preliminary shunt curve. This will be followed by the noted larger dilution curve.

With the encouragement of the somewhat extensive animal (pig) data, it now becomes necessary to improve fluorescing photon intensity measurement and to explore human physiology with respect to the transit of the indicator, its optimum
10 injection site and timing, the use of the characteristics of a Valsalva Maneuver, improving fluorescing photon intensity measurement as well as overall testing reliability. This called for bench-testing for sensor optimization, extensive medical literature searching to improve the overall procedure and additional animal (pig) as well as human trials.

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BRIEF SUMMARY

The present system is addressed to system, method and apparatus for detecting and quantifying right-to-left pulmonary shunts. The preferred indicator, which is employed, is indocyanine green dye (ICG) which will fluoresce when
20 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 monitor/controller having a visual display and capable of providing cues to both the operator and the patient. A vein access catheter is employed in connection with a peripheral vein such as the antecubital vein in an arm. Sensing of the indicator
25 concentration takes place at an arterial vasculature of the animal body, preferably at the pinna of the human ear. The system performs using fluorescence sensor arrays each with three indicator fluorescing lasers, which are directed to an artery of the scaphoid fossa of the ear pinna, where relatively thin tissue contains an arterial blood network. These sensors are configured for transmission mode
30 measurement wherein three lasers are combined with aspheric collimating lenses for positioning at one side of the ear, and at the opposite side of the ear tissue, there is positioned a photon collimating orifice and an optical band pass filter, selected to permit only fluorescing photons to reach a photodetector. The two branches of these fluorescence sensor array configurations are preferably spring
35 biased, to be held in proper and stable positions at the ear.

The preferred method preferably incorporates a Valsalva Maneuver of

about six seconds duration, during which two protocols for controls over injection of indicator may be carried out for a given session. As an adjunct to the control system, a Doppler ultrasound arrangement is utilized with a pickup positioned on the left parosternal position of the chest. This provides an output signal
5 corresponding with the movement of normal saline solution into the right side of the heart. To assure proper termination of the Valsalva Maneuver, a solenoid actuated pneumatic valve may be incorporated in the monitor/controller to release pressure in an exhalation tube at the proper instant in the procedure.

The monitor/controller may be configured to calculate an area under a
10 normal indicator/dilution curve associated with indicator and blood flow through a normal pathway in the lungs. Additionally, the monitor/controller can calculate the area under any premature indicator dilution curve, which will be associated with a right-to-left shunt. The monitor/controller further corrects the main indicator curve for a recirculation phenomenon, and to quantify any right-to-left
15 shunt, calculates conductance associated with such shunts.

Other objects of the invention will, in part, be obvious and will, in part, appear hereinafter. The various embodiments of the invention, accordingly, comprises the method, apparatus and system possessing the construction, combination of elements, arrangement of parts and steps which are exemplified
20 in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

For a full understanding of the nature and objects of the various embodiments of the invention, reference should be had to the following detailed description taken in connection with the accompanying drawings, in which:

5 Fig. 1 is a schematic and sectional representation of a heart showing a right-to-left heart shunt;

 Fig. 2A-C is an enlargement of a portion of the schematically illustrated heart of Fig. 1 showing cardiac shunts of differing configurations;

10 Fig. 3 is a schematic diagram showing the interrelationship of the right and left sides of the heart in conjunction with lungs and a right to left shunt;

 Fig. 4A-B show representative indicator dilution curves with a preliminary curve indicating a shunt and showing the relative timing of a Valsalva Maneuver along with a time for injecting indicator into a vein;

15 Fig. 5 is a graph relating pressures between the right and left side of the heart and showing a reversal of such pressures at the point in time of the release of a Valsalva Maneuver;

 Fig. 6 is a perspective view of a phantom material containing carriage mounted in the support of Fig. 7;

20 Fig. 7 is a front view of the carriage shown in Figs. 6 and 8B revealing height adjustment features and laser beam cross sections;

 Fig. 8A is a perspective view of a bench-testing device for utilizing a phantom tissue material;

 Fig. 8B is a perspective view of an outer support described in connection with Fig. 6;

25 Fig. 9 is a sectional view taken through the plane 9-9 in Fig. 6;

 Fig. 10 is a transmission curve showing the performance of an interference filter employed with the instant system;

 Fig. 11 is a graph showing the performance of the interference filter with respect to the angle of incidence of photons reaching it;

30 Fig. 12 is a graph showing measured signal level change with respect to the structure of six collimator plate designs and the utilization of a 1 mm internal diameter tube within a bench test device as described in connection with Fig. 9;

 Fig. 13 is a similar chart showing the performance of various aperture structures in conjunction with a 0.5 mm internal diameter tube as utilized in
35 connection with the test rig of Figs. 6 and 9;

Fig. 14 is a chart relating ICG concentration with an observed signal level change/base-line ratio for transmission as well as reflector mode sensing systems;

Fig. 15 is a schematic view of a human ear showing arterial structure at the scaphoid fossa of such ear;

Fig. 16 is a schematic sectional view of fluorescent excitation and detection at the ear of Fig. 15 utilizing a transmission mode detector system;

Fig. 17 is a schematic sectional view of fluorescent excitation and detection at the ear of Fig. 15 when utilizing an array of two or more transmission mode detectors;

Fig. 18A-18G illustrate the structure of a biased clip type fluorescent sensor array intended for use with tissue and arterial structure at the scaphoid fossa of the ear as shown in Fig. 15;

Fig. 19 is a schematic view of the head of a patient with a headband configured to support biased clip type fluorescence sensing arrays;

Fig. 20A-18G illustrate the structure of a fixed jaw type fluorescent sensor array intended for use with tissue and arterial structure at the scaphoid fossa of the ear as shown in Fig. 15;

Fig. 21 is a schematic representation of the alignment orientations of three fluorescence generating and sensing devices utilized with a device of Figs. 18 and 20

Fig. 22 illustrates a headband apparatus for positioning the sensor arrays on the ears of a human patient;

Figs. 23A-D illustrates the components of a headband system for aligning sensor arrays with human ears;

Fig. 24 is a perspective view of the cable connector for use with two sensing arrays;

Fig. 24A is a rear view of a human patient wearing the headband apparatus of Fig. 22 and related components of a headband system of Figs. 23A-D, with the cable connector of Fig. 24 positioned for use of the sensor arrays;

Fig. 25 is a stylized curve showing an indicator curve with a recirculation effect and its relation to a baseline;

Fig. 26 is an animal generated indicator concentration curve showing the recirculation effect;

Fig. 27 is a representation of an indicator dye-dilution signal curve in conjunction with a preliminary shunt curve;

Fig. 28 shows the curves of Fig. 27 plotted in conjunction with a semi-log graphical representation;

Fig. 29 is a perspective view of a monitor/controller, which may be used with the disclosed system;

5 Fig. 30 is a perspective rear view of the monitor of Fig. 30;

Fig. 31A-B show perspective views of the monitor/controller apparatus with the rear cover removed to show the internal apparatus components;

Fig. 32 is a top view of an indicator delivery system;

10 Fig. 33 is a perspective view of the disposable kit components of the apparatus and system;

Fig. 34 is an exploded view of a fluid flow detector utilized in a delivery system;

Fig. 35 is a side view of the flow detector of Fig. 34;

15 Fig. 36 is a perspective view of the configuration of a flow detection system;

Fig. 37 is a planar view of a flexible circuit employed with the device in Fig. 34;

Fig. 38 is a sectional view taken through the plane 38-38 shown in Fig. 35;

20 Fig. 39 is a perspective view of the flow sensor connector, with the cover removed, used to connect the flow sensor to the monitor/controller;

Fig. 40 is a contact end view of the flow sensor connector shown in Fig. 39;

Fig. 41 is a side view of the flow sensor connector shown in Fig. 39;

25 Fig. 42 is a bottom view of the flow sensor connector shown in Fig. 39;

Fig. 43 is a top view of the flow sensor connector shown in Fig. 39;

Fig. 44 is a schematic drawing of the components of the monitor/controller system shown in Figs. 29-31;

30 Fig. 45 is a wiring diagram of the fluorescence sensor array cable connector shown in Fig. 24;

Fig. 46 is a wiring diagram of the flow sensor circuit and flow sensor cable connector shown in Fig. 32;

Fig. 47 is a schematic perspective view of a patient being tested with the disclosed system;

35 Figs. 48A-C are charts showing human generated Valsalva pressure and dye dilution curves generated at the ears of patients tested using the system and

apparatus, with Fig. 48A displaying signal levels measured by each sensor in an array, and Figs. 48B-C displaying shunt conductance indexes calculated from the signal levels measured by each sensor in the array;

Fig. 49 is a chart describing Protocol 1 as utilized with a preferred
5 embodiment of the present disclosure;

Fig. 50 is a chart similar to Fig. 49, but showing a second protocol according to the present disclosure;

Figs. 51A-51F combine as labeled thereon to show a flow chart of the procedure associated with a preferred embodiment;

10 Fig. 52 shows one display of a monitor according to the present disclosure as utilized in improving the Valsalva procedure; and

DETAILED DESCRIPTION

When a right-to-left shunt is present in the heart or the pulmonary
15 circulation of the human body, in effect a system with two or more alternative blood flow pathways exist. As described above, the most common form of right-to-left shunt in the heart is known as a Patent Foramen Ovale or 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 mother's oxygen-rich blood
20 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 year following birth. This opening fails to permanently close in the remaining 20% of the population.

For some individuals, this normally closed flap (i.e., Foramen Ovale)
25 temporarily opens allowing blood to flow directly from the right side to the left side of the heart. As a consequence, any blood clots or other metabolically active agents bypass the critical filtering/metabolic functions of the lungs and flow through the brief opening in this flap and directly to the left side of the heart. Once in the left side of the heart, any unfiltered blood clots or agents such as
30 serotonin 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
35 certain forms of severe migraine headaches.

For further discussion, see the following publications:

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);

5 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);

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

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

As disclosed herein, a right-to-left pulmonary shunt is detectable and quantifiable utilizing a biocompatible indicator, which is injected into a peripheral vein of the patient. In connection with this injection, the patient typically is called upon to carry out a Valsalva Maneuver, wherein exhalation into a manometer to achieve a certain pneumatic pressure is called upon for a relatively short interval of time. The release of this maneuver reverses the pressure differential between the right and left atria. The consequence typically is an opening of the noted flap allowing venous blood to flow directly into the left atrium. That flow will be premature with respect to the normal flowpath of venous blood toward the lungs.

20 The discourse to follow tracks further animal and initial human testing and presents a review of published research, resulting in a diagnostic approach which permits a practical survey for the phenomena over a large patient population.

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. 1A 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 14 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). As illustrated in Fig. 1, the atypical presence of a patent foramen ovale 22 results from, for example, the presence of displaceable tissue flap 24, creating opening 26. Shunt flow of venous blood from the right to

left atria through opening 26 is represented in Fig1A 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.

5 Not all cardiac shunts (or other circulatory anomalies) are present in the same configuration. Fig. 2 shows several examples of the manner in which shunt configuration can alter the relative shunt conductance of an atrial shunt. Fig 2A-2C show enlargements of the portion of the schematically illustrated heart of Fig. 1A, in three differing theoretical manifestations. Fig. 2A shows heart 10A with a
10 simple portal, 20A in the interauricular septum 24A separating atria 12A and 14A. The amount of fluid flow through such portal in the open condition, is relatively simple to calculate, when provided with estimates of portal thickness 21A, and diameter 23A. Similarly, if the amount of conductance through the portal is known, the relative size of a portal can be calculated, thus providing assistance in
15 determining a therapeutic regimen. Fig. 2B shows heart 10B with a deeper, narrower foramen ovale 20A in the interauricular septum 24B separating atria 12B and 14B. In this situation, transit path 21B and diameter 23B would be expected to provide more resistance to shunt conductance than a foramen ovale such as shown in Fig.2A. Fig. 2C shows heart 10C with a complex foramen ovale
20 20C in the interauricular septum 24C separating atria 12C and 14C. The path of passage 20C is more complex, and may present further fluid flow resistance, thereby constricting overall shunt conductance. Thus, the amount of fluid flow through foramen ovale 20C is not easily calculated, and the shunt may only be open transiently in certain conditions, whereas a simple shunt, such as shunt
25 20B, may be latent and susceptible to relatively easier detection and monitoring.

In general, the preferred embodiments of the present disclosure observe that an indicator such as an externally detectable indicator dye material will traverse through the venous system toward the right atrium within a detectable transit time. Accordingly, venous blood containing such an indicator will pass
30 through the opening 26 between the right and left atria, and progress through the arterial system ahead of indicator carried through the normal circulatory system (i.e., through the lungs).

Looking to Fig. 3, such an indicator bolus premature condition and delay by spacing through the lungs is represented schematically. In the figure,
35 indicator being introduced to the venous blood stream is represented at arrow 36. Preferably, arrow 36 represents the injection of a predetermined amount of

indicator in a peripheral vein (i.e., the antecubital vein in the right arm of a patient). This is followed by an injection of isotonic saline. The indicator in venous blood at blood stream 34 is directed to the right side of the heart as represented at block 38. A right-to-left shunt is represented by the small conduit 5
40, which is shown extending to the left side of the heart as represented at block 42. Meanwhile, the lungs are represented within the dashed boundary 44, a circuitous route of filtering and aeration being represented by conduit 46 as it extends from the right side of the heart to conduit 48. As it travels from the right side of the heart following filtering and aeration, the refreshed blood now enters
10 the left side of the heart as at block 42, whereupon it is distributed as represented at conduit 50. From conduit 50 the refreshed blood is distributed to multiple arterial conduits represented in general at 52. One conduit of the conduit array 52 is seen at 54 being analyzed by the sensor and controller function of the instant system represented by arrow 56. Other such arterial conduits may be
15 simultaneously analyzed to provide a plurality of sensing outputs, which are time and intensity based dilution curves, for example, generated by a dye indicator. Such dilution curves based upon signal intensity level and time are represented schematically at 58, only one such curve being shown. These curves at display 58 result from the intensity of the indicator and its transit time from injection as
20 represented at arrow 36. The principle of the dilution curve at display 58 is that it is the detection of an indicator bolus resulting from the passage of indicator 60. However, note that a premature and smaller indicator detection and dilution curve 62 is present which results from the passage of indicator along the shunt 40. Curve 62, representing, for example, a PFO can be quantified by a ratiometric
25 analysis, with reference to dilution curve 60. Thus, not only is the presence of a PFO detected but it is quantified. Any recirculation component of the indicator will have been removed from the principal curves as at 60 and 62. It is possible that more than one of the premature curves as at 62 can occur.

Referring to Fig. 4A, a stylized representation of the indicator dilution
30 curves and associated procedures for their use is stylistically presented by graph 66. In the figure, a principal dilution curve representing indicator passage through the lungs is represented at larger curve 70. Idealized curve 70 is shown commencing at a time represented at t_2 , and is shown to reside just above a baseline represented at horizontal dashed line 72. The peak of curve 70 is
35 shown to reside between vertical dashed lines 74 and 76 and exhibits a peak indicator concentration at horizontal dashed line 78. The descending component

of curve 70 as shown at 70' is calculated to accommodate for recirculation phenomena and the like.

5 Occurring prior to curve 70 is a premature indicator curve 80 commencing at time, t_1 , and representing a pulmonary shunt condition, which can be quantified with respect to and in relation to curve 70, the primary indicator curve, commencing at time t_2 . Analysis of the plotted indicator curves can identify premature peak 80, and primary peak 84 as part of the quantification of the relative shunt size.

10 Returning momentarily to Fig. 1, under normal pulmonary conditions, the opening 26 in the heart will be closed, for example, by flap 24 and the presence of a differential pressure having a higher level in the left atrium 14. This pressure differential can be reversed by applying and releasing an exhalation pressure, for example, between 30 and 45 milliliters of mercury. Looking momentarily to Fig. 5, the pressure differential between the left side of the heart and the right side of the heart is plotted with respect to time. In the figure, measured pressure on the left side of the heart (PCWP) is shown at plot 82 extending in time during a Valsalva Maneuver, starting at vertical dashed line 84 and ending with release represented at dashed line 86. Pressure on the right side of the heart (RAP) is represented at plot 88. Note that initially at the commencement of the Valsalva Maneuver, pressure on the right side of the heart is lower than that on the left. However, at the release of the Valsalva Maneuver as represented at dashed vertical line 86, the differential pressure between the left and right side of the heart reverses, pressure on the left side of the heart being lower than that on the right. This procedure is believed to tend to open any flap-type valving as shown in Fig. 1 at opening 26. (See: Pflieger 2001).

20 Returning to Fig. 4A, as is apparent, the timing of the Valsalva Maneuver as well as the injection of indicator are important components of the instant system. In the figure, the Valsalva Maneuver with respect to curves 70 and 80 is represented within the dashed boundary 94 showing the release of the Valsalva Maneuver at the cessation of time period, V1. The time of injection of the indicator is represented by the bar and dashed line 96, the figure showing injection commencing after time period V1, and the time between the commencement of injection and release of the Valsalva Maneuver being represented as time period V2.

35 Fig. 4B shows a stylized representation of indicator dilution curves stylistically presented by graph 68. In the figure, the timing of the Valsalva

release is not closely coordinated with the injection of indicator dye. A principal dilution curve representing indicator passage through the lungs is represented again at larger curve 70. In Fig. 4B, idealized curve 70 is shown commencing at a time represented at time t_2 , yet time V_2' is extended such that there is
5 substantial overlap between premature curve 82 and primary curve 84. Occurring prior to curve 70 is a premature indicator curve 82 commencing at time, t_1 , and representing a pulmonary shunt condition, and curve 70, the primary indicator curve, commencing at time t_2 . Analysis of the plotted indicator curves is limited by the ability to resolve and identify premature peak 82, and primary peak
10 84 as part of the quantification of the relative shunt size. Thus, proper implementation of the Valsalva procedure, can be critical for detecting shunts, especially shunts of relatively limited conductance.

Now looking to the indicator, a circulatory tracking reagent is called for. Studies at the outset of the research leading to the present invention indicated
15 that a preferred embodiment was to employ fluorescing dyes, certain of which had been approved for use in humans. Two such exemplary dyes were available at the time of the study, fluorescein and indocyanine green dye (ICG). The latter indicator was elected.

A number of additional circulatory tracking reagents are available for use
20 with the system at hand including such indicators as follows: U.S. Patent No. 3,412,728 describes the method and apparatus for monitoring blood pressure, utilizing an ear oximeter clamped to the ear to measure blood oxygen saturation using photocells which respond to red and infrared light; U.S. Patent No. 3,628,525 describes an apparatus for transmitting light through body tissue for
25 purposes of measuring blood oxygen level; U.S. Patent No. 4,006,015 describes a method and apparatus for measuring oxygen saturation by transmission of light through tissue of the ear or forehead; and U.S. Patent No. 4,417,588 describes a method and apparatus for measuring cardiac output using injection of indicator at a known volume and temperature and monitoring temperature of blood
30 downstream. This and several similar systems in the art suffer from an inability to effectively quantify the magnitude, i.e., functional conductance of shunts, as opposed to the presently disclosed embodiments.

A number of patents describe potential reagent systems that if adapted could be utilized with the present system method and apparatus. U.S. Patent No.
35 4,804,623 describes a spectral photometric method used for quantitatively determining concentration of a dilute component in an environment (e.g., blood)

containing the dilute component where the dilute component is selected from a group including corporeal tissue, tissue components, enzymes, metabolites, substrates, waste products, poisons, glucose, hemoglobin, oxy-hemoglobin, and cytochrome. The corporeal environment described includes the head, fingers, hands, toes, feet and ear lobes. Electromagnetic radiation is utilized including infrared radiation have a wavelength in the range of 700-1400 nanometers. U.S. Patent No. 6,526,309 describes an optical method and system for transcranial in vivo examination of brain tissue (e.g., for purposes of detecting 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.

Looking to the indocyanine green dye (ICG), excitation curves have been illustrated as having a peak excitation wavelength at about 785 nanometers. Correspondingly, for the fluorescent emission of the two fluorescent dyes, a peak wavelength of fluorescing photons resides at about 830 nanometers.

To use this fluorescing form of indicator in carrying out pulmonary shunt detection and quantification, a sensor having the capability to direct laser excitation illumination to a blood vessel as well as to collect and filter an emitted fluorescent response, was developed. The sensors so developed operate either in a reflection mode or a transmission mode.

In initial studies the reflective mode was utilized for the sensor. A relatively simple sensor was evolved utilizing fiberoptic technology. At the center of the sensor is a fiberoptic channel, which projects excitation emissions, for example, at 785 nanometers for ICG. Surrounding central fiber are seven glass fibers. All of these glass fibers have an outside diameter of, for instance, about 600 microns. When an ICG indicator within the bloodstream reaches the site of irradiation with 785nm prime laser (light), the fluorescent moiety within the ICG indicator is excited 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 (e.g., 830nm), and the difference between the excitation wavelength (785nm) and the fluorescence emission wavelength (vis 830nm) is known as the Stokes Shift. This Stokes Shift of nominally 45nm allows the fluorescent emission to be extracted by using a wavelength band of interest (vis 820-840nm). Such a reflection mode sensor was used initially in a bench top test to determine the light scattering influence of a thin human tissue. One tissue employed was the human hand with the tip of sensor being located against the web portion of the hand. Laser excitation light is directed downwardly through the sensor fiberoptic to pass

through the skin region and into the material within the sensor tube. This causes a fluorescence to enter the outside fiberoptic components as represented by upwardly pointing arrows. One design for a reflection mode sensor system comprises a conically-shaped sensor having a tapered aluminum body
5 surmounting a circuit board supporting three photodiodes. These photodiodes are positioned above an interference filter, which encounters and passes 830nm fluorescence generated photons. Above the filter is a blocking filter for 785nm excitation photons as is known in the art. The fluorescing photons are collected by optical fibers. These fibers extend to lenses intended for focusing wide-angle
10 fluorescent photons into the fibers. These fibers extend through a platform to pass the photons through a collimating lens. Coupled to the underside of platform is a combination of a laser diode (785nm) and collimating lens. The collimating lens combination feeds red region laser light energy to a laser fiber, which extends to excite the indicator, which may be carried within a blood vessel
15 located within tissue. It is recognized that a reflectance mode sensor array system may be applicable to the present system. Based on additional testing, it was determined that a transmissive array system was preferred.

The results of testing with a reflectance mode system were used to develop a bench top phantom test rig. Sensors performing in a transmission
20 mode as opposed to a reflection mode were developed in conjunction with a tissue phantom holder designed for bench top experimentation and analysis.

Referring to Fig. 6, the test apparatus used for bench top testing is represented in general at 160. Apparatus 160 includes a generally U-shaped optic support shown generally at 162 which supports a laser diode at a front face
25 164 and a spaced apart back face 166 supporting a photodiode. The spacing and support of faces 164 and 166 is by a base plate 168. Note the attachment of plate 166 with base plate 168 by cap screws at 170a and 170b. Back face 166 supports a photodiode assembly, which is retained in place by a retainer block 172, attached to plate 166 by cap screws 174a and 174b. Electrical leads
30 extending to the photodiode are represented at 176 and 178. Front face 164 supports a laser diode assembly (not shown) which is supported electrically and mechanically by a laser diode retainer 180 shown having electrical leads extending therefrom in general at 182. U-shaped subassembly is shown in isolation in Fig. 8A. It may be seen that one of two adjustment screws is present
35 at 184a.

Between the faceplates 164 and 166 there rides a phantom carriage represented generally at 190. Carriage 190 is formed of two plates, 192 and 194 which are held together by four bolt and nut assemblies, the bolts of which are shown at 196a-196d. Plates 192 and 194 are joined together to form a phantom tissue defining cavity having an uppermost slot accessing entrance at 198. Looking additionally to Figs. 7 and 8B, the cavity is represented generally at 200 and is surmounted by two circular windows, one of which is shown at 202 within plate 194. Cavity 200 is configured to retain a tissue emulating material marketed under the trade designation "Intralipid" which is adjusted to emulate human tissue having a thickness of about 3 mm. The tissue characteristic emulated is derived from the experimentation of Fig. 6. During that test, tubes of 1 mm and 0.5 mm were used with varying concentrations of ICG. Extending through the cavity 200 is a glass tube 206, having an internal diameter, for example, of 0.5 mm or 1 mm, emulating the size of a blood vessel at the ear pinna. Tube 206 is connected for fluid input and return by flexible tubing 208 and 210. Fig. 7 reveals that the phantom carriage 190 is adjustable vertically by adjusting screws 184a and 184b. The optics within support 162, as well as the phantom carriage 190, cooperatively perform in a transmission mode wherein laser energy is projected through one side of the skin (here tissue emulating material), and resulting fluorescing photons are detected on the opposite side of the tissue component being examined. This is revealed in the sectional presentation of Fig. 9. In that figure, cavity 200 reappears in conjunction with circular windows 202 and 204 formed within respective carriage plates 194 and 192. Nuts 216c and 216d are seen to be threadably attached to respective bolts 196c and 196d. A laser diode 218 is seen coupled with retainer 180 and is retained in position within plate 164 by a ring retainer 220. Positioned to intercept and collimate photons from the infrared diode 218 is a collimating aspheric lens 222, the resulting collimating photons being represented in general at 224, impinging upon the glass tube 206. Laser diode 218 may, for example, be a type DL7140-201S(785MM), marketed by Tottori Sanyo Electric Ltd of Tachikawa, Japan.

Returning to Fig. 9, fluorescing photons having a wavelength of about 835 nm are caused to pass through an aperture of an opaque collimator (collimator plate) 226 from which they encounter an interference filter 228. The performance of filter 228 is represented at band pass curve 230 shown in Fig. 14. The structure of the collimator 226 was developed using the bench top assembly

160, as will be discussed in relation to Figs. 12 and 13. Looking additionally to Fig. 11, the performance of interference filter 228 is represented at curve 232, which reveals that its performance is dependent upon the angle of incidence of photons reaching it. For example, from curve 232 one may observe that for a
5 zero angle of incidence, a full 835nm wavelength photon will pass. Performance degrades as that angle of incidence increases. The output of the laser 218 is shown at dashed line 234.

Returning to Fig. 9, a photodiode is represented at 236 along with earlier-described leads 176 and 178. Photodiode 236 may be a type DPW34BS,
10 marketed by OSRAM. The device at 236 is retained in position by retainer block 172 and a foam insert 238.

Referring to Figs. 12 and 13, bench top tests of various collimating plates as at 226 for a transmission mode of performance, in combination with two different interference filters are depicted. In Fig. 12, the tests were performed
15 utilizing a glass tube 206 having an internal diameter of 1 mm. The curves represent a measured signal increase between water and ICG using a 4.5% Intralipid tissue phantom. By contrast, Fig. 13 shows the same test carried out but with a glass tube 206 having an internal diameter of 0.5 mm. A preferred embodiment is utilizing a collimator plate with an aperture of approximately 0.081
20 inch and a plate thickness of 0.082 inches and the 5550 interference filter, which provided results consistent between the 1 mm and 0.5 mm glass tubes. For sake of reference, Fig. 14 is a chart relating ICG concentration with an observed signal level and computed base-line ratio for transmission as well as reflector mode sensing systems, encompassing a range of ICG concentrations from 0.5 µg/ml to
25 12.5µg/ml. Curve 244 shows the relative signal level for particular concentrations, and curve 242 shows the ratio of the signal level to baseline detection.

The system outline in Fig. 6, and the disclosure in connection therewith is useful for testing a variety of parameters useful for optimizing the system and apparatus. Although ICG is the presently preferred indicator dye, other dyes may
30 be even better adapted, and proof of concept of the system, using tissue phantoms, actual tissue and other factors can be readily screened with the apparatus shown in Fig. 6. Moreover, improvements to the detection system itself are amenable to bench top testing for system optimization.

The transmission mode of sensing as described in connection with Fig. 9
35 finds advantageous application at regions of the body in which surface tissues are relatively thin. The transmission mode of sensing is preferably applied to

locations of the patient body wherein the arterial vasculature is arranged such that the transmissive sensors can be placed opposite the photodetectors in a noninvasive manner. Preferred locations on the human body include the pinna of the ear, the hand, including the web of skin between the thumb and forefinger, the neck, including distendable skin about the neck, the leg, and the arm, including distendable skin of the arm proximal to the shoulder. Non-human patients, such as dog, pig or horse, also provide ready locations for sensors on the pinna, in addition to other vascularized extremities. A preferred embodiment of the system is to place sensor arrays at symmetrically paired locations distal to the heart, such as at is both ears, both hands, paired locations on the neck, the leg, and the arm.

A particularly preferred embodiment is placement of sensor arrays on both pinna of the ears of the human patient. Looking to Fig. 15, the human ear pinna is revealed in conjunction with the outline of the transmission mode sensor having three laser driven transmissive sensors arranged at that portion of the ear termed herein as the scaphoid fossa and identified generally at 244. Arterial vessels are shown in this region as lines 246. Further regions of the ear are identified as the triangular fossa shown generally at 248; the helix shown generally at 250; the concha is shown generally at 252; the tragus shown generally at 254; the acoustic meatus shown generally at 256; the intertragic notch shown generally at 258; the anti helix shown generally at 260; the anti tragus shown generally 262; and the lobule shown generally at 264. For a more detailed discussion of the ear see: Tilotta, F, et al., Surg. Radiol. Anat.,31:259:265 (2009).

In order to better optimize the application of an external sensor apparatus to the ear, the thickness of the schapoid fossa of several adult patients was determined. Measurements were made at three locations on the schapoid fossa for each patient, using a micrometer. The mean thickness was 0.101 inches. The range of lobe thickness was from 0.082 inches to 0.141 inches. Thus, a maximum distance between the arrays on the sensor apparatus of about 0.150 inches (3.8 mm) is expected to accommodate most patients, with an opening range of about 0.05 inches to 0.175 inches being preferred, and even more preferred an opening of about 0.075 to 0.15 inches (2 mm to 4 mm).

Turning now to Fig. 16, a portion of the scaphoid fossa again is identified at 274 in conjunction with an arterial vessel as earlier described at 246. A transmission mode of sensing is shown associated with that part of the ear. The

components of the transmission mode sensor include a laser diode 270, the output of which is associated with an aspheric collimating lens 272. Laser light as represented at 276 is directed into the scaphoid fossa 274 to impinge upon arterial vessel 246. Laser light and fluorescence-generated photons then occur
5 as represented in general at 276, passing a transparent window 278, the bore of an opaque collimator 280, and interference filter 282. Filter 282 passes essentially only the photons resulting from fluorescence to impinge upon a photodetector 284.

Following experimentation, and the implementation of multiple emitters
10 and detectors in a sensor array, it was recognized that the efficacy of the bandpass filter, and collimating plates were limited by cross-talk between related channels in the sensor array. It should also be noted that such cross-talk may be even more pronounced when utilizing reflectance mode excitations and detection. The interference filter is necessary in order to reduce incident light arising from
15 the excitation lasers, with the detectors being tuned to detect light emitted as a result of fluorescence. When the interference (i.e. bandpass) filter is ineffective, the excitation light may overwhelm the detection system. Turning now to Fig. 17, an emitter and detector pair as shown in Fig. 16 are accompanied by another emitter/detector pair, forming sensor array. (Although 2 emitter/detector pairs are
20 shown, it is recognized that three or more such pairs are preferred.) A portion of the scaphoid fossa again is identified at 274 in conjunction with an arterial vessel as earlier described at 246. The laser diodes are represented at 270 and 270' with their output being directed onto aspheric collimating lenses 272 and 272'. Laser light as represented at 276 and 276' is directed into the scaphoid fossa 274
25 to interact with indicator present in arterial vessel 246. Laser light and fluorescence generated photons then continue, until passing transparent window 278, multiple bores of an opaque collimator 280, and interference filter 282.

Filter 282 is designed to pass essentially only the photons resulting from fluorescence to impinge upon photodetectors 284 and 284'. However, when
30 emitted laser light interacts with tissue 274, a portion of such light is scattered, as shown in part by dashed lines 286 and 286'. Such scattered light would be prevented from entering the detector when a single emitter is present, as in Fig. 16, by the collimating plate 280. When multiple emitters are present, the scattered light may strike the interference filter 282 at an angle less than
35 perpendicular. Since the filter is most efficient when the angle of incidence is 90 degrees, as the angle of incidence is reduced, scattered light (such as excitation

laser light) as at 286 and 286' can pass unimpeded through the filter, and substantially increase the noise detected by the detectors 284 and 284'. Recognizing this phenomenon, a preferred embodiment of the array system provides an additional collimator as at 283, thereby maximizing the efficiency of the interference filter, and reducing the light of low angle of incidence that can pass through the interference filter.

The components described in connection with Fig. 16 are implemented with a sensing array fixture shown in perspective and identified in general at 290 in Fig. 18A. Fixture 290 is formed with a three laser array support 292 which is hinged at 294 to a photodiode array support 296. Supports 292 and 296 are biased toward each other by a spring seen in Fig. 18C at 298. A laser "power-on" light emitting diode provides a yellow colored light output at 300. As seen in Fig. 18D, a similar yellow LED is located in support 296. It has been found to be beneficial to incorporate a Velcro-type pad for the support of device 290. Such a pad is represented at 304. A three-laser array along with collimating aspheric lenses are mounted within a protrusion 306 extending inwardly from support 292. That protrusion is seen, particular, at Figs. 18C, 18D and 18F. Complementing the three laser array is an aligned array of three photodiodes located within protrusion 308 which also is seen in Figs. 18C, 18D and 18G. Looking to Fig. 18F, protrusion 306 is seen to support an array of three lasers and associated aspheric collimating lenses as represented at 310a-310c, aligned with those laser and collimating lens as are corresponding photodiodes along with an associated collimator and interference filter. The collimator openings for orifices are seen at 21G at 312a-312c. Also seen in Figs. 18F and 18G are windows 314 and 316, utilized in providing a laser interlock system.

Looking to Fig. 18D a sectional view is shown through the section identified at 18D-18D in Fig. 18B. The figure shows that a circuit board 320 is mounted in support 292, which is shown supporting a laser diode and an aspherical lens 310b, as well as cable connector 322 intended for connection with a cable component 324. Circuit board 320 additionally supports laser diodes 310a and 310c, diode 310b being seen in this sectional view.

In similar fashion, support 296 incorporates a circuit board 326 which supports three photodiodes, one of which is seen at 328b, located beneath interference filter 330, collimator 332 having orifice 312b and a transparent window 334. Circuit board 326 also incorporates a cable connector 336, which

also is coupled to cable 324. A laser power-on LED is shown at 302 as well as at 300.

Referring to Fig. 18E, a section of device 290 is shown taken through the plane 18E-18E shown in Fig. 18B. In the figure, circuit boards 320 and 326
5 reappear, board 320 supporting a light emitting diode 338 which operationally performs with an aligned photodetector 340, light from the LED 338 extending through the windows 314 and 316 to excite the photo detector 340 and provide an optical interlock having a signal utilized by the control circuitry.

A variety of techniques are available for supporting fluorescence sensor
10 array structures at the scaphoid fossa of the ear. In this regard, a more or less simple surgical cap has been utilized. Another approach is with a reusable headband referring to Fig. 19 such as headband set is represented generally at 390 located on the forehead of a patient 392. The front to back encircling portion of the band 390 is shown at 394, which is configured with a knob-actuated ratchet
15 395 for adjustment with respect to head diameter. Correspondingly, a head size height adjustable band is shown at 396 with a Velcro type fastener which may be used with a tape fastener 398, which may be used with a tape extending to a fluorescence sensor array as described at Fig. 18A and here identified at 400, or with respect to the array shown in Fig. 20. Note that the device 400 is attached
20 to the scaphoid fossa of the ear 402 and is stabilized with a Velcro type tape attached between Velcro type patches 406 and 408. Note that device 400 is similarly coupled to the right ear. Looking to Fig. 28, a head support is shown in perspective fashion in general being identified at 410. A head-encircling band is shown at 412 having a ratchet form of head size adjustment at 454. A vertical
25 band 416 is physically attached to band 412 and incorporates a head size adjustment 418. Fluorescent sensing components are seen for right and left ears as at 422 and 424. From each of these, a respective cable 426 and 428 extends to a communication hub shown generally at 430. Hub 430 additionally connects to a controller/monitor as represented by the cable 432. Device 422 is coupled to
30 band 416 by strap 423, while device 424 is coupled to Velcro type patch 420 by strap 421.

An alternative embodiment of the flow sensor array optimized for use on the human ear is described in connection with Fig. 20A-20G. It is recognized that spring biased type arrays, such as disclosed in connection with Fig. 18, must be
35 carefully placed in order not to impinge upon the arterial flow. With the relatively small size of the human pinna, the vasculature of the human ear is relatively easy

to impede, simply by clamping the sensor array too tightly on the ear, or by simply bending the ear, and pinching closed the arteriols as a result. An improved version of the sensor array provides for a fixed throat size that it is suitable for placement on most human schapoid fossa. The sensing array fixture is shown at 330 in Fig. 20A-20G. Fig. 20A shows a perspective view of array 330, with fixture 330 being formed of array body 332 with a three laser emitter array support 348 which is integrally connected to a photodiode array detector support 352. The sensor array is connected to the monitor/controller through cable 334. The spaced apart emitter and detector arrays, are separated by sensor throat 336, and plate 338 is used, to connect the array to a support system. Said features are also shown in relation to the front view of fixture 330 in Fig. 20B, and with respect to side view Fig. 20C. Fig. 20C demonstrates the configuration of throat 336, with the throat opening shown as 337. A top view of the sensor array fixture is in Fig. 20D. Fig. 20E is a longitudinal cross-section of the fixture 330 along plane 20E of Fig. 20B. Contact plate 338 is used to connect the array to a support system, and plate 338 is shown as subtended by magnet 339. It is also practical to alternatively incorporate a Velcro-type pad for the support of device 300.

Array body 332 is formed of two parts, main body 342 and body cap 344. Cap 344 is retained by press fit, adhesive, or ear 346 capturing pin 347. Inside the body 332 are found connector board 354, detector board 355, and emitter board 356. A three-laser array and collimating aspheric lenses 346A-C are mounted within a protrusion/emitter head 350 extending outwardly from support body 332. That protrusion is seen, particularly, at Figs. 20B, 20C and 20F. Complementing the three-laser array is an aligned array of three photodiodes detectors 350A-C located within protrusion 352 which also is seen in Figs. 20B, 20C and 20G. The cross section in Fig. 20E shows window 360, collimator 280 and 283, and interference filter 352.

Looking to Fig. 20F, a sectional view is shown through the plane identified at 20D-20D in Fig. 20C. Protrusion 350 is seen to support an array of three lasers and associated aspheric collimating lenses as represented at 346A-346C, aligned with those laser and collimating lenses, as are corresponding photodiodes along with an associated collimator and interference filter. The collimator openings for orifices are seen at Fig. 20G at 350A-350C. Looking to Fig. 20G, a sectional view is shown through the plane identified at 20G-20G in

Fig. 20C. The figure shows that a circuit board 355 is mounted in body 344, with connector board 354, body 344 supporting detector array 352.

Referring to Fig. 21, an alignment diagram shows the relative positioning of the components of the fluorescence sensor array employed with devices as at
5 290 and 330. In the figure, the physical diameter of the laser emitter diodes is represented at 350. These devices are identified as Sanyo Laser Diodes, catalog number DL-7140-201S, and have a 0.220 inch diameter. Circle 353 represents the outer diameter of an unmounted Edmund Optics interference filter, while circle 354 represents the clear aperture of a mounted Optasigma interference
10 filter. Circle 357 represents the centerline of the laser diodes and photo diodes. Square 358 represents the active area of the photodetectors marketed by Osram and circles 360 represent the elliptical cross-section of the laser beams.

Fig. 22 shows the headband system for optimally positioning the sensor array systems on the head and the schapoid fossa of the human ear. Headband
15 system 362 is comprised of band 364, adjustment cam 366, and ferrous plates 368. Figs. 22B-22E show views of magnetic connector wedges 370 which allow precise positioning of the detector arrays about the ear. Wedges 370 comprise body 372, shaped as a grapefruit slice, and triangular in cross section as at end 374. Magnets 376 penetrate body 372, and magnetically attach to ferrous plate
20 368 of headband system 362, and plate 338 of the sensor arrays. Fig. 24 shows the assembled headband mounting system 362 place on a human head 378. Pinna 380A and 380B slide into the throat of arrays 330A and 330B, and are positioned via connector wedges 370 in order to be accurately placed on the schapoid fossa, and avoid impingement on the vasculature of the ear.

25 In order to connect the sensor array apparatus to the monitor controller, as reusable connection cable 420 is provided. As shown in Fig. 24, communication connector hub 422, a left ear connector 425, extending from device 428, receives an input as well as provides outputs and is coupled to device 428. In similar fashion, a right ear connector 425' couples to device 430.
30 Finally, a connector for cable 423 is directed to a monitor controller as shown at 424.

Referring to Fig. 25, a theoretical dye dilution curve is represented at 366 in conjunction with a baseline 368. In order to compute the area under such curves, account must be made of the recirculation effect. That effect is
35 represented by the dashed curve 370. In general, the controller circuitry used with the system will compute the exponential decay shown as solid line region

372, whereupon area under the curve represented at 366 and 372 may be computed.

Looking to Fig. 26, a dye dilution curve 376 derived in an animal (pig) study. Curve 376 shows a recirculation effect at curve portion 378. Before
5 computing the area represented by the curve an exponential decay represented at dashed curve portion 380 must be computed. Where a preliminary curve occurs, representing a shunt, a ratiometric analysis is made of the area under the corrected curve and the area under the shunt curve. Looking to Fig. 27 another theoretical curve is represented having a principal component 384 in association
10 with a preliminary shunt related curve 386. The control features of the system can operate upon such curves. For example, curve 384 is reproduced in Fig. 28 in semilog fashion in conjunction with shunt curve 386. By so treating the signals, calculations can be improved in an electronic sense.

Referring to Figs. 29 and 30, a monitor controller for use with the system
15 is represented in general at 450. The monitor 450 may be mounted on a pole, e.g., an IV pole, includes a housing 452 which provides a display 454 which performs in conjunction with touch switches shown as an array represented generally at 456. At the bottom of housing 452 there is an input 458 for receiving the exhalation pressure occurring with a Valsalva Maneuver. Next, adjacent to
20 the input 458 is input 460, which receives an injection flow signal. Adjacent to input 460 is 462 which is coupled with the earlier described main cable 432 extending from hub connector 440. The lasers are enabled with a key-actuated switch 464 and a flash drive recorder may be received at slot 466. Looking to the rear view at Fig. 30, the housing 452 may be pole mounted using C-type and
25 shaped clamp 468. Electrical power input and the switching thereof is provided at switch receptacle 470.

Referring to Figs. 29 and 30, a monitor/controller for use with the system is represented generally at 450. The monitor 450 may be mounted on a pole – e.g., an IV pole – and includes a housing 452 and a display 454, which
30 performs in conjunction with touch switches or buttons shown as an array represented generally at 456. At the bottom of housing 452 there is an input 458 for receiving the exhalation pressure occurring with a Valsalva Maneuver. Next, adjacent to the input 458 is input 460 which receives the injection flow signal. Adjacent to input 460 is input 462 which receives the signals from the sensor
35 arrays, being coupled with the earlier described connector cable 420 extending from hub connector 422. The lasers are enabled with a key-actuated switch 464

and a flash drive recorder may be received via the USB or other comparable communications port at slot 466.

Looking to the rear view at Fig. 30, the housing 452 may be pole mounted using C-type and shaped clamp 468. The electrical power input is shown at 478 and the switching thereof is provided at power switch 470. During the operation of the system, several audible cues or prompts are used. Volume pot 472 is used to control the volume of these cues and prompts, and a perforated speaker outlet is provided at 474. The vent 480 adjacent to the speaker outlet provides for system cooling. Pressure outlet 476 provides the Valsalva valve with an atmospheric vent, and permits circulation through the pressure system to provide fresh air and evaporation of any incidental collected fluids.

Figs. 31A and 31B provide perspective views of the interior of the monitor/controller. Tubing 482 provides a volume and a connection between the exhalation pressure input 458 and the Valsalva valve 488. Valsalva exhaust tubing 484 provides the connection between the Valsalva valve 488 and the pressure outlet 476 (not shown). A small intentional leak is introduced into the Valsalva system, as at 486, so that the patient is forced to continue exhaling in order to maintain the proper pressure levels.

The present procedure incorporates visual and oral cueing in connection with display 454. This involves, *inter alia*, the placement of a vein access catheter in a peripheral vein; for example the antecubital vein in the right arm. Fig. 32 illustrates the preferred dye indicator and saline solution delivery mechanism. Looking to the figure, such equipment is illustrated in general at 468. Equipment 468 includes a relatively short catheter with a 20 gauge needle as represented in general at 476, the needle being shown at 478 and a connector to main tubing being represented at 480. The principal tubing is shown at 482, a flexible elongate delivery tube extending between proximal and distal ends, with an auxiliary catheter coupled in fluid transfer relationship with the distal end defining the outlet. An indicator fluid flow detector represented generally at 484 is coupled in fluid transfer relationship with the proximal end, deriving signals corresponding with the commencement and termination of fluid flow through the system. The indicator flow detector has an output signal at a cable represented in general as ending with flow detector connector 475. Just upstream of flow detector 484 is a 3-way valve represented in general at 488. Connected to valve 488 is a first syringe 490, containing indocyanine green dye (ICG), which initially

is injected into the principal tubing 482. Following such injection, the valve 488 is switched and saline solution from a second syringe 492 is injected to, in effect, push the ICG into the antecubical vein. Flow detector 484 detects the dye flow and provides a corresponding signal to the monitor at input 460. It is from this
5 signal that the monitor determines the commencement of transit time.

A further embodiment of the system is a kit supplying consumable materials necessary for quantifying a circulatory anomaly. Fig. 33 shows the contents of one version of a kit for providing the necessary consumable materials and providing for safety checks for utilizing the apparatus. Indicator delivery
10 tubing system, shown generally at 475, provides a single use apparatus for performing the injection procedure. Delivery tube 476 terminates in catheter connection 478, or as a needle suitable for intravenous injection. Flow sensor 484 connects to the system, providing for logging the initiation of injections, and is clamped about tube 476. As described, a single use flow sensor is preferred,
15 providing for a safety factor that apparatus such as tubing set 475 is not reused, to the potential detriment of patients. Clip 480 allows secure attachment of the delivery tubing to the apparatus or patient. Three way valve cock 488 allows the practitioner to load tube 476 from syringe 492, and then switch to a connection with tube 491, which allows flushing of the contents of tube 476 with the contents
20 of syringe 490. Vial 493 comprises one or more doses of indicator dye reagent as a shelf stable material. Vial 494 is a saline diluent for preparing the dose of indicator dye reagent for injection into a patient. and a syringe and needle apparatus for mixing the dose of indicator dye reagent and the diluent. The syringe and needle provided are suitable for injecting the indicator dye dose into
25 the system injection port, and will typically be supplied as a first and second syringe suitable to introduce the indicator dye reagent and saline bolus into the patient. Finally, a saline solution, for instance, is provided to supply a dose of nonreactive blood-compatible clearing reagent for completing the injection and pushing the indicator dye dose into the bloodstream of the patient. Valsalva
30 mouthpiece apparatus 495 comprises a mouthpiece 496, a connector tube 497, and monitor connector coupling 498. Finally, in order to ensure patient safety, all the contents of the kit can be packaged in a single sterile package, such as a sealed plastic tray containing the kit contents in a sterile condition until opened. Sterility can be accomplished by gamma radiation for instance, and the kit
35 contents can be formed of materials that cannot be readily sterilized by an

autoclave. Thus, the patient is assured that infectious disease or the like cannot be transmitted by reuse of the disposable system components.

Referring to Figs. 34 through 38, a dye flow detector 484 is revealed in enhanced detail. Fig. 34 shows two inter-connectable clamp housings 500 and 502 placed on either side of the portion of delivery tubing 504. Additionally, clamp-housing 502 is configured with 4 pins, two of which are seen at 508a and 508b. Two similar pins (not shown) are located on the opposite side of clamp housing 502. These pins are intended to be inserted within holes 510a-510b, within clamp housing 500. Note additionally that clamp housing 500 has a slot 512 formed therein, which provides connector registry. Device 484 performs in conjunction with a flexible circuit shown generally at 514. Flexible circuit 514 is retained in a wrap-around orientation by oppositely disposed support components 516 and 518.

Turning to Fig. 37, the flexible circuit 514 is represented at a higher level of detail. In that figure, outboard printed circuit leads 520, 521 and 529 extend to a laser 524. Leads 526, 527 and 528 extend to an array of three photodetectors shown generally at 530. A fuse 532 extends between flat leads 528 and 529. This fuse reappears in Figs. 35 and 37. Looking to Fig. 36, laser 524 is seen emitting laser light through the tube 504 and into the array 530. Note the alignment slot 534 in the flexible circuit 514. This slot aligns with that shown at 512 at Fig. 33. Fig. 36 shows that openings 536 and 538 in support component 516 permit the laser light distribution and reception shown at dashed line 540 in Fig. 38.

As shown in Fig. 32, the flow sensor connector cable terminates on one end with a flow sensor connector 475, into which a flow sensor is inserted to conduct a test. Figs. 39-43 depict a configuration of this connector, shown generally as 535. The receptacle into which the flow sensor connective area is inserted is shown at 537, which is in turn connected to board 539 via connection leads 537'. The connective receptacle 537 includes contacts 534' for blowing the flow sensor fuse to prevent unsafe reuse of the reusable testing kit components. The LEDs 541 and 542 provide a visual indication to the practitioner conducting the test that it is time to inject the solution into the patient's vein. Controller 544 generally controls the operation of the LEDs 541 and 542, as well as communicate the signals received from the flow sensor to the monitor/controller.

Turning for a moment to Fig. 44, a schematic diagram of the monitor/controller is shown generally at 700. The monitor/controller consists of

two main controller boards, the drive board 702 and the single board computer 704, which provide the communicative connections between the various system inputs and outputs, as well as assist in the implementation of the methods disclosed herein. The flow sensor, discussed in more detail in connection with
5 Figs. 32-38 herein, connects to the flow sensor connection 760, which is turn connected to the drive board 702. The fluorescence sensing arrays, discussed in more detail in connection with Figs. 18-24 herein, connect to the fluorescence sensor array connection 762 and is also connected to the drive board 702. The key-actuated switch input 764 and Valsalva pressure port input 758 are also
10 connected to the drive board 702. The pressure port input 758 is in airflow connection with the Valsalva valve 788. Induced pressure leak outlet is shown as 786. The exhaust port for the Valsalva valve 788 is represented as 776.

As described in connection with Figs. 29 and 30, the drive board powers a speaker for providing audible cues and prompts, shown as 774, with the
15 volume being controlled by volume pot 772. The system cooling fan is controlled by the drive board 702 via connection 714. The power connection and switch are shown at 770, wherein the power enters the system and drives medical grade power supply 706, which is grounded at 707. The single board computer 704 drives the display device 754 and receives input from USB input ports 766 for
20 storing test data and results, importing patient data, or the like. The button or control array is provided generally at 756, in connection with the drive board 702 and the single board computer 704. The monitor/controller may also include a tooled access panel 712 wherein a USB port 708 and Ethernet port 710 are provided, allowing for administrative maintenance and updates to the device.

25 Fig. 45 generally shows the connection schematics for the fluorescence sensor arrays described in connection with Figs. 18-24 herein. Signal leads 790 provide the communicative pathway between the left 792 and right 794 fluorescent sensing arrays and the fluorescent sensing array connector 796 that is coupled to the monitor/controller as described in connection with Fig. 44 (at
30 connection 762). The detection signals are collected at these arrays, 792 and 794, and are transmitted to the monitor/controller for further processing and calculation in order to calculate a shunt conductance index.

The monitor/controller also requires input from a flow sensor, in order to ensure that proper timing has been achieved in relation to the Valsalva Maneuver
35 and the injection timing. The schematics for the flow sensor are shown generally in Fig. 46. The disposable portion of the testing kit includes the flow sensor flex

circuit 765, wherein a re-use prevention fuse 767 is provided that will disable the disposable portion of the testing kit, barring further use. The circuit includes the use of a flow illumination LED light source 773 which projects fluorescence exciting light into the tubing. Indicator solution passing through the tube at the point occupied by the flow sensor flex circuit 765 will be sensed by flow detection
5 photosensor 769 coupled with amplifier 771, and a signal indicating indicator solution flow will be transmitted to the monitor/controller.

The flow signal received by the flow sensor flex circuit 765 will be transmitted to the monitor/controller by way of the flow sensor cable 751, which is
10 the reusable portion of the flow sensor assembly. The flow sensor cable 751 includes the flow sensor cable connector board 759, to which the flow sensor flex circuit 765 is connected during a practitioner's preparation to conduct a test procedure. The opposing end of the cable terminates in a monitor flow sensor connector 757, which attaches to the monitor/controller (as at 760 in Fig. 44) to
15 provide flow sensor input to the system. The flow sensor cable includes injection signal LEDs 753 and 755, which provide a visual cue to the practitioner to initiate the injection procedure, actuatable by the monitor/controller drive board 702. The flow sensor cable 751 is the preferred location for such visual indicators, as they are removed from a position in which they may cause any appreciable
20 interference with the flow detection photosensor 769.

Turning to Fig. 47, a stylized representation of the present system is presented. In the figure, a patient is shown in general at 550 reclining upon an examination bench represented generally at 552. Patient 550 should either be supine or the head and trunk can be elevated about 30°, which is the
25 arrangement depicted herein. The monitor is shown in general at 554 having a display 556 which can be observed by both the patient 550 and the practitioner represented generally at 558. Monitor 554 is mounted such that patient 550 may carry out a Valsalva Maneuver under visual cueing provided at display 556. That maneuver is carried out with a tube and mouthpiece 562, which as described
30 earlier is connected with the monitor 554. Monitor 554 both times the Valsalva Maneuver and provides a bar chart showing when proper air exhalation pressure is present. It also indicates the Valsalva timing, which may in the instant system be about 6 seconds. Wearing a headband 564, both ears are connected with a fluorescent sensing array in the manner describing in connection with Fig. 27 and
35 in particular the scaphoid fossa of the ear pinna. Such signals are collected at hub 566 and are directed by cable 568 to the monitor 554. Practitioner 558 is

holding the injection equipment described in conjunction with Fig. 32 as is illustrated in general at 475 with a cable delivering an indicator flow providing a signal to monitor 554. The catheter arrangement 475 is shown in the instant figure having been inserted within the antecubital vein in the right arm of patient
5 550.

The present system is applicable to non-human patients, as well as human patients. In general the system is operable with a variety of mammalian patients, including working animals, such as dog and horse. In particular, certain very valuable animals, such as pets, companion animals, race horses, and show
10 horses may at times be afflicted with PFOs, or be adaptable for the other features of the system. As such, the disclosed monitoring system can be utilized in conjunction with essentially any large mammal of interest.

As a practical matter, inducing the Valsalva maneuver required to detect a right-to-left shunt is restricted in use in animals (e.g., dog) to those animals
15 under anesthesia and intubated, to enabling use of a respirator. As suggested by Banas (1971), a shunt detection procedure such as disclosed herein is likely to require full anesthesia, utilizing intubation and manipulation of the respirator pressure to simulate a Valsalva maneuver. As Banas describes, it is possible to detect a PFO in a dog utilizing a more complex procedure than is required for
20 human patients that can respond to instructions.

Referring to Fig. 48, the results of a human trial involving a volunteer without a right to left pulmonary shunt is displayed. The trial was configured very much like that described in Fig. 47. In this regard, the Valsalva Maneuver is represented at curve 576. During that maneuver, an injection was made at the
25 point in time represented by the vertical dashed line 578. Fluorescent sensing arrays were mounted at each ear and dye dilution curves commenced to be formed within about five seconds. The array of six curves as identified in the tabulation is shown in general at 580. Array 580 reveals that six opportunities are present to detect indicator.

As indicated earlier herein, any indicator incorporated to discover a right
30 to left shunt must arrive in the right atrium as the normal pressure difference between those cavities reverses. That reversal will continue for about three to five heart beats with a minimum duration of about 3 seconds. A literature study was carried out concerning the starting of the Valsalva Maneuver and the point in
35 time when injection into a vein was made, for example, the antecubital vein. Results of published literature studies are presented in the works of: Droste

(1999), Droste (1999a), Schwarze,(1999), Droste (2002), Devuyst (2004), Jauss (2000), Saqqur (2004), Schwarze (1997), and Schwarze (1997a). Additional references associated with this timing of injection are Zanette (1996), Schwarze (1999), Heckman (1999), Sasery (2007), Uzuner (2004), and Schwarze (1997a).

5 References utilizing the introduction of air bubble contrast about two seconds prior to the commencement of a five second Valsalva Maneuver associated with this entry are Horner (1997), and Hamann (1998). The references disclosing an injection that occurs about two seconds following the commencement of a ten second Valsalva Maneuver include Karnick (1992), and Devuyst (1997).

10 References associated with injection that occurs at the commencement of a ten second Valsalva Maneuver include Zannete (1996), and Spencer (2004). Thus a wide variety of strategies have been attempted to optimize the implementation of a Valsalva maneuver to increase the efficacy of PFO detection using traditional detection methods. These include Chimowitz (1991), Albert (1997), Anzolar (1995), Harms (2007), and Greim (2001). Also see, Banas (1971), Karttunen (1998), and Karttunen (2001). (two seconds before the end of a ten second Valsalva Maneuver).

In light of the extensive literature memorializing experimental efforts with limited reproducible success, an experimental approach was undertaken using

20 the present method with several of different protocols in order to determine a protocol that provided optimal (and useful) results using the presently disclosed system. These included Protocol Number 1: an injection of indocyanine green dye, two seconds after the commencement of a Valsalva Maneuver. (after Niggemann (1987); Protocol 2: indocyanine green dye four seconds into a six second Valsalva Maneuver.

25

Referring to Fig. 49 a chart in which what is herein referred to as Protocol 1 is set forth. In the figure a six-second Valsalva Maneuver is shown at Bar 594. Vertical line 596 shows that at three seconds into the Valsalva Maneuver an audible cue is given to the operator to be ready to inject indicator dye. One

30 second later, the operator is cued audibly to inject the indicator at the antecubital vein as represented at vertical line 598. At five seconds, represented Line 600, a "3-2-1" countdown is displayed on the screen alerting both the patient and practitioner that Valsalva release will occur in one second. Such release is represented by vertical line 602 along with an audio and visual cue to the patient.

35 Looking to Fig. 50, a corresponding Protocol 2 is charted with respect to a six second Valsalva Maneuver as represented at Bar 604. Vertical line 606

occurs one second into the Valsalva Maneuver and it cues the operator to be ready to inject. One second later as represented at Vertical line 608 an audible cue is given to the operator to inject the indicator dye into the antecubital vein. Four seconds later, as represented at vertical line 610, an audio and visual cue is given to the patient to release the Valsalva Maneuver. One second prior to this release as represented at vertical line 612, a "3-2-1" count down is displayed at the display screen.

Figs. 51A through 51F combined as labeled thereon to provide a flow chart describing the system and method at hand. Beginning as represented by symbol 1000 and continuing as represented by arrow 1002 to block 1004, the controller carries out system initialization with default parameters. The δt_{LIMIT} represents the permitted interval past the pressure release in an ideal Valsalva Maneuver that may be produced in the actual Valsalva Maneuver. Should this limit be exceeded during testing, data may be invalid. PFLAG is set to zero and the elapsed time clocks t_1 , t_2 and t_3 are set to zero. Next, as represented at arrow 1006 and block 1008, the 5-volt power supply output voltage is measured, and if the measured output falls within the 4.8- to 5.3-volt range, arrow 1010 is followed to block 1012. At block 1012, the 12-volt power supply output voltage is measured and must be within the 11.0- to 12.7-volt range to continue via arrow 1020. If the measured output voltage of either the 5-volt power supply or the 12-volt power supply do not fall within the respective desired ranges, as at 1014 and 1016, respectively, then at block 1018, a system fault is displayed and the test ends.

If the voltage output levels are within the acceptable ranges, arrow 1020 is followed to block 1022, where the physician identification number, the patient identification number, age, sex and intended injecting dose(s) are entered into the monitor. As represented at arrow 1024 to block 1026, $\delta t_{RELEASE, i}$ is set to the required time delay from the start of indicator injection to Valsalva release. In this case, $\delta t_{RELEASE, 1}$ is set to 1.0 second as a first protocol, and $\delta t_{RELEASE, 2}$ is set to 2.0 seconds as a second protocol.

Next, as represented at arrow 1028 to block 1030 the delay flag is set to zero and, as represented at arrow 1032 to block 1034, $\delta t_{RELEASE}$ is set to $\delta t_{RELEASE, 1}$, corresponding to Protocol 1. The program continues as represented at arrow 1036 to block 1042 where the indicator solution for injection is prepared, for example by mixing a known weight of indocyanine green dye with a predetermined volume of sterile water. A predetermined volume of that mixed

indicator is withdrawn into a first syringe. That syringe is shown as 492 in Fig. 32. The program continues as represented at arrow 1044 to block 1046. Block 1046 provides for filling a second syringe with a predetermined volume of isotonic saline. That isotonic saline is used to "flush" the flow sensor, extension tubing, catheter, peripheral vein, and the like, so that all of the injected indicator is promptly delivered into the vein leading to the right atrium of the heart. As represented at arrow 1048 to block 1050, the first syringe is connected to a three-way valve and the second syringe is connected to the proximal end of the extension tubing, which is in turn connected to a second port on the three-way valve. The three-way valve setup has been described in more detail in connection with Fig. 32. As represented at arrow 1052 to block 1054, the indicator solution from the first syringe is injected into the extension tubing that is in turn connected to the three-way valve, in order to pre-fill the extension tubing with indicator solution. From block 1054 the program continues as represented at arrow 1056 to block 1058, the latter block describing what was found during testing to be beneficial, in that a local anesthetic may be injected at the site of intended catheter injection. The program continues as represented at arrow 1060, which reappears in Fig. 51B leading to block 1062.

Block 1062 provides for placing the vein access catheter in a peripheral vein and preferably in the antecubital vein in the right arm. The flow sensor is also attached at block 1062 between the proximal terminus of the extension tubing and the three-way valve. The three-way valve is turned off in the direction of the flow sensor. This flow sensor has been described in connection with Figs. 34-38 and may be utilized by the control system in conjunction with elected Valsalva start and timing to achieve an effective transit time of the indicator. The fluorescent sensing indicators are then positioned at a blood vessel site – the scaphoid fossa of the ears of the patient, for example – as represented at arrow 1064 to block 1066.

From block 1066, arrow 1068 leads to the query posed at block 1070 determining whether or not the test is to be performed with a Valsalva Maneuver. In the event that it is not, then the program proceeds as represented at arrow 1072. In the event of an affirmative determination at block 1070, then as represented at arrow 1074 and block 1076, the mouthpiece of the Manometer tubing set is positioned in the mouth of the patient and connected to the monitor. This is shown in Fig. 47 as tube 562 extending to an input at monitor 554. The

system can be programmed also to allow the patient to practice the Valsalva Maneuver in conjunction with a readout at the monitor display.

Next, as represented at arrow 1078 to block 1080, the tests of connections and operational status of the flow sensor, manometer, indicator
5 sensors and the pickup are internally made. In the event there is an error, then as represented at arrow 1082 to block 1084 a warning cue is made. Next, the program starts measurement as represented at arrow 1086 to symbol 1088. Such measurement commences as represented at arrow 1090 which reappears at Fig. 51C extending to block 1092, wherein instructions are provided to the
10 patient to begin the Valsalva Maneuver by exhaling into the mouthpiece to reach and maintain the target pressure level until they are instructed to stop.

Generally, the Valsalva Maneuver is accompanied by some form of display at the monitor. Turning momentarily to Fig. 52, a line graph 1600 is provided along with an indicator line 1602, represented as a solid line, giving the
15 patient the actual measurement of the pressure being produced by the patient during the Valsalva Maneuver. The graph shows pressure versus elapsed time. The ideal pressure curve for the Valsalva Maneuver that the patient should attempt to mimic is indicated by the line overlay 1604, represented as a dotted line. In Fig. 52, the patient has just released the pressure, finishing the Valsalva
20 Maneuver with the graph 1600 displaying that the patient held the proper pressure (with some acceptable variation) during the duration of the Valsalva Maneuver. Returning to Fig. 51C, as represented at arrow 1094 to block 1096, the exhalation pressure created by the patient during the Valsalva Maneuver is continuously measured and displayed on the monitor/controller, as explained in
25 connection with Fig. 52, and is compared to the ideal Valsalva curve or required minimum exhalation pressure P_{VALSALVA} . As represented by arrow 1098 to block 1100, the exhalation pressure is queried and it is determined whether it falls within a measurable range, for example from 0-4000 ADC units. If not, arrow 1102 is followed to block 1104, wherein a system fault is displayed and the test is
30 ended. If the exhalation pressure is measured, arrow 1106 is followed to block 1108.

Block 1108 poses the query as to whether the exhalation pressure is above or equal to the targeted pressure, for example 35 mm of mercury. In the event that it is not, as represented at arrow 1110 and block 1112, the practitioner
35 is alerted with an audible alarm or visual error message to instruct the patient to increase pressure to meet target. PFLAG is set to zero and the program reverts

as represented at arrow 1114 to arrow 1090, where the Valsalva Maneuver is retried. Where the exhalation pressure is appropriate, represented at arrow 1116, PFLAG is set to 1 at block 1118. Then the program continues as represented at arrow 1120.

5 As represented at arrow 1072 extending from the query at block 1070 and leading to block 1124, PFLAG is set to 2 and the program diverts as represented at arrow 1126 to arrow 1120. With this arrangement, the Valsalva Maneuver is bypassed to the program as shown at arrow 1128 extending from block 1122. Block 1122 sets elapsed time clock t_1 at time $t_1 = 0$.

10 Arrow 1128 reappears in Fig. 51D extending to block 1130, which looks to obtaining base line data. Then as represented by arrow 1132 to block 1134 the query is posed as to whether the time for instructing injection is present. In the event that it is not, the program reverts as represented at arrow 1136. Arrow 1136 continues in Fig. 51C, to arrow 1094. As described in connection with Fig.
15 50, this timing looks to the anticipated end of the Valsalva Maneuver. When the time to inject is present, as represented by arrow 1138 to block 1140, the practitioner is instructed, first to be ready, immediately followed by instructions to commence the injection of the second syringe containing saline, which forces the indicator solution into the vein, followed by the isotonic saline flush solution. The
20 practitioner may be provided with a visual cue via, for example, an illuminated LED light affixed on or near the flow sensor, so that the cue may be conveyed without difficulty. The flow sensor will detect the flow of indicator, as represented by arrow 1142 to block 1144. The flow sensor will make such a detection within a predetermined time after the injection cue is made to the practitioner at block
25 1140. For example, at block 1144, the flow sensor attempts to detect the presence of indicator solution for a six second period following its issuance of the cue to indicate the start of the injection. If no detection is made within this time, as at arrow 1146 to block 1148, the procedure is deemed invalid and the test is ended. When such a flow is detected, as represented by arrow 1150 to block
30 1152, time clock t_2 is set to zero at the moment the flow sensor detects the start of the injection of indicator.

Next, as represented at arrow 1154 to block 1156, the post-injection Valsalva elapsed time clock t_2 is set to zero and the program continues as represented at arrow 1158. Arrow 1158 reappears in Fig. 51E extending to block
35 1160, where the program continues. Block 1160 represents a query as to whether the post injection elapsed time clock t_2 has reached the time for Valsalva

release. In the event that it has not, the system dwells as represented by arrow 1162 returning to arrow 1158. Where an affirmative response is received from the query at block 1160, then as represented at arrow 1164 to block 1166, the solenoid-operated pressure release Valsalva valve is opened in the monitor/controller to effect the end of the Valsalva Maneuver. As at arrow 1168 to block 1170, the practitioner is notified that the exhalation pressure of the Valsalva Maneuver has stopped, and instructs the patient to breathe normally.

The time of release can be developed from the pressure transducer within the monitor/controller accordingly and, as represented at arrow 1172 to block 1174, the pressure transducer measures the actual time that the Valsalva Maneuver is ended. This may occur with an exhalation pressure dropping to 2 mm of mercury, for instance. Thus, the system provides an electromagnetically-operated pneumatic valve at the monitor/controller coupled with the pneumatic tube and actuateable to a vent-to-atmosphere orientation from an open to venting orientation and actuateable by the monitor/controller in response to the provided cue.

From block 1174, an arrow 1176 is seen directed to block 1178. At block 1178, a query is posed as to whether the absolute value of the time of release minus t_2 is greater than or equal to the pre-designated limit time. In the event that it is, then as represented at arrow 1180 to block 1182, a warning is output at the display indicating that the Valsalva release did not occur within an allowed time interval and data may be invalid. This limiting time may, for example, be 1.5 seconds. However, such time window may be zero seconds. If the query posed at block 1178 results in a negative determination, then as represented at arrow 1184, the program continues to Fig. 51F. Note in that figure that arrow 1184 reappears extending to block 1186.

Block 1186 measures the peak amplitude, and for each of the channels N , calculates the peak amplitude signal, $S_{\text{NORMAL}}(N)$ for normal indicator/dilution curves associated with indicator and blood flowing through a normal pathway in the lungs. Then, as represented at arrow 1188 to block 1190, a query is made as to whether the measured signal for at least one channel is equal to or greater than a minimum designated signal. Where it is not, then as represented at arrow 1192 to block 1194, the practitioner is alerted with an audible/visual error message that there is insufficient coupling between the sensor and blood-born indicator in the tissue.

Where that signal is greater than the minimum signal, then as represented at arrow 1196 and block 1198, the peak amplitude signal for each channel with a premature indicator/dilution curve prior to the normal indicator/dilution curve, or an inflection in the up-slope portion of the start of the normal curve (both being associated with a right-to-left shunt), are measured. Where a non-zero signal result is occurring, then as represented at arrow 1200 to block 1202, conductance associated with a right-to-left shunt is calculated. This can be done using a ratio of the shunt signal peak amplitude over the normal curve signal peak amplitude, for each pair of normal curve peak amplitudes and shunt signal peak amplitudes existing for each channel. The maximum ratio of the shunt signal peak amplitude over its corresponding normal curve peak amplitude is displayed as the shunt conductance index.

Next, as represented at arrow 1204 to block 1206 an inquiry is made to whether the delay flag is now zero. Where it is not, then as represented at arrow 1214 to symbol 1216, the test is ended. Where the delay flag is zero, then as represented at arrow 1208 the delay flag is set to one and $\delta t_{\text{RELEASE}}$ is set to $\delta t_{\text{RELEASE}, 2}$. The program then continues as represented at arrow 1212 to Node A 1038. The program is now prepared to enter Protocol 2. In this regard, Node A 1038 reappears in Fig. 51A in conjunction with arrow 1040 extending to arrow 1036.

Examples

The following examples are provided to more fully explain the system and apparatus. However, they should not be viewed as limiting. A series of studies were performed in humans, and the following examples describe the results of studies of a total of 25 human patients utilizing the flow detection system disclosed herein for the detecting of right-to-left cardiac shunts. These results disclose both indicator dosing trials and pilot tests of analytic efficacy. The trials disclosed were performed at the Columbia University Medical Center (CUMC) over a period of about nine months. One study was conducted to determine the effective dose of intravenously injected indicator dye necessary to enable the detection of the presence of a cardiac shunt with high sensitivity.

Example 1: Indicator dosing trials.

Objectives of the indicator dosing trials and comparative analysis tests included optimization of the injection protocol and timing of provocative breathing

maneuvers to further increase the system sensitivity for the detection of right-to-left cardiac shunts. Another objective was to determine test procedure parameters in preparation for subsequent trials. Further objectives included providing additional data for developing the disclosed method for the calculation and display of the functional flow conductance of a patient's right-to-left cardiac shunt i.e., "Shunt Conductance Index".

A kit, similar to that disclosed in relation to Fig. 33, was provided in a single-use procedure tray. The kit contents included Indocyanine Green (ICG) dye (Pulsion Medical Systems AG, Munich) as a vial containing 25 mg of ICG powder. A second vial provided solvent for preparation of a solution of ICG dye solution at the desired concentrations. The kit also contains a single-use, sterile catheter set with associated flow sensor, and a single-use Valsalva tubing set.

Two reusable Fluorescence Sensor Array units, of the type disclosed in Figs. 18 or 20 were connected to the Controller/Monitor via a cable (as shown in Fig. 24), providing for the measurement of fluorescence-based ICG concentration level measurements at six sensor locations. Each of the Fluorescence Sensor Array (FSA) units were comprised of three independent transmissive sensors, and were positioned at the scaphoid fossa of each ear of the patient, as illustrated in Fig. 47. The power level and the duration of the laser pulses were selected to meet laser safety requirements, with the maximum power delivered within the laser beam is less than 0.28 watts/sq. cm. (below the recommended Maximum Permissible Exposure (MPE) of 0.30 watts/sq. cm. specified in Table 7 of ANSI Z136.1-2007). Utilizing the disclosed optical filtering and collimation to block the 785 nm excitation photons, the emitted fluorescence photons are selectively received by a photodetector, digitally processed and recorded by the Controller/Monitor unit as described above. The use of multiple channels (viz. three at each ear) allowed for analysis of the positioning of the sensors, and the sufficiency of a three sensor array in providing that at least one sensor (channel) would always be closely positioned relative to an underlying and invisible blood vessel in the Scaphoid Fossa region of the patient's ears. Thus, by utilizing a pair of three sensor arrays, the probability of a high sensitivity test result was increased.

Eight patients, between the ages of 18 and 65 years, with a known right-to-left shunt, based on echocardiographic techniques, were tested within the same period of less than 30 minutes using both the TCD method and with the presently disclosed system as illustrated in Figure 47.

A single-use, sterile catheter set was connected to the AngioCath catheter similar to that illustrated in Figs. 32, 33, and 47. Within 30 minutes of initiating the test, the ICG powder supplied was reconstituted with sterile water, as described in its package insert, to create an ICG dye solution having a concentration of 2.5 mg/ml. This ICG dye solution was either then injected at this concentration of 2.5 mg/ml or further diluted with isotonic saline to yield a concentration of 1.25 mg/ml. The catheter set provided the means to either (a) sequentially inject a bolus of ICG dye followed by an isotonic saline flush or (b) inject using a single syringe of either dilute ICG or a pre-loaded bolus of ICG pushed by a 17 ml volume of isotonic saline. A single-use Valsalva tubing set was connected to the quick-disconnect port on the front panel of the Monitor/Controller. At the initiation of a practice Valsalva maneuver or actual shunt test, the patient exhaled into the mouthpiece of the Valsalva tubing set while the pressure sensor within the Monitor/Controller enabled the measurement, recording, and display of the patient's exhalation pressure in real time on the display screen of the Monitor/Controller.

A 20 gauge Angiocath AutoGuard catheter (Becton, Dickinson and Company, Franklin Lakes, New Jersey) was first placed in a vein in the antecubital fossa and was subsequently used in the performance of both the contrast TCD method and the Cardiox method. Each patient initially performed a TCD evaluation, while awake, so that the patient could perform a graded/measured Valsalva and release.

The supplied, single-use Catheter Set (see Fig. 33) was next connected to the same Angiocath catheter in preparation for the performance of the present shunt detection test. A transcutaneous fluorescence sensor was placed at the scaphoid fossa of both the left and right ears as illustrated in Fig. 19. As shown in Fig. 21, a total of three independent sensor channels are provided on the Fluorescence Sensor Array (FSA) unit placed at the Scaphoid fossa of each ear. The use of multiple sensor channels at each ear greatly increases the probability that at least one channel of one of the two FSA units will be closely aligned with an underlying blood vessel within the scaphoid fossa of one of the ears.

The patient was then guided through a Valsalva practice procedure with a display on the front panel of the Monitor/Controller providing visual feedback to assure that the proper level of exhalation pressure (nominally 40 mm Hg) was maintained throughout the guided Valsalva maneuver and the patient released the exhalation pressure when an audible and visual prompt was issued by the

Monitor/Controller. Further embodiments of the system as described herein provide for automated release of the Valsalva pressure.

Once the patients have demonstrated their ability to perform the Valsalva maneuver in the prescribed manner, the test was performed, utilizing audible and visual prompts issued by the Monitor/Controller. The patient was then instructed to observe the Monitor/Controller display screen and begin a nominal six-second Valsalva maneuver by exhaling into the Valsalva tubing. The screen display provided visual feedback to the patient when the exhalation pressure was reached and the remaining period during which the Valsalva maneuver needed to be sustained. The Monitor/Controller measured and recorded the actual exhalation pressure exerted by the patient as well as the starting and ending time for the Valsalva maneuver.

Once the required Valsalva pressure threshold was reached, the elapsed time clock within the Monitor/Controller started and issued an audible cue to the operator to start the ICG injection at a precise time interval (viz., Time Interval A) before the subsequent cue for the release of the Valsalva maneuver. Upon the initiation of the test, the measured ICG concentration levels at all six channels (three per FSA unit) were continuously monitored and recorded. At a predetermined time interval after the first cue was issued for the start of ICG injection, a second visual and audible cue was issued to the patient to release (i.e. terminate) the Valsalva maneuver. The patient was next instructed by the display on the Monitor/Controller unit to remain still for the next 60 seconds while the ICG signal levels were continuously measured and recorded. Within about one minute after the end of the test period (nominally two minutes after dye injection), the monitor displayed a graph showing the recorded Valsalva pressure level and ICG concentration levels from the six fluorescence sensors over the 60 second period of the test.

After an elapsed time of five minutes after the end of the first test procedure, the test procedure just described above was repeated but with a different time interval between the cue for the start of injection and the cue for Valsalva release (viz., Time Interval B). For the test cases with increasing ICG dose levels, the test procedure could be repeated for up to two additional times.

In addition to the exhalation pressure level and ICG concentration levels measured and recorded automatically by the Monitor/Controller, other manually recorded parameters included (a) patient weight, height, age, sex, skin color; (b) time interval between the start of injection cue and Valsalva release cue, (c) ICG

dose, concentration and bolus volume; (d) isotonic saline flush volume (if used); (e) TCD bubble track count (displayed by Spencer Technologies TCD unit) and (f) measured duration of injection of ICG dye and any optional isotonic saline injected immediately after ICG injection.

- 5 For the first three indicator dosing trial patients, four different tests were performed at ICG dose levels of 2.5 and 5.0 mg and cueing time intervals of 2.0 and 4.0 seconds between the start of injection and Valsalva release for a total ICG dose of 15 mg per patient. In order to increase the ICG signal level and volume of ICG dye injected into the right atrium, subsequent indicator dosing trial
- 10 tests for the remaining 5 patients were performed at nominal dose levels of 12 mg per test procedure performed at two different time intervals for a total ICG dose per patient not exceeding 25 mg.

- The results of the dye indicator dosing trial are summarized in Table 1. These results include a total of 8 patients having a confirmed PFO with a
- 15 Spencer Grade of 4 or 5 determined through TCD testing.

Table I
INDICATOR DOSING TRIAL

Test ID/ Cath location	Sex/ Test #	Wgt. [lbs.]	Hgt (in.)	Grade/ #(BT)	Int/rel (sec)	Act. Int/rel (sec)	[ICG] / Dose (mg)	ICG Inj.	Shunt Curve?	Calc. SCI [%]
D1	Female						2.5 mg/ml			
(20G, RAF)	1-01	100	60	SG 4	4	2.73	2.5	1-2/10	Yes	0.212
	1-03			(270)	2	4.53	5	1-2/10		
D2	Male						2.5 mg/ml			
(20G, RAF)	2-01	220	74	5	4	2.85	2.5	1/10	Yes	0.087
	2-02			(302)	2	4.77	2.5	1/10		
D3	Female						2.5 mg/ml			
(20G, RAF)	3-01	130	64	5	4	3.41	2.5	1/10	Yes	0.185
	3-02			(>300)	2	4.84	2.5	1/10		
D4	Female						1.25mg/ml			
(20G, RAF)	5-02	120		4	2	2.67	12.5	10 /0	Yes	0.194
	5-03			(159)	4	5.77	11.3			
D5	Female						1.25mg/ml			
(20G, RAF)	7-02	150		5	2	2.91	12.5	10/10	Yes	0.056
	7-03			(>300)	1	2.05	11.3	10/10		
D6	Female						1.25mg/ml			
(20G, LAF)	8-02	134		4	2	3.04	12.5	10/10	**	0.02
	8-03			(178)	1	1.92	11.3	10/10		
D7	Female						1.25mg/ml			
(20G, RAF)	9-02	130		5	2	2.48	12.5	10/0	Yes	0.025
	9-03			(>300)	1	1.55	11.3	10/0		{Note 3}
D8	Female						1.25mg/ml			

	e				I				
(20G, RAF)	10-01	138	5	1	1.61	12.5	10/0	Yes	0.141
	10-02		(>300)	2	2.67	11.3	10/0		

Legend

Test ID/ Cath location: Test Number Identification; Size and Location of AngioCath Placement. RAF refers to right antecubital fossa and LAF refers to left antecubital fossa placement of the AngioCath catheter.

Sex/ Test #: Patient Sex/ Patient Number and Test Number

Wgt. (lb.): Patient Weight [pounds]

Hgt. (in.): Patient Height [inches]

Grade/ #(BT): TCD Spencer Grade/number Bubble Tracks (BT)

Int/Rel (sec): Specified Time Interval Between Start Of Injection and Valsalva Release [seconds]

Act INT/REL (sec): Actual Time Interval Between Start Of Injection and Valsalva Release [seconds]

For test 8-02, **: Actual Time Interval was determined to be too long for predicted efficacy.

[ICG] / Dose (mg): ICG concentration (mg/ml) and ICG Injection Dose in milligrams

ICG Injection Method

Test 1: 1 or 2 ml ICG bolus injection promptly followed by 10 ml Isotonic Saline flush

Test 2: 1 ml ICG bolus Injection promptly followed by 10 ml Isotonic Saline Flush

Test 3 : 1 ml ICG bolus Injection promptly followed by 10 ml Isotonic Saline Flush

Test 4: 10 ml ICG bolus injected without prompt Isotonic Saline Flush

Test 5: 10 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Test 6: 10 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Test 7: 10 ml ICG bolus injected without prompt Isotonic Saline Flush

Test 8: 10 ml ICG bolus injected without prompt Isotonic Saline Flush

For tests in which the number of injection steps required was 2, a 3-way stopcock was required to alternate injection from a first syringe containing the ICG dye and second syringe containing the isotonic saline leading to increased and variable.

Shunt Curve?: Shunt Curve Present ? (Yes or No)

Calc. SCI [%]: Calculated Shunt Conductance Index Using Controller/Monitor Computer Program. Value derived from semi logarithmic graph of measured ICG concentration vs. time, as described in the disclosure above.

Based on the results of the Dosing Study and Pilot Trial, several modifications were developed for the injection protocol and to the Controller/Monitor hardware in order to improve the sensitivity, specificity, PPV and NPV in preparation for the start of subsequent the Pivotal Trials. The Monitor/Controller software was also expanded to include the calculation and display of the Shunt Conductance Index, as described above. Suggested modifications include incorporating an optical flow sensor into the Catheter Set, in order to optically detect the initiation of injection by the operator. The detection of the start of the injection is further utilized by an

internal clock within the Controller/Monitor to automatically control the Valsalva release at a precise predetermined time interval after the initiation of injection. Thus, a reduction in operator error and reduced compliance of the patient related to the start of ICG injection Valsalva release is provided.

5 A further embodiment arising from the testing procedures was to incorporate a solenoid valve unit within the Controller/Monitor, which is electronically opened by the Controller/Monitor computer at the precise predetermined time interval following the start of injection. This modification eliminates patient error related to the inability to timely release of the Valsalva maneuver, and to remove issues of patient
10 compliance with the timing mechanisms. Testing also led to the development and incorporation of a controlled leak in the solenoid valve unit, which assures that the patient properly performs a diaphragm-based exhalation procedure during the Valsalva maneuver. This modification prevents the patient from exerting pressure only using cheek muscle contraction and assures the performance of the required
15 Valsalva maneuver in a manner that is calculated to best detect right to left shunts.

The Controller/Monitor software was reconfigured to display a numerical value at the end of the test corresponding to the functional conductance of a right-to-left shunt, if one were present. This numerical value, the Shunt Conductance Index, as described above, is ratiometrically derived based on the amplitude of the shunt
20 curve peak or inflection relative to the peak of the large indicator-dilution curve associated with that amount of the ICG dye which follows the normal pathway through the lungs of the patient. Thus the testing regime led to the development of a quantitative algorithm, i.e., a measured Shunt Conductance Index.

The data contained in Table 1 is based on actual patient parameters, procedural parameters as well as measured Time Intervals and calculated Shunt
25 Conductance Index values. The measured Time Interval was derived from the recorded values of the exhalation pressure decrease to effectively zero pressure following Valsalva release. The Shunt Conductance Index values were calculated using the method described in the disclosure above.

30

Example 2: Comparative analysis of Dye dilution detection system and existing trans-cranial Doppler detection.

A total of 17 patients, between the ages of 18 and 65 years, 10 with a known right-to-left shunt (i.e., PFO), based on echocardiographic techniques and 7 without a right-to-left shunt, were tested within the same period of less than 30 minutes using both the trans-cranial Doppler (TCD) method and with a system similar to as illustrated in Figure 47. A cohort of 10 consented patients with known right-to-left shunts (RTLS) were included. For purposes of this study RTLS were graded by TCD as 4 (101-300 microbubbles detected) or 5 (>300 microbubbles detected or uncountable) on the Spencer scale. A control group of 7 consented patients without RTLS, i.e., graded at TCD as 0 (no bubbles detected) or 1 (1-10 microbubbles detected) on the Spencer scale, were also included. Patients were studied using the dosage of ICG and injection protocols established in Example 1 described above. The 10 study cohort was recruited from patients that came to the cardiac catheterization laboratory specifically for closure of an intracardiac defect that produces a RTLS. The 7 control patients were recruited from patients in the catheterization laboratory for coronary artery or other electrophysiologic procedures.

Within 30 minutes of initiation of the dye indicator shunt detection test, ICG powder supplied by Pulsion Medical Systems AG (Munich, Germany) was reconstituted with sterile water also supplied by Pulsion Medical Systems, as described in its package insert, to create an initial ICG dye solution having a concentration of 2.5 mg/ml to 5.0 mg/ml. This ICG dye solution was then injected at either a concentration of 1.25 mg/ml (after further dilution with isotonic saline) or a concentration of 5.0 mg/ml. As described above in connection with Example 1, a 20-gauge Angiocath catheter was first placed in a vein in the antecubital fossa and was subsequently used in the performance of both the contrast TCD method and the dye indicator shunt detection method. Each patient initially performed a TCD evaluation. During the evaluations, the patients were not sedated, allowing the patient to perform a graded/measured Valsalva and release.

The previously described, single-use catheter set was next connected to the same Angiocath catheter in preparation for the performance of the dye indicator shunt detection test. The procedure next provided for the placement of a transcutaneous fluorescence sensor at the scaphoid fossa of both the left and right

ears as described in connection with Figs. 19 and 47. As seen in Fig. 22, a total of three independent sensor channels are provided in the Fluorescence Sensor Array (FSA) unit placed at the scaphoid fossa of each ear.

The patient was then provided with the Valsalva Tubing Set, which connects
5 to a port on the front panel of the Controller/Monitor and to a calibrated pressure sensor within the Controller/Monitor. The patient was then guided through a Valsalva practice procedure with a display on the front panel of the Controller/Monitor providing visual feedback to assure that the proper level of exhalation pressure (nominally 40 mm Hg) was maintained throughout the guided Valsalva maneuver
10 and the patient released the exhalation pressure when an audible and visual prompt is issued by the Controller/Monitor. Once the patient demonstrated his/her ability to perform the Valsalva maneuver in the prescribed manner, the actual test was performed.

The Comparative Analysis Trial, as described herein in Example 2, involved
15 the essentially the same steps as described above in connection with Example 1, and were guided by audible and visual prompts issued by the Controller/Monitor. The only difference between the procedure followed in the Comparative Analysis Trial and the dye indicator dosing trials was the ICG dose level (10 to 12 mg for all tests in the comparative analysis trial), the injected ICG and isotonic saline volumes
20 and the time intervals between the start of injection and Valsalva release. The comparative analysis trial involved the following steps, which were guided by audible and visual prompts issued by the Controller/Monitor:

(1) Patient was instructed to observe the Controller/Monitor display screen and begin a nominal 6 second Valsalva maneuver by exhaling into the
25 Valsalva Tubing Set; the screen display provided visual feedback to the patient when the exhalation pressure had reached the required level and the remaining period during which the Valsalva maneuver was sustained; the Controller/Monitor measured and recorded the actual exhalation pressure exerted by the patient as well as the starting and ending times for the Valsalva maneuver.

30 (2) Once the required Valsalva pressure threshold was reached, an elapsed time clock within the Controller/Monitor started and issued an audible cue to the operator to start the ICG injection at a precise time interval (viz., Time Interval A) before the subsequent cue for the release of the Valsalva maneuver; upon the start

of the test, the measured ICG concentration levels at all six channels (three per FSA unit) were continuously monitored and recorded.

(3) At a predetermined time interval after the 1st cue was issued for the start of ICG injection, a 2nd visual and audible cue was issued to the patient to release (end) the Valsalva maneuver.

(4) The patient was next instructed by the display on the Controller/Monitor unit to remain still for the next 60 seconds while the ICG signal levels was continuously measured and recorded.

(5) Within about one minute after the end of the test, a graph was displayed showing the recorded Valsalva pressure level and ICG concentrations levels from the six fluorescence sensors over the 60 second period of the test.

(6) After an elapsed time of 5 minutes after the end of the first test, the comparative analysis trial procedure as described in Steps 1 through 5 above was repeated but with a different time interval between cue for the start of injection and the cue for Valsalva release (viz., Time Interval B); for the case of tests with different ICG dose levels, the Cardiox test could be repeated for up to two additional times.

In addition to the exhalation pressure level and ICG concentration levels measured and recorded automatically by the Controller/Monitor, other manually recorded parameters included (a) patient weight, height, age, sex, skin color; (b) time interval between the start of injection cue and Valsalva release cue, (c) ICG dose, concentration and bolus volume; (d) isotonic saline flush volume (if used); (e) TCD bubble track count (displayed by Spencer Technologies TCD unit) and (f) measured duration of injection of ICG dye and any optional isotonic saline injected immediately after ICG injection.

For the comparative analysis trial patients 1 through 7, two tests were performed at cueing time intervals of 1.0 and 2.0 seconds between the start of ICG injection and Valsalva release. The ICG dose levels for these tests were either 10 or 12.5 mg for a total ICG dose of 20 to 25 mg per patient. In order to assure that ICG promptly reached the right atrium for even the largest patients, the ICG bolus injection was promptly followed by a 10 ml isotonic saline flush for Pilot Trial patients 3 through 7. In order to further minimize the variation in the time of arrival of the ICG in the right atrium, the injection protocol for the comparative analysis trial was further modified by pre-loading the ICG dose (2 ml volume at concentration of 5.0 mg/ml) in

the Catheter Set. This revised injection protocol enabled the ICG bolus injection and isotonic saline flush to be accomplished with a single syringe injection step wherein 17 ml of isotonic saline is used to "push" 2 ml of ICG into the vein at the antecubital fossa. This 17 ml volume of isotonic saline was selected to assure that all of the ICG bolus is forced into the right atrium during the syringe injection "push" for the case of patients with the largest vein volume between the antecubital vein fossa and the inferior vena cava.

The principal findings from the 25 patients tested at Columbia University Medical Center (CUMC) using the disclosed system include the following. All 18 patients with a known PFO of Spencer Grade 4 or 5 exhibited a Shunt Conductance Index that was greater than zero (i.e., disclosed non-invasive test indicated the presence of a PFO). However, the magnitude of the measured Shunt Conductance Index in several of the tests was less than the expected value based on the magnitude of the PFO confirmed using the Trans-Cranial Doppler method.

A total of 6 out of 7 patients with a Spencer Grade of 0 using TCD testing (i.e., Control patients without a predicted PFO) exhibited a Shunt Conductance Index value of zero using the disclosed system. One patient with Spencer Grade 0 exhibited a positive Shunt Conductance Index using the disclosed system. Since the published rate of false negatives for TCD method ranges from 5 to 10 percent (Droste 1999, Lao 2008 and Onorato 2009), it is plausible that the TCD method provided a false negative result, and that a previously undetected PFO was identified by the system.

The lower than expected Shunt Conductance Index for several of the tests is attributable to several factors. For larger patients, the volume of the dye injectate and isotonic saline flush (when used) was inadequate to assure rapid transport of the ICG dye to the right atrium during the injection step. Another factor believed to contribute to a lower than expected Shunt Conductance Index in some tests was the protracted time interval between the start of the indicator dye injection and the release of the Valsalva maneuver by the patient. The extended time interval is attributable to a naturally delayed response time of the patient audible and visual cues prompting the patient to release the Valsalva.

It is believed that another factor contributing to a lower than expected Shunt Conductance Index in some tests was the injection duration, which was extended in

some tests when a two-step injection protocol was employed (i.e., steps including first injection of indicator dye, followed by manually changing stopcock position and then second step involving injection of isotonic saline flush). Throughout the disclosed trials, it should be noted that the actual measured time interval values
5 between the start of injection and the Valsalva release were generally longer than the Controller/Monitor specified (via cueing) time intervals. The lack of conformance between the specified and actual time interval values was the direct result of the unavoidable delay in the Valsalva release due to the patient's response time to the visual and audible cues issued by the Controller/Monitor.

10 The calculated Shunt Conductance Index values for each of the 10 comparative analysis trial patients with a measured Spencer Grade 4 or 5 shunt are summarized in Table 2 and ranged from 0.5% to 26.9%. These shunt tests performed using the disclosed system confirmed that a shunt was detected in all 10 patients. The calculated Shunt Conductance Index values for 6 of the 7
15 comparative analysis trial patients with a measured Spencer Grade 0 (Control patient cohort) was 0.0% as seen in Table 2. However, comparative analysis trial Patient Number 14, whose measured Spencer Grade value was 0, showed clear evidence of a right-to-left shunt using the system as seen in Table 2. Note that the calculated Shunt Conductance Index values for each of the 8 Dosing Study patients are
20 summarized in Table 1 and ranged from 2% to 21.2%. These shunt tests performed using the disclosed system confirmed that a shunt was detected in all 8 patients with a measured Spencer Grade 4 or 5 shunt.

An example of the graphical display provided by the Cardiox Controller/Monitor is shown in Figure 44 for the case of a Pilot Trial Cohort patient
25 with a Spencer Grade 5 PFO at TCD test. The calculated values for the Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value based a comparison of Cardiox and Transcranial Doppler tests results are presented below:

1. Sensitivity is defined as the proportion of actual positives (i.e., patients with clinically significant PFO) that are correctly diagnosed. The calculated Sensitivity
30 for patients with known shunts (n=18) is 100%

2. Specificity is defined as the proportion of actual negatives (i.e., patients without a clinically significant PFO) that are correctly diagnosed. The calculated Specificity for patients with no or very small shunts (n=8): 89%

3. Positive Predictive Value (PPV) is defined as the proportion of patients with positive test results that are correctly diagnosed. The calculated PPV for comparative analysis trial was 95%.

4. Negative Predictive Value (NPV) is defined as the proportion of patients with negative test results that are correctly diagnosed. The calculated NPV for comparative analysis trial was 75%

The total dose of ICG injected for all patients was well below the recommended daily limit of 2.0 mg/kg body weight. The safety factor (i.e., total permissible ICG dose divided by actual total ICG dose) ranged from a 6.1x to 11.8x in the comparative analysis trial. This safety will not be less than 4.1x for even the smallest adult patient at a weight of only 90 pounds.

Table 2 Comparative analysis of Dye dilution detection system and existing trans-cranial Doppler detection.

Test ID/ Cath location	Sex/ Test #	Wg t[lb]	H gt (In .)	Grade/ #(BT)	Int/ rel (se)	Act. Int/rel (sec)	[ICG] / Dose (mg)	ICG Inj.	Shunt Curve?	Calc. SCI [%]
CA 1	Male						1.25mg/ml			
	11-01	270	75	4	1	1.8	12.5	10/0	Yes	0.005
(20 G, RAF)	11-02			(168 BT)	2	2.54	11.25	10/0		{Note}
CA 2	Male						1.25mg/ml			
	12-01	160	70	5	1	2.11	12.5	10/0	Yes	0.12
(20 G, RAF)	12-02			(>300)	2	2.79	11.25	10/0		
CA 3	Male						1.25mg/ml			
	13-01	230	73	4	1	2.17	12.5	10/10	** No	0.003
(20 G, RAF)	13-02			(290 BT)	2	2.67	12.5	10/10	**	{Note}
CA 4	Male						1.25mg/ml			
10/15/10	16-02	220	74	0	1	2.29	12.5	10/10	No	0
(20 G, RAF)	16-03			Control	2	3.22	12.5	10/10		

CA 5	Male						2.5 mg/ml			
10/26/10	17-02	260	76	4	1	1.92	10	4/10	Yes	0.046
(20 G, RAF)	17-03			(299 BT)	2	2.98	10	4/10		
CA 6	Male						2.5 mg/ml			
10/27/10	18-02	220	72	0	1	2.11	10	4/10	No	0
(20 G, RAF)	18-03			Control	2	2.73	10	4/10		
CA 7	Male						2.5 mg/ml			
10/27/10	19-01	165	72	5	1	2.11	10	4/10	** Yes	0.018
(20 G, RAF)	19-02			(>300)	2	2.6	10	4/10	**	
CA 8	Female						5.0 mg/ml			
11/23/10	20-02	150	62	5	1	2.17	10	2/17	Yes	0.045
(20 G, RAF)	20-03			(>300)	2	2.85	10	2/17		
CA 9	Female						5.0 mg/ml			
11/23/10	21-01	210	70	5	1	1.98	10	2/17	Yes	0.023
(20 G, RAF)	21-02			(>300)	2	2.6	10	2/17		
CA 10	Male						5.0 mg/ml			
11/30/10	22-01	180	68	5	0.6	1.98	10	2/17	Yes	0.122
(20 G, RAF)	22-02			(>300)	1.6	3.1	10	2/17		
CA 11	Male			Dark skin			5.0 mg/ml			
12/3/10	23-01	240	74	0	0.6	2.42	10	2/17	No	0
(20 G, RAF)	23-02				1.6	2.73	10	2/17		
CA 12	Male						5.0 mg/ml			
12/3/10	24-01	200	72	0	0.6	1.3	10	2/17	No	0
(20 G, RAF)	24-02			Control	1.6	2.67	10	2/17		
CA 13	Female			Dark skin			5.0 mg/ml			
12/15/10	25-01	171	61	4	0.6	1.67	10	2/17	Yes	0.052

(20 G, RAF)	25-02			(124 BT)	1.6	2.42	10	2/17		
CA 14	Female			Latino			5.0 mg/ml			
12/17/10	26-01	165	67	0	0.6	2.48	10	2/17	Yes	0.043
(20 G, RAF)	26-02			Control	1.6	2.11	10	2/17		**
CA 15	Male						5.0 mg/ml			
12/21/10	27-01	180	70	5	0.6	1.3	10	2/17	Yes	0.269
(20 G, RAF)	27-02			(>300)	1.6	2.79	10	2/17		
CA 16	Male						5.0 mg/ml			
1/14/11	29-01	160	66	0	1.6	2.05	10	2/17	No	0
(20 G, RAF)	29-02			Control	0.6	1.18	10	2/17	No	
CA 17	Female			Dark Skin			5.0 mg/ml			
1/14/11	30-01	179	64	0	1.6	2.79	10	2/17	No	0
(20 G, RAF)	30-02			Control	0.6	1.55	10	2/17	No	

See legend for Table 1, above.

Patient CA01 10/0: 10 ml ICG bolus injected without prompt Isotonic Saline Flush

Note: ICG arrived too late-both tests reducing shunt peak, total vein volume too large for ICG bolus volume

Patient CA02 10/0: 10 ml ICG bolus injected without prompt Isotonic Saline Flush

Patient CA03 10/10: 10 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Note ** ICG arrived too late-both tests reducing shunt peak; actual Time Interval too long and injection duration too long.

Patient CA04 10/10: 10 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Patient CA05 4/10: 4 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Note: Patient Spencer Grade 2 at rest.

Patient CA06 4/10: 4 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Patient CA07 4/10 4 ml ICG bolus injected promptly followed by 10 ml Isotonic Saline Flush

Note: ICG arrived too late-both tests; injection duration was too long

5 **Patient CA08 2/17:**2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Patient CA09 2/17:2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Patient CA10 2/17:2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

10 **Patient CA11 2/17:**2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Patient CA12 2/17:2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

15 **Patient CA13 2/17:**2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Patient CA14 2/17 2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Note ** Clear evidence of smaller shunt on multiple Fluorescence Sensors on both ears in 2nd test

20 **Patient CA15 2/17:** 2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

Patient CA16 2/17: 2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection

25 **Patient CA17 2/17:**2ml ICG bolus pre-loaded into extension line and pushed into vein with 17 ml Isotonic Saline in single injection.

Example 3: Calculation of Shunt Conductance Index.

To calculate the shunt conductance index the sequence of computation steps is described below. For a detector system with 6 sensor pairs, there are 6 ICG fluorescence level measurements performed corresponding to the 6 laser diode/photodetector pairs located in the two Fluorescence Sensor Array units, it is implied that many of the steps described below are performed on each of the six channels and subsequent data processing is channel specific. For example, peak values and baseline values are specific to each channel of data being processed and are not averaged among all 6 channels. Hence, the ratio of the shunt curve amplitude to the Normal curve amplitude is channel specific, i.e., the ratio value known is calculated for all 6 channels of data. The specific computation steps are as follows where the index *i* refers to a channel number between 1 and 6 and the index *j* refers to an elapsed time, Time Elapsed (*j*), where all times steps have a duration of 0.062 seconds:

15

1. Select values for algorithm assumptions:
 - a. Maximum period during which shunt curve/inflection must occur following Valsalva release: Time Max = 12.0 seconds
 - b. Minimum positive value of slope of signal change to indicate presence of shunt curve or inflection: Slope Min = 4.0 signal units/second
 - c. Minimum time period after Valsalva Release before shunt curve or inflection can occur: Time Min = 1.0 seconds
 - d. Fractional amount of slope decrease to indicate presence of start of shunt curve or inflection in a single time step: Slope Delta Min = 0.91
 - 25 e. Minimum elapsed time interval between shunt curve peak and Normal curve peak: Time Peak Offset = 2.0 seconds
 - f. Minimum positive value of slope of signal change to indicate to indicate start of shunt curve: Shunt Start Slope Min = 1.3 signal units/second
- 30 2. Determine peak value of fluorescence signal level for each channel, *i*: S_{peak} [*i*]
3. Determine elapsed time of injection based on non-zero value in Column AA of data file obtained during test procedure: Time Inject

4. Determine baseline for each channel, i based on average of 22 consecutive time steps of values (1.36 seconds) immediately prior to start of injection, Time Inject: S baseline [i]
5. Calculate relative signal level, S [i,j] by subtracting baseline value, S baseline [i] from absolute signal level, S [i,j]: S relative [i,j]
6. Calculate relative peak signal level by subtracting baseline value, S baseline [i] from peak signal level, S peak [i]: S relative peak [i]
7. Calculate elapsed time when peak occurs for channel, i: Time Peak [i]
8. Calculate Slope A of ICG signal for each channel based on the difference between a two time-step interval for relative signal levels, S[i , j]: Slope A [i , j] = $\{((S \text{ relative}[i , j+2] - S \text{ relative}[i , j])) * 100 / ((\text{Time}[j+2] - \text{Time}[j]) * S \text{ relative peak}[i])\}$
9. Calculate Slope B of ICG signal for each channel based on the difference between a two-value average for relative signal levels, S[i , j] divided by time interval corresponding to three time steps between averages: Slope B [i , j] = $\{(AVERAGE(S \text{ relative}[i , j+3 \text{ and } j+4]) - AVERAGE(S \text{ relative}[i , j \text{ and } j+1])) * 100 / ((\text{Time}[j+3] - \text{Time}[j]) * S \text{ relative peak}[i])\}$
10. Determine elapsed time when Valsalva maneuver is released (i.e., ends) based on pressure transducer signal level decreasing to less than 500 signal units or ~4 mm Hg of gauge pressure: Time Valsalva End
11. Determine earliest time that shunt curve can occur after Valsalva Release: Time Earliest[i] = Minimum{IF{((Time Elapsed[j] > Time Valsalva End) AND (Slope B[i,j] > Shunt Start Slope Min), Time Elapsed[j] if TRUE, 1000 if FALSE}}
12. Determine allowed elapsed time period when shunt curve can possibly occur based on assumptions 1(a) and 1(c) above and the detected elapsed time at which the Valsalva Release actually occurs (see columns BB through BG of Excel computation spreadsheet): Time Allowed B [i,j] = IF{((Time Elapsed [j] > Time Earliest[i]) AND ((Time Peak [i]-Time Elapsed [j] - Time Peak Offset) > 0, THEN Time Elapsed [j] if TRUE, THEN 0 if FALSE)}
13. Determine upper limit for the allowed elapsed time for the occurrence of any shunt curve where value is 1 if limit not exceeded and 0 if limit exceeded: Time Upper Limit Flag[i] = IF{ (Elapsed Time[j] < (Time Valsalva End + Time Max)) AND (Elapsed Time[j] > (Time Valsalva End + Time Min)), THEN 1 if TRUE, THEN 0 if FALSE}

14. Determine possible signal values, $S[i]$ for each channel, j using method for finding occurrence of premature shunt curve: $S[i] = \text{IF}\{(\text{Time Allowed } B[i,j] > 0) \text{ AND } (\text{Slope } A[i,j] < (\text{Slope Delta Min} * \text{Slope } A[i,j-1]) \text{ AND } (\text{Slope } A[i,j-1] < (\text{Slope Delta Min} * \text{Slope } A[i,j-2]) \text{ AND } (\text{Slope } A[i,j] < \text{Slope Min}, \text{ THEN } (S[i,j] * \text{Time Upper Limit Flag}[i] \text{ if TRUE, 0 if FALSE})$
15. Determine maximum value of $S[i]$: $\text{Max } S[i] = \text{Maximum}\{S[i]\}$
16. Calculate Shunt Conductance Index, $\text{SCI}[j]$ by dividing maximum possible shunt related signal value by peak signal level of Normal indicator-dilution curve: $\text{SCI}[i] = \text{Max } S[i] / S_{\text{peak}[i]}$
17. Determine maximum value of calculated Shunt Conductance Index values: $\text{Max SCI} = \text{Maximum}\{\text{SCI}[i]\}$
18. If two or more tests are performed for a patient, then find the global maximum value from among the set of Max SCI values and display this global maximum value as the result of the shunt conductance index. Value displayed in units of percent. Hence, if peak of shunt curve or inflection for a given channel, i for test, k is 200 signal units and peak of signal for that channel is 1000 signal units, then displayed Shunt Conductance Index value would be 20%.

The present application herewith provides reference to United States application for patent Serial No. 12/418,866, filed April 6, 2009 and entitled "Hemodynamic Detection of Circulatory Anomalies" which, in turn, makes reference to U.S. Provisional application Serial No. 61/156,723, filed March 2, 2009, and to U.S. Provisional application Serial No. 61/080,724, filed July 15, 2008, the disclosures of which are incorporated by reference. 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 Edition.

Since certain changes may be made in the above-described system, apparatus and method without departing from the scope of the invention herein involved, it is intended that all matter contained in the description thereof or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense. The disclosed invention advances the state of the art and its many advantages include those described and claimed.

We claim:

1. A system for detecting the presence of a right-to-left cardiac shunt in a patient, comprising:

an indicator delivery system having an outlet locatable in a vein of the patient
5 in blood flow communication with the right side of the heart and actuatable to deliver a fluorescing biocompatible indicator into the vein such that the indicator will arrive at the right side of the heart within an anticipated transit time;

at least one non-invasive optical sensor positionable along a skin surface of
10 the patient to detect the presence of at least a portion of the indicator as it flows through the underlying arterial vasculature and comprising a fixture, a plurality of laser diode emitters located in the fixture along one side of a tissue receiving gap therein and energizable to emit light at a first wavelength that will transcutaneously excite the indicator, and a like number of photodetectors located in the housing along
15 an opposite side of the tissue receiving gap therein for detecting the concentration-indicating intensity of fluorescing photons that will be emitted by the indicator at a second wavelength as a result of excitation light from the emitters being transmitted through the subject tissue and underlying vasculature;

one or more sensor outputs corresponding with the instantaneous
concentration of indicator flowing through said vasculature at the sensor location; and

20 a monitor/controller having a display, the monitor/controller programmed to cue actuation of the indicator delivery system, to commence timing of the anticipated indicator transit time, to display one or more premature and/or normal indicator dilution curves and, when a shunt is detected, to calculate a shunt conductance index by comparing the ratio of the peak amplitude of a premature indicator dilution curve
25 to the peak amplitude of an associated normal indicator dilution curve.

2. The system of claim 1 wherein the at least one sensor is adapted for location at one or more ears, the nose, either or both the top and bottom lip, the hand, one or more fingers, the neck, the leg, one or more toes, or the arm.

3. The system of claim 1 further comprising:

30 a manometer in communication with said monitor/controller and having an air pressure responsive input and a corresponding pressure output signal;

a pneumatic tube with a mouthpiece engageable with the mouth of the patient
for receiving the exhalation of a Valsalva maneuver performed by the patient;

means for determining the interval of said Valsalva maneuver; and

an electromagnetically operable pneumatic valve coupled with the pneumatic tube and switchable from a non-venting to a vent-to-atmosphere orientation when signalled by the monitor/controller;

5 wherein the monitor/controller is adapted to display the start and cue the release of the Valsalva maneuver and to cue the time of actuation of the indicator delivery system with respect to such Valsalva maneuver start and release.

4. The system of claim 1 in which:

10 the circulatory anomaly is one or more of a cardiac shunt, an atrial septal defect, a patent foramen ovale, a patent ductus arteriosus, a ventral septal defect, and a pulmonary arteriovenous malformation.

5. The system of claim 1 in which:

the indicator delivery system includes a flow sensor responsive to derive signals corresponding with the commencement and termination of fluid flow through the system; and

15 the monitor/controller is responsive to such commencement and termination signals to provide an audible alarm to the operator when the time interval of indicator injection is excessive.

6. The system of claim 1 in which the fluorescing biocompatible dye is one or more of indocyanine green dye, infracyanine green (IfCG) dye, another cyanine dye, 20 methylene blue dye, trypan blue (TB) dye, patent blue (PB) dye, brilliant blue G (BBG) dye, lymphazurin blue dye, any of the various colors (Green, Yellow to Red, Far red and Near infrared, Blue) of Alexa Fluor dyes, sodium fluorescein (SF), a radioisotope, another radionuclear substance, or fluorescent nanoparticles.

7. The system of claim 1 in which the at least one sensor further comprises:

25 two or more paired excitation laser diodes and filtered photodetectors and the laser diodes being energizable in a sequence or simultaneously; and

an aspheric collimating lens, a collimator plate and an interference filter associated with each laser diode and located in the transmission path to the photodetector;

30 wherein the laser diodes are energizable to emit light at a wavelength of 785 nanometers; and

wherein the monitor/controller is responsive to select the laser diode-photodetector pair detecting a fluorescing output of highest intensity.

8. The system of claim 2 in which two sensors are present, the sensors comprising fluorescence sensing array fixtures with sensing array arms and being removably attached to a headband, and wherein a sensor is located at the schaphoid fossa of each ear of the patient.

5 9. The system of claim 1 in which:

the indicator delivery assembly comprises a flexible elongate delivery tube having proximal and distal ends, an auxiliary catheter coupled in fluid transfer relationship with the distal end defining the outlet, a indicator fluid flow detector coupled in fluid transfer relationship with the proximal end and deriving signals
10 corresponding with the commencement and termination of fluid flow through the system, a three-way valve connected upstream to the fluid flow sensor, a first indicator containing syringe coupled in indicator flow relationship with the valve and actuatable to cause indicator to flow through the valve, and a second isotonic saline fluid containing syringe coupled in fluid flow relationship with the valve and actuatable
15 to cause isotonic saline to flow through the valve; and

wherein the flexible elongate delivery tube is preloaded with a quantity of indicator from the first indicator containing syringe, the valve is actuatable to connect with the second isotonic saline fluid containing syringe, and upon actuation of the second syringe the fluid flow sensor signals will be transmitted to the
20 monitor/controller; and

wherein the monitor/controller is responsive to cue an operator first to actuate the first syringe and immediately thereafter to actuate the second syringe, and is responsive to monitor the corresponding fluid flow sensor signals.

10. The system of claim 1 in which

25 the at least one non-invasive optical sensor further comprises a fixture having a laser diode array support and a photodetector array support, each of which extends outward from a base portion with a tissue-receiving gap therebetween;

a spring connecting the laser diode array support and a photodetector array support at the base portion thereof and biasing the laser diode array support and
30 photodetector array support toward each other;

a protrusion extending from near a distal end of each of the laser diode array support and photodetector array support toward the tissue-receiving gap;

an array of three laser diodes and corresponding collimating lenses located within the protrusion of the laser array support and oriented to emit light toward the
35 tissue receiving gap; and

an array of three photodetectors and a collimating lens and interference filter located within the protrusion of the photodetector array support, the photodetectors aligned with the laser diodes and oriented to receive light passing through the tissue receiving gap;

5 wherein the fixture can be placed in a clamped arrangement on the exterior of the patient body by compressing the spring to expand the tissue-receiving gap, placing subject tissue within the expanded tissue-receiving gap, and subsequently releasing the spring, thereby allowing the laser diode array support and photodetector array support to move toward each other and trap the tissue
10 therebetween.

11. The system of claim 1 wherein the at least one sensor further comprises a control board located within the fixture, the control board in electrical communication with the laser diodes and photodetectors.

12. The system of claim 11 wherein the control board is programmed or otherwise
15 adapted to sequentially operate the laser diode/photodetector pairs, such that only one laser diode/photodetector pair at a time is operational.

13. The system of claim 8 further comprising positionable wedges for positioning the sensors on the ear.

14. The system of claim 11 wherein the control board is programmed or otherwise
20 adapted to repeatedly sequentially operate the laser diode/photodetector pairs over some predetermined period of time.

15. The system of claim 11 wherein:
 the control board is programmed or otherwise adapted to determine which laser diode/photodetector pair detects the highest peak indicator photon fluorescence
25 level during operation of the at least one sensor.

16. The system of claim 10 wherein:
 the fixture is a clip that facilitates the temporary coupling of the sensor over a section of tissue associated with a body part selected from the group consisting of the pinna of the ear; the hand, including the web of skin between the thumb and
30 forefinger; the neck, including distendable skin about the neck; the leg; and the arm, including distendable skin of the arm proximal to the shoulder.

17. The system of claim 10 further comprising:
- an additional emitter located on the laser diode array support and an additional detector located on the photodetector array support;
 - wherein when the additional emitter and additional detector form an optical interlock when in sufficiently close proximity to one another, the optical interlock providing a signal useable by control circuitry with which the at least sensor is associated.
- 5
18. The system of claim 1, further comprising a kit of consumable materials necessary for detecting and quantifying a right-to-left cardiac shunt, the kit comprising:
- a) an indicator delivery tubing system providing a valve, syringe connectors, a flow sensor and sterile intravenous injector;
 - b) one or more doses of circulatory indicator reagent as a shelf stable material;
 - c) a diluent for preparing the dose of circulatory indicator reagent for injection or for delivering an indicator bolus;
 - d) a dose of nonreactive blood compatible clearing reagent for completing the injection; and
 - e) a Valsalva mouthpiece apparatus with a mouthpiece and monitor connector coupling.
- 10
- 15
19. The system of claim 18 further comprising a single-use flow sensor having a circuit in communication with the monitor-controller, the circuit becoming disabled for repeat use after initiation of a testing procedure.
- 20
20. The system of claim 18 further comprising a sealed tray containing the kit contents in a sterile condition until opened.