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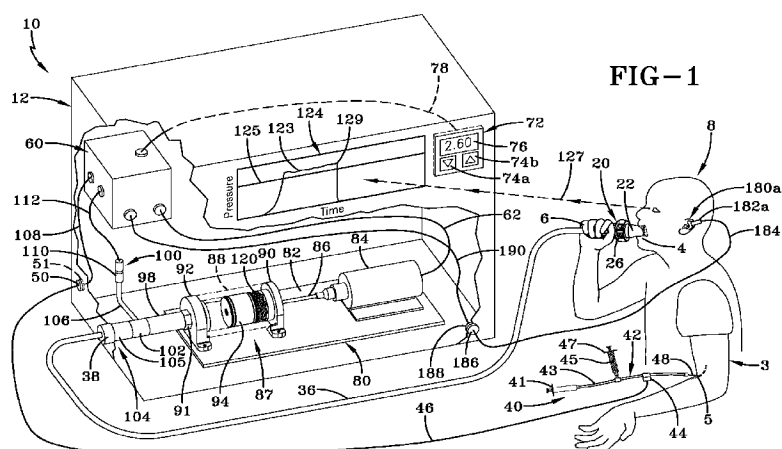
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- (54) Title:** METHOD, APPARATUS AND SYSTEM FOR THE PERFORMANCE OF VALSALVA MANEUVERS



- (57) Abstract:** Methods, apparatus and systems for precisely controlling a Valsalva maneuver and the timing thereof in conjunction with testing a patient for a cardiac shunt, and for ensuring that a patient performing a Valsalva maneuver creates a required pressure using their diaphragm. Embodiments of a Valsalva maneuver mouthpiece assembly are also disclosed for use with the invention methods, apparatus and systems. The mouthpiece assembly is adapted to selectively operate between a state that produces resistance to the exhalation pressure of a patient into the mouthpiece and a state wherein the pressure resistance is rapidly removed so as to cause an involuntary exhalation of the air in the patient's lungs at a time of desired Valsalva maneuver release.

METHOD, APPARATUS AND SYSTEM FOR THE PERFORMANCE OF VALSALVA MANEUVERS

BACKGROUND

5 **[0001]** The present invention generally relates to a method, system and apparatus for the performance of a maneuver essential for the detection of circulatory anomalies in the mammalian body. Important types of such anomalies involve the heart and include anomalies generally referred to as right-to-left cardiac shunts.

10 **[0002]** An anomaly commonly encountered in humans is an opening between the chambers of the heart, particularly an opening between the left and right atria (i.e., an Atrial Septal Defect (ASD) that creates a right-to-left atrial shunt), or between the left and right ventricles (i.e., a Ventricular Septal Defect (VSD) that creates a right-to-left ventricular shunt. A right-to-left shunt
15 may occur as a defect within the vasculature leading to and from the heart, for example a Pulmonary Arteriovenous Malformation (PAVM) may be present, reflecting a direct connection between the pulmonary vein and pulmonary artery. Alternatively, a right-to-left shunt may occur as a defect between great vessels. For example, a Patent Ductus Arteriosus may be present, allowing
20 shunting between the aortic arch and the pulmonary artery.

[0003] The passage of a thrombotic embolism via a cardiac right-to-left shunt is a widely recognized cause of cerebral ischemia (e.g., stroke). Over 780,000 patients suffer strokes each year in the U.S. resulting in 250,000 stroke related deaths. The total cost associated with stroke was reported to
25 be \$66 billion in the U.S. in 2007. (Rosamond 2008). Of the patient population presenting with stroke or the early warning sign known as transient ischemic attack (TIA or mini stroke), as many as 260,000 are reported to be the result of a right-to-left shunt in the heart and/or pulmonary vasculature, allowing paradoxical emboli.

30 **[0004]** The most common form of right-to-left shunt is a patent foramen ovale (PFO), which is an opening in the wall of the heart that separates the right side of the heart from the left side of the heart. The right side of the heart receives oxygen-depleted blood from the body and then pumps this blood into

the lungs for oxygenation. The lungs not only oxygenate the blood, but also serve as a “filter” for any blood clots or other emboli, and also 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
5 atria of the heart to enable circulation of the mother’s oxygenated blood throughout the vasculature of the fetus. This opening between the right and left side of the fetal heart (known as the foramen ovale) permanently seals shut in consequence of the closure of an overlying tissue flap in about 80% of the population within the first eighteen months following birth. The noted flap
10 often remains in a sealing orientation because of a higher pressure at the left side of the heart. However, in the remaining approximate 20% of the population, this opening fails to permanently close and is referred to as a patent foramen ovale or PFO.

[0005] Most of the population with a PFO never experience any symptoms
15 or complications associated with the presence of a PFO, since many such PFOs are small enough to remain effectively “closed”, or emboli may not form and travel to the right atrium, or they may not pass through a PFO even if it is present and open; thus the paradoxical nature of these emboli. However, for more than 20% of the adult population, this normally closed flap covering the
20 foramen ovale temporarily opens during various types of exertion or coughing, allowing blood to temporarily flow directly from the right side to the left side of the heart.

[0006] As a consequence, emboli such as blood clots or other active
agents escaping through the PFO bypass the critical filtering functions of the
25 lungs and flow through the temporarily open foramen ovale and directly to the left side of the heart. Once in the left side of the heart, these emboli pass directly into the arterial circulatory system. Since a significant portion of the blood exiting the left side of the heart flows to the brain, any unfiltered blood clots or agents, such as serotonin, may be delivered to the brain. The
30 presence of these now cerebral emboli in the brain arterial flow can produce debilitating and life-threatening consequences. These consequences are known to include stroke, heart attack and are also 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);

5 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
10 Ovale in Patients with Migraine Headache." *Journal of Interventional Cardiology* 19(6): 552-557 (2006).

[0007] Transesophageal Echocardiography (TEE), involving an ultrasound transducer positioned in the patient's esophagus in close proximity to the heart, is widely used as part of the diagnostic evaluation of patients with
15 cerebral ischemia. Numerous studies have demonstrated the value of TEE for the detection of a PFO or an ASD as a possible cause of cerebral ischemia. Currently, TEE, enhanced by an injected echo-contrast agent (e.g., a 10 ml solution containing contrast air bubbles), is used somewhat as a last resort. While the so-called TEE "bubble study" has not been reviewed by the U.S.
20 Food and Drug Administration, and so is performed "off-label", it is still is considered the "gold standard" for the detection of a cardiac right-to-left shunt. The air bubbles contained in the echo-contrast agent used for this test are essentially unable to pass through the pulmonary capillary bed. The echogenic air bubbles passing through a right-to-left shunt and entering the
25 left atrium, within about three heart beats after said contrast arrives at the right atrium, produce visible images on the ultrasound monitor screen and ultrasound recording and indicate the presence and relative conductance of the right-to-left shunt based on the number of air bubbles observed in the left atrium. For further background on TEE methods, see for example:

30 5) O'Brien PJ, Thiemann DR, McNamara RL, Roberts JW, Raska K, Oppenheimer SM, Lima JAC. "Usefulness of transeophageal echocardiography in predicting mortality and morbidity in stroke patients

without clinically known cardiac sources of embolus.” *American Journal of Cardiology* 81: 1144–1151 (1998);

6) Leung DY, Black IW, Cranney GB, Walsh WF, Grimm RA, Stewart WJ, Thomas JD. “Selection of patients for Transesophageal
5 Echocardiography after stroke and systemic embolic events.” *Stroke* 26: 1820–1824 (1995).

7) Rauh G, Fischereider M, Spengel FA. “Transesophageal Echocardiography in patients with focal cerebral ischemia of unknown cause.” *Stroke* 27: 691–694 (1996).

10 8) Nighoghossian N, Perinetti M, Barthelett M, Adeleine P, Trouillas P. “Potential cardioembolic sources of stroke in patients less than 60 years of age.” *European Heart Journal* 17: 590–594 (1996).

[0008] Alternatively, a test referred to as transthoracic echocardiography (TTE), which also uses an injected echo-contrast agent (containing air
15 bubbles), can be used for the detection of a PFO or a ASD as a possible cause of cerebral ischemia. The air bubbles contained in the echo-contrast agent used for this test are essentially unable to pass through the pulmonary capillary bed. The echogenic air bubbles passing through a right-to-left shunt and entering the left atrium, within about three heart beats after said contrast
20 arrives at the right atrium, produce visible images on the ultrasound monitor screen and indicate the presence and relative conductance of the right-to-left shunt based on the number of air bubbles observed in the left atrium. Unlike TEE, which requires insertion of an ultrasound transducer into the esophagus, TTE is performed by placing the ultrasound transducer on the surface of a
25 patient's chest near the heart. For further background on the TTE methods, see for example:

9) Gonzalez-Alujas, T. et.al. “Diagnosis and Quantification of Patent Foramen Ovale. Which Is the Reference Technique? Simultaneous Study With Transcranial Doppler, Transthoracic and Transesophageal
30 Echocardiography.” *Rev. Esp. Cardiology* 64(2): 133-139 (2011).

[0009] In addition to TEE and TTE, a cardiac right-to-left shunt can also be identified by the use of contrast-enhanced Transcranial Doppler (TCD)

sonography. This technique is based on the detection of an intravenously injected contrast agent (containing air bubbles) within intracranial arteries, e.g., the middle cerebral arteries (MCAs). The air bubbles contained in the echo-contrast agent used for this test are essentially unable to pass through the pulmonary capillary bed. In case of a right-to-left shunt, the contrast agent bypasses the pulmonary capillary bed and enters the arterial circulation via a right-to-left shunt. The echogenic air bubbles passing through a right-to-left shunt and, upon entering the arterial circulation via the left atrium, produce microembolic signals (MES) during the TCD ultrasound recording, thus mimicking the pathway of paradoxical cerebral emboli. For further background on TCD methods, see for example:

10 10) Teague SM, Sharma MK. "Detection of paradoxical cerebral echo contrast embolization by Transcranial Doppler ultrasound." *Stroke* 22: 740–745 (1991).

15 11) Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. "Consensus on microembolus detection by Transcranial Doppler ultrasound." *Stroke* 29: 725–729 (1998).

[0010] The contrast agent most widely used in the performance of TEE, TTE and TCD is agitated saline containing tiny air bubbles. The mean microbubble size for a 10% air - 10% blood - 80% saline mixture is 26.7 ± 7.2 microns and for a 10% air – 10% plasma – 80% saline mixture is 25.3 ± 7.4 microns. However, it is possible for some bubbles at the very small end of the size range to pass through the pulmonary capillary bed. For that reason, the timing or window for the observation of the presence of air bubbles in either the left atrium or middle cerebral arteries, relative to the performance of a maneuver such as the Valsalva maneuver, is critical following the injection of air bubble contrast agent.

[0011] Yet a fourth method for the detection of right-to-left cardiac shunts employs an injectable dye rather than air bubbles to detect the presence of a right-to-left cardiac shunt. A description of this method, apparatus and system for the detection of circulatory anomalies is described in co-pending U.S. Patent Application Serial Nos. 12/754,888 filed April 6, 2010 and 12/418,866

filed April 6, 2009; in U.S. Provisional Application Nos. 61/156,723 filed March 2, 2009 and 61/080,724 filed July 15, 2008; and in PCT applications PCT/US09/50630 filed July 15, 2009 and PCT/US11/31433 filed April 6, 2011.

[0012] The presence of a right-to-left shunt is determined with this fourth method, apparatus and system by first deriving the magnitude of the peak amplitude of a measured indocyanine green (ICG) dye concentration for a premature shunt curve or inflection that may occur in advance of a normal indicator-dilution curve associated with ICG dye following a normal pathway through the lungs. A premature shunt curve or inflection can only occur if the ICG dye arriving in the right atrium follows a shorter pathway between the right atrium and the left atrium than the normal pathway through the lungs. The peak amplitude of the measured ICG dye concentration (relative to baseline) associated with a premature shunt curve or inflection, if present, is divided by the peak amplitude of the measured ICG dye concentration (relative to baseline) for the normal indicator-dilution curve. This ratio, expressed in percent, approximates the relative amount of ICG dye that passes through a shunt, if present, to the total amount of blood otherwise flowing through the normal pathway of the heart.

[0013] Another alternative method for the detection of the presence of a right-to-left cardiac shunt uses an injectable indicator dye in combination with a densitometer positioned at the ear of a subject. This alternative method measures the relative concentration of an injected dye as a function of time by measuring the instantaneous absorption of the dye-specific wavelength by transmitting light through the thickness of the ear. The presence of a right-to-left shunt is again determined with this method, apparatus and system by detecting the presence of a premature shunt curve or inflection that may occur in advance of the normal indicator-dilution curve associated with ICG dye following the normal pathway through the lungs. A premature shunt curve or inflection can only occur if the ICG dye arriving in the right atrium follows a shorter pathway between the right atrium and the left atrium than the normal pathway through the lungs. Regarding this shunt detection method, see: 12) Karttunen, V., et.al. "Dye Dilution and Oximetry for Detection of Patent

Foramen Ovale.” *Acta Neurol Scand* 97:231-236 (1998).

[0014] For all four of the above shunt detection methods, it is essential that a maneuver be performed in order to increase the right-to-left pressure gradient between the right and left atria of the heart. Normally, the localized
5 blood pressure within the left atrium is higher than the right atrium. By way of example, during normal activities that do not involve any provocations such as exertion, straining or coughing, the presence of a right-to-left shunt will result in blood flow from the left atrium of the heart to the right atrium of the heart and, accordingly, pose no risk of embolic ischemia since there is no blood
10 flow directly from the right atrium to the left atrium across the atrial septum. However, during activities such as lifting, straining during defecation, physical sports, coughing and scuba diving, the pressure in the right atrium can briefly become larger than the pressure in the left atrium, thereby allowing a portion of the venous blood flowing through the right atrium to briefly flow directly from
15 the right atrium to the left atrium, thereby circumventing the filtering benefit provided by the lungs.

[0015] Under the conditions of such provocations, any embolus or emboli (viz., tiny blood thrombus or thrombi) in the right atrium during the period of a positive right-to-left atrial pressure gradient can be transported directly to the
20 left atrium. Once in the left atrium, said embolus or emboli can follow any of the normal arterial circulatory pathways which include pathways leading to the brain or the coronary arteries of the heart. Those pathways allowing any embolus or emboli to reach the brain or heart can lead to stroke or heart attack, respectively.

[0016] Several types of maneuvers have been reported that can create the
25 required right-to-left pressure gradient to purposely induce the flow of an injected indicator or contrast agent through a right-to-left shunt, if present. Alternative maneuvers of this type include the Valsalva maneuver and coughing. The most widely used type of Valsalva maneuver is a breathing
30 procedure involving the following three-steps: (1) inspiration (i.e., deep breath) to fill the lungs with air, (2) generation of exhalation pressure to a predetermined pressure level of about 40 mm Hg into a closed mouthpiece

(usually incorporating a pressure sensing device) for a minimum period of five seconds; and (3) abrupt release of exhalation pressure followed by normal breathing.

[0017] Published clinical studies involving humans have demonstrated that a Valsalva maneuver performed according to the above three steps provides the most consistent method for inducing the right-to-left pressure gradient required to induce a temporary blood flow through any right-to-left shunt (e.g., PFO) that may be present in the heart, so as to thereby reveal the presence of said right-to-left shunt by any of the aforementioned detection methods. These published clinical studies have also confirmed that the right-to-left pressure gradient required to induce blood flow across a shunt (if present) (a) only begins upon the release or end of the Valsalva maneuver and (b) only persists for two or three heart beats or about two to three seconds following the Valsalva maneuver release. Consequently, it is critically important that the release or end of the exerted exhalation pressure occurs at the precise time period when the indicator dye or contrast agent arrives in the right atrium of the heart since the right-to-left pressure gradient persists for only two to three seconds beyond the release of the Valsalva maneuver exhalation pressure. Further background on maneuvers including Valsalva maneuvers and coughing maneuvers is found in the following articles:

- 13) Pflieger, S. et. al. "Haemodynamic Quantification of Different Provocation Manoeuvres by Simultaneous Measurement of Right and Left Atrial Pressure: Implications for the Echocardiographic Detection of Persistent Foramen Ovale." *Eur J Echocardiography* 2: 88–93 (2001).
- 14) Dubourg O, Bourdarias JP, Farcot JC et al. "Contrast echocardiographic visualization of cough-induced right to left atrial shunt through a patent foramen ovale." *J Am Coll Cardiol* 4: 587–594 (1984).
- 15) Droste DW, Kriete JU, Stypmann J et. al. "Contrast Transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of different procedures and different contrast agents." *Stroke* 30: 1827–1832 (1999).

[0018] In addition to the critical timing of the release of the Valsalva maneuver exhalation pressure that is coincident with the time when an

injected indicator dye agent arrives in the right atrium, it is also important to account for the differences in transit time between the site of injection (e.g., antecubital vein fossa in the arm) and the right atrium. This transit time is critical since the indicator dye or contrast agent needs to arrive at right atrium during the brief two to three second period that the right-to-left pressure gradient exists in order to cross directly into the left atrium during that brief period.

[0019] A further complication confronting methods employing indicator dye based shunt detection methods is the variability in said transit time due to differences in the venous volume in the pathway between the antecubital vein and the right atrium associated with subjects of varying size. That is, even if the indicator dye and a flushing solution is injected at a nominally constant rate, the transit time between the antecubital vein and the right atrium can vary by as much as two seconds due to vascular differences between patients. Therefore, in order to compensate for known transit time differences, it is advantageous to inject the indicator dye at two or more different time intervals (i.e., the time interval from the start of indicator injection and time of Valsalva maneuver release) in order that at least one of several selected time intervals will be appropriate to ensure that the indicator dye arrives in the right atrium during the brief period when the required right-to-left pressure gradient exists between the right and left atria.

[0020] If the indicator dye arrives too early relative to the release of the Valsalva maneuver exhalation pressure and creation of the essential right-to-left pressure gradient, then all of the dye will proceed along the normal pathway through the lungs and into the left atrium even if a right-to-left shunt is present. As a consequence, a false negative shunt test result may be returned and any existing right-to-left shunt may not be detected. Likewise, if the indicator dye arrives too late relative to the release of the Valsalva maneuver exhalation pressure, the essential right-to-left pressure gradient will have ended. Again, a false negative shunt test result may be returned.

[0021] As discussed above, the ability to detect the presence of a right-to-left shunt in the heart depends on performing a maneuver of adequate

pressure intensity (viz., exhalation pressure of at least 40 mm Hg), adequate duration (viz., exhalation exertion for at least 5 seconds) and precise timing with regard to the injection of the indicator dye or contrast agent.

[0022] One known system and method for measuring exhalation pressure for the purpose of determining abdominal pressure surrounding the bladder is disclosed by de Menezes in Published U.S. Patent Application No. US2010/0234758. The system and method includes a pressure monitor with display, tubing extending from the pressure monitor to a mouthpiece and a mouthpiece. The subject exhales into the mouthpiece and the exhalation pressure level is displayed.

[0023] Another known method currently used in the conduct of Valsalva maneuvers include attaching a length of tubing to a pressure gauge or mercury manometer. The patient exhales into the tube and the exhalation pressure is dynamically displayed.

[0024] Both of the above-described methods allow the exhalation pressure to be dynamically measured. As stated above, it is essential that the pressure-producing maneuver be adequate to create a positive right-to-left atrial pressure gradient that is sufficient to induce blood flow directly from the right atrium to the left atrium (in the event a right-to-left cardiac shunt is present). In addition, it is also essential that the indicator dye or contrast agent (i.e., "indicator") arrives in the right atrium during the brief 2 to 3 second period when the positive right-to-left pressure gradient persists so that indicator may traverse the atrial wall and reveal the presence of a right-to-left shunt.

[0025] The short time period during which the indicator dye must arrive in the right atrium is further complicated by the fact that the transit time for dye travel from the injection site (e.g., the antecubital vein at the elbow or the arm) to the right atrium depends on a number of patient specific factors. These factors include at least (a) the average lumen diameter, vein length and volume of the venous pathway between the right atrium and the injection site, and (b) the cardiac output of the patient.

[0026] To ensure that the indicator dye arrives in the right atrium in the

precise window of time when the required right-to-left pressure gradient persists and to accommodate the expected, but unknown, differences in the transit time between the injection site and the right atrium, at least two tests should be performed using transit time assumptions that bracket the expected range of shortest to longest travel times from the injection site to the right atrium. By way of example, anatomical and clinical studies performed by the applicant have confirmed that two time intervals should be used between the time when the indicator dye is injected and the patient releases (i.e., ends) the Valsalva maneuver. These two time intervals have been empirically determined to be about 1.6 and 2.6 seconds.

[0027] However, clinical studies by the applicant involving over 70 patients have confirmed that the patient is not capable of consistently releasing (i.e., ending) the Valsalva maneuver precisely at a specified time interval (e.g., 1.6 and 2.6 seconds) after the time of the start of injection of the indicator dye. The inability of patients to end the Valsalva maneuver at the precise moment commanded using both visual and audible cues is due to the patient's natural response time and level of concentration during the test. This inability of the patient, for the reasons cited above, has been observed to result in variations in actual time intervals as long as 3.0 seconds beyond the intended time interval of 1.6 or 2.6 seconds. Since the response time of the patients is highly variable, no correction can be effectively applied to compensate for the natural delay associated with response to audible or visual cues.

[0028] There is, therefore, the need for a method, apparatus and system to precisely control the time interval between the detected start of indicator dye injection and the release (i.e., end) of the Valsalva maneuver when testing a patient for a right-to-left shunt as described above. There is also a need to ensure that a patient performing a Valsalva maneuver creates the required pressure using their diaphragm and not their cheek muscles, as it is known that the creation of pressure using only the cheek muscles will not create the hemodynamic conditions necessary to effect a right-to left pressure gradient between the right and left atria of the heart. There is further a need for a Valsalva mouthpiece component that can be manufactured at sufficiently low

cost to enable its single and disposable use - thereby avoiding cross-contamination and pathogen transfer between patients. All of these needs are met by embodiments of the invention.

5

SUMMARY

[0029] The present invention is directed, in part, to a method, apparatus and system to precisely control the time interval between the detected start of indicator dye injection and the release (i.e., end) of a Valsalva maneuver, both of which are performed during a right-to-left shunt detection test. To this end,
10 a mouthpiece assembly is provided that comprises an ergonomic tube for insertion into the mouth, a tubular body that contains a movable shuttle that alternately isolates and exposes vent holes, an extension tube that provides hydraulic communication between the mouthpiece tubular body and a quick-disconnect fitment to enable removable attachment of the extension tubing to
15 a mating fitment at the front panel of a controller.

[0030] The tubular body of the mouthpiece assembly may include baffle plates to direct the exhaled air away from the face of the patient when the vents are exposed at the end of the Valsalva maneuver and air is rapidly expelled from the patient's lungs. The movable shuttle component may
20 include a pair of O-rings in combination with a biocompatible lubricant on the inner walls of the tubular body to minimize the static and dynamic friction and enable the movement of the shuttle when a negative pressure (i.e., vacuum) or positive pressure is applied by a solenoid-driven vacuum/pressurization assembly.

[0031] A solenoid-driven vacuum/pressurization assembly is provided and comprises a vacuum/pressurization body that contains a movable piston, a compression spring to return the piston to its starting position after de-energizing the solenoid, an electronically actuated solenoid, a pull rod connected between the solenoid plunger and the piston and tube support
25 members at either end of the tubular vacuum/pressurization body to enable mounting. A pressure sensor is further provided to continuously measure the exhalation pressure exerted by a patient during performance of the Valsalva maneuver.
30

[0032] The shuttle within the tubular body of the mouthpiece assembly incorporates a small diameter hole that provides (a) a sufficiently large flow factor to enable pressure equalization and dynamic exhalation pressure measurement and (b) a sufficiently small flow factor to enable negative pressures (i.e., vacuum) or positive pressures (i.e., pressurization) rapidly created in the solenoid-driven vacuum/pressurization assembly to induce rapid movement of the shuttle within the mouthpiece assembly from a “vents closed” position during the period of the Valsalva maneuver to a “vents open” position at the moment of intended Valsalva maneuver pressure release.

[0033] A microprocessor of the controller receives an input via an analog/digital converter from an optical sensor that detects the start of injection of an optically opaque indicator dye, e.g., ICG dye, which is a step of the right-to-left shunt detection test. The microprocessor starts a clock and when the elapsed time is equal to a specified time interval (e.g., 1.60 or 2.60 seconds), a command is issued to a digital/analog converter to effect the actuation of a solenoid (e.g., a pull-type solenoid). The actuation of the solenoid causes the piston of the solenoid-driven vacuum/pressurization assembly to quickly retract, thereby rapidly creating a partial vacuum within the mouthpiece assembly. The partial vacuum created within the mouthpiece assembly causes the shuttle to rapidly retract from the “vents closed” proximal position to the “vents open” distal position within the tubular body of the mouthpiece assembly.

[0034] As a consequence, within a very brief period from the actuation of the solenoid valve, the opening of the vents causes a rapid release of the pressure resistance produced by the mouthpiece assembly. This forces the patient to rapidly exhale, thereby releasing (ending) the Valsalva maneuver at the desired time.

[0035] In order to accommodate the variability in the transit time between the site of indicator dye injection and the right atrium, embodiments of the present invention employs the use of two sequential tests at two different time intervals (e.g., 1.60 and 2.60 seconds). Accordingly, at the end of the first test (e.g., time interval of 1.60 seconds) and within a brief period after the

mouthpiece assembly vents are opened (e.g., 5 seconds), the solenoid is de-energized and a compression spring forces the piston of the vacuum/pressurization device to rapidly return to its original position. This rapid return to the piston's original position re-pressurizes the mouthpiece assembly. As a consequence, the shuttle within the mouthpiece assembly rapidly returns to its original position, which corresponds to the vents being closed. At this stage, the mouthpiece assembly is ready for the second test procedure, viz., a test procedure at the second of the two selected time intervals (e.g., 2.6 seconds).

10 **[0036]** Embodiments of the present invention are further directed to a method of manufacture and assembly of a Valsalva maneuver mouthpiece assembly that may be cost-effectively provided in sterile condition for a single test session by a patient and then discarded. The single use of the mouthpiece assembly is preferred due to the necessary movable shuttle component within the mouthpiece assembly, the benefit to providing a lubricant on the interior of the tubular body of the mouthpiece assembly and the inaccessibility of the interior portions of the mouthpiece assembly to enable essential cleaning and sterilization of the mouthpiece assembly between uses.

20 **[0037]** Other aspects and features of the invention will become apparent to those skilled in the art upon review of the following detailed description of exemplary embodiments along with the accompanying drawing figures.

BRIEF DESCRIPTION OF THE DRAWINGS

25 **[0038]** In addition to the features mentioned above, other aspects of the invention will be readily apparent from the following descriptions of the drawings and exemplary embodiments, wherein like reference numerals across the several views refer to identical or equivalent features, and wherein:

[0039] FIG. 1 is a partially sectioned and cut away perspective view, of an exemplary embodiment of a system showing a monitor, catheter set and mouthpiece assembly for performance of a Valsalva maneuver and controlled release of the Valsalva maneuver by a patient being tested for the presence of a cardiac shunt using an indicator dye method;

- [0040] FIG. 2 is an exploded view of mouthpiece assembly of FIG. 1;
- [0041] FIG. 3 is a cross-sectional view of the mouthpiece assembly showing a shuttle in initial proximal position in preparation for the start of a Valsalva maneuver;
- 5 [0042] FIG. 4 is a cross-sectional view of the mouthpiece assembly showing the shuttle in a most distal position at the release (end) of a Valsalva maneuver;
- [0043] FIG. 5A is a side view of a shuttle component used in a mouthpiece assembly;
- 10 [0044] FIG. 5B is a cross-sectional view of a shuttle component used in a mouthpiece assembly;
- [0045] FIG. 5C is a perspective view of a shuttle component used in a mouthpiece assembly, showing a proximal end of the shuttle;
- [0046] FIG. 5D is a perspective view of a shuttle component used in a mouthpiece assembly, showing a distal end of the shuttle;
- 15 [0047] FIG. 6 is a perspective view, partly in section, of an exemplary embodiment of a vacuum/pressurization subassembly;
- [0048] FIG. 7 is an exploded view of vacuum/pressurization subassembly of FIG. 6;
- 20 [0049] FIG. 8A is a cross-sectional view of an exemplary piston used in a vacuum/pressurization subassembly;
- [0050] FIG. 8B is a perspective view of an exemplary piston used in a vacuum/pressurization subassembly;
- [0051] FIG. 9 is a perspective view of an exemplary vacuum/pressurization tube used in a vacuum/pressurization subassembly;
- 25 [0052] FIG. 10A is a cross-sectional view of an exemplary first tube support end plate used in a vacuum/pressurization subassembly;
- [0053] FIG. 10B is a perspective view of an exemplary first tube support end plate used in vacuum/pressurization subassembly;
- 30 [0054] FIG. 11A is a cross-sectional view of an exemplary second tube support end plate used in vacuum/pressurization subassembly;

[0055] FIG. 11B is a perspective view of an exemplary second tube support end plate used in vacuum/ pressurization subassembly;

[0056] FIG. 12A-12E combine as labeled thereon to show a flow chart of a procedure associated with an exemplary method of the invention for performing a Valsalva maneuver as part of a indicator dye based procedure for the detection of a right-to-left shunt;

[0057] FIG. 13A-13C combine as labeled thereon to show a flow chart of a procedure associated with an exemplary embodiment of the invention for performing a Valsalva maneuver; and

[0058] FIG. 14 is a partially sectioned and cut away perspective view of an exemplary system showing a monitor and mouthpiece assembly for performance of a Valsalva maneuver and for the controlled release of a Valsalva maneuver by a patient being tested for the presence of a cardiac shunt, in general.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENT(S)

[0059] Referring to FIG. 1, an illustrative embodiment of the present invention is described showing the principal components of a system for controlling the performance of Valsalva maneuvers. As seen in FIG. 1, patient **8** grasps mouthpiece assembly **20** with hand **6** and positions ergonomic tube **22** in his or her mouth **4**. By way of example as seen in FIG. 1, patient **8** is performing a Valsalva maneuver as one essential step in the detection of a right-to-left cardiac shunt based on an indicator dye method.

[0060] An exemplary embodiment of a monitor **10** for the detection of a right-to-left cardiac shunt, as seen in FIG. 1, includes a catheter set **40** for injection of an indicator dye **45** into the blood stream of patient **8** at the antecubital vein **5** of the arm **3** of patient **8**. Injection of indicator dye **45** may be achieved by depressing a plunger of a dye syringe **47** containing indicator dye **45** and attached to flexible catheter **42**. By depressing plunger of dye syringe **47**, indicator dye **45** (e.g., liquid volume of 1 to 10 ml) is forced to flow via catheter **42** past a flow sensor **44** to a venous access needle **48** and into the antecubital vein **5** in arm **3** of patient **8**.

[0061] As the indicator dye passes through flow sensor **44**, it is detected

using, by way of example, a measured change in the level of light transmission through the flowing liquid for the case of an indicator dye **45** that has a lower transmission of light photons than water or isotonic saline solution residing in catheter **42** prior to the start of injection of indicator dye **45**.

5 Alternatively, the indicator dye **45** that passes through flow sensor **44** may be detected by measuring a temperature decrease within a pre-heated flow sensor **44** as injected liquid induces heat removal from the heated flow sensor and an associated decrease in its measurable temperature.

[0062] Still referring to FIG. 1, immediately after indicator dye **45** has been
10 injected, a second injection of isotonic saline may be injected via catheter **42** using a flush syringe **41** positioned at the proximal end of catheter set **40** to deliver any residual indicator dye **45** residing in catheter **42** into the blood stream of patient **8**. The detection of indicator dye **45** by flow sensor **44** is communicated to a controller **60** of monitor **10** via a cable **46** that is
15 removably connected to monitor **10** at a connector **50**, which is inserted into a receptacle **51** connected to controller **60** via a cable **108**.

[0063] Still referring to FIG. 1, a cut away view of an enclosure **12** of exemplary monitor **10** reveals controller **60**, a solenoid-driven vacuum-pressurization assembly **80** and an internal tubing assembly **100**. In one
20 exemplary embodiment of the solenoid-driven vacuum-pressurization assembly **80**, a solenoid **84** (e.g., a Pull-Type Tubular Solenoid, Ledex 150, from Johnson Controls, Vandalia, Ohio) is securely attached to a platform **82** and the plunger of solenoid **84** is mechanically coupled to a piston **94** in vacuum/pressurization subassembly **87** with a solenoid pull rod **86**.

25 [0064] By way of example, prior to energizing solenoid **84**, piston **94** is initially maintained against the inner face of a second tube support end plate **92** at the distal position within a vacuum/pressurization tube **88** due to the force applied by a compression spring **120**. When solenoid **84** is energized by a power source (not shown) through controller **60** and an associated cable
30 **62**, the plunger within solenoid **84** rapidly retracts, typically within a period of less than 0.1 seconds. Upon the rapid retraction of the plunger (not shown) in solenoid **84**, piston **94** rapidly moves to a fully retracted position while

contracting compression spring **120** based on the allowable stroke length of the plunger in solenoid **84** and as a result of the pull force applied through solenoid pull rod **86**.

[0065] The rapid retraction of piston **94** creates a negative pressure within the enclosed air space comprising vacuum/pressurization tube **88**, the interior volume of an inner tubing assembly **100**, the interior volume of associated extension tubing **36**, and the internal volume at distal end of mouthpiece assembly **20**. The negative pressure created by rapid withdrawal of piston **94** when solenoid **84** is energized causes a shuttle (not shown) within mouthpiece assembly **20** to be retracted from its starting proximal position to a distal position within a tubular body (not shown), thereby exposing a multiplicity of vent holes **26**. The processes involved and the effect of the alternating negative pressure and positive pressure created by operation of the solenoid-driven vacuum/pressurization assembly **80** are described in greater detail in the discussion that follows.

[0066] Still referring to FIG. 1, the rapid retraction of the shuttle (not shown) within the mouthpiece assembly **20** results in a low flow resistance pathway between the ergonomic tube **22** in mouth **4** of patient **8** and the surrounding atmosphere external to the mouthpiece assembly **20**. Said low flow resistance pathway causes patient **8** to rapidly exhaust all of the compressed air in the lungs of patient **8**, thereby ending the Valsalva maneuver. Within a time period (e.g., 5 seconds) sufficient to ensure both (a) complete expiration by the patient and (b) sufficient ingress of air into the enclosed air space comprising vacuum/pressurization tube **88**, interior volume of inner tubing assembly **100**, interior volume of extension tubing **36** via pressure equalization conduit **18**.

[0067] The latter ingress of air provides for the return of the air pressure within this air space to approximately atmospheric pressure. Following this ingress of air over a brief period (e.g., 5 seconds), solenoid **84** within solenoid-driven vacuum/pressurization assembly **80** is de-energized. Upon de-energizing solenoid **84**, the magnitude of the pull force previously applied by solenoid **84** on piston **94** through solenoid pull rod **86** becomes zero. The

retraction of piston **94** also induces contraction of compression spring **120**.

[0068] When the pull force exerted by solenoid **84** rapidly decreases to zero as solenoid **84** is de-energized, the energy stored in compression spring **120**, while in its contracted state, forces piston **94** to rapidly return to its most distal position adjacent to second tube support end plate **92**. The rapid return of piston **94** to its distal position, under the force applied by compression spring **120**, creates a positive pressure within the enclosed air space comprising vacuum/pressurization tube **88**, interior volume of inner tubing assembly **100**, interior volume of extension tubing **36** and internal volume at distal end of mouthpiece assembly **20**. The positive pressure created by the rapid displacement of piston **94** to its most distal position when solenoid **84** is de-energized causes the shuttle (not shown) within mouthpiece assembly **20** to be displaced from its distal position to a proximal position within tubular body (not shown), thereby once again isolating the multiplicity of vent holes **26** in mouthpiece assembly **20** from the interior of the ergonomic tube **22** in preparation for the performance of a subsequent Valsalva maneuver.

[0069] In the above discussion of the cyclic operation of solenoid **84** in conjunction with FIG. 1, a power supply (not shown) within controller **60** applies power to solenoid **84** through power cable **62** based on a predetermined time interval, T_{in} . By way of example, said time interval, T_{in} may be electronically selected in monitor **10** at a time interval control unit **72** using manually actuatable switches **74a** and **74b** to effect increasing and decreasing time increments, respectively. The process of selecting the time interval, T_{in} may be accomplished with the time interval display **76** as seen in FIG. 1. The selected time interval, T_{in} is communicated to controller **60** via a cable **78**. In an exemplary embodiment, the selected time interval, T_{in} is combined in controller **60** with the detected start of the injection of indicator dye **45** by flow sensor **44** to determine when solenoid **84** is to be energized, i.e., when the Valsalva maneuver is to end.

[0070] Another exemplary embodiment of the invention is the provision of a visual display of the exhalation pressure exerted by patient **8** during the Valsalva maneuver. As discussed in the Background of the Invention, prior

clinical studies have confirmed that the required level of exhalation pressure exerted by a patient during a Valsalva maneuver is at least about 40 mm Hg in order to induce a right-to-left atrial pressure gradient sufficient to reveal the presence of a right-to-left shunt (e.g., a PFO). In addition, prior clinical studies have confirmed that the exertion of an exhalation pressure of at least about 40 mm Hg by the patient during a Valsalva maneuver needs to be at least 5 seconds in duration. As seen in FIG. 1, the Valsalva pressure level **123** exerted by patient **8** is visually displayed, by way of example, in the form of a real-time graph as seen by patient **8** at Valsalva screen display **124** of monitor **10**. In the example Valsalva pressure screen display **124** seen in FIG. 1, a horizontal line representing the minimum required Valsalva pressure level **125** provides visual feedback to patient **8** to guide their exertion level during the Valsalva maneuver.

[0071] In actual practice, monitor **10** is preferably positioned such that the Valsalva pressure screen display **124** is in the direct line-of-sight of patient **8**. However, to facilitate the illustration of all of the components of monitor **10**, mouthpiece assembly **20** and catheter set **40** in FIG. 1, the Valsalva pressure screen display **124** is not in the line-of-sight of patient **8** but said line-of-site is represented by sighting path **127**.

[0072] In the example graph of exhalation pressure as a function of time seen in Valsalva pressure screen display **124** of FIG. 1, the Valsalva maneuver has been completed and the Valsalva release **129** is seen at the end of the period of exhalation exertion corresponding to the moment when the shuttle (not shown) in mouthpiece assembly **20** is rapidly translated to said distal position by the negative pressure rapidly induced by solenoid-driven vacuum/pressurization unit **80**, thereby exposing one or a multiplicity of vents **26** and, thereby, forcing complete expiration of the air within the lungs of patient **8**. This complete expiration of the air within the lungs of patient **8** represents the release or end of the Valsalva maneuver.

[0073] Referring now to FIG. 2, an exploded view of one exemplary embodiment of mouthpiece assembly **20** is shown in greater detail, and can be seen to comprise an ergonomic tube **22**, tubular body **24**, shuttle **28** and

end cap **25**. A compliant foam rubber sleeve (not shown) may optionally be positioned over tubular body **24** and end cap **25** to facilitate grasping of mouthpiece assembly **20** in either the left or right hand **6** of a patient as illustrated by patient **8** in FIG. 1. Still referring to FIG. 2, an exemplary embodiment of a subassembly **19** may be injection or otherwise molded using a suitable biocompatible plastic offering a relatively low coefficient of friction relative to shuttle O-rings **14a** and **14b**, and also offering good dimensional control through the injection molding process. By way of example, one usable injection moldable plastic for subassembly **19** is acrylonitrile butadiene styrene (ABS) or blends containing ABS, such as those manufactured by Bayer AG (distributed through Bayer USA, Pittsburgh, PA).

[0074] The subassembly **19** of this embodiment comprises ergonomic tube **22**, tubular body **24**, one or more vent holes **26**, first and second baffle plates **27a** and **27b**, radial ribs **23a-23d** and a leak hole **29**. The circular bore of tubular body **24** is accurately dimensioned to receive shuttle **28**, including first and second shuttle O-rings **14a** and **14b**. Embodiments of shuttle **28** may be injection molded using a suitable plastic offering good dimensional control through the injection molding process.

[0075] Radial ribs **23** in combination with first and second baffle plates **27a** and **27b** prevent the hand **6** of a patient from grasping and covering over one or more vent holes **26** and, thereby, causing interference with the air flow exiting the vents when shuttle **28** is translated to its distal position (i.e., the “vents open” position). As seen in FIG. 2, first and second baffle plates **27a** and **27b** are positioned on subassembly **19** just distal to ergonomic tube **22**. During use, as illustrated in FIG. 1, the ergonomic tube **22** is placed in the mouth **4** of patient **8**. Upon the forward translation of the shuttle **28** to its most distal position and exposure of one or more vents **26**, said baffle plates **27a** and **27b** serve to direct the rapidly expelled air (issuing from the lungs of patient **8**) away from the face and eyes of patient **8**.

[0076] Still referring to FIG. 2, the interior circular bore of tubular body **24** is dimensioned so that the static friction between shuttle O-rings **14a** and **14b** and interior wall of tubular body **24** is (a) sufficiently large such that exhalation

pressure exerted by patient **8** does not prematurely translate shuttle **28** to a distal position that exposes a portion or all of the one or more vents **26** yet (b) sufficiently small that the negative pressure induced by displacement of the piston in the solenoid-driven vacuum/pressurization assembly creates the force necessary to rapidly translate the shuttle from its starting (proximal) position in which it covers one or more vents **26** to its distal position exposing one or more vents **26**.

[0077] In one exemplary embodiment and still referring to FIG. 2, and end cap **25** is inserted into and adhesively bonded to tubular body **24** to provide a seal to prevent the egress of air during the Valsalva maneuver. This particular end cap **25** also includes a noise-dampening elastomeric washer **30** to absorb and dissipate the impact energy associated with the rapid translation of shuttle **28** to its most distal position, thereby reducing the noise associated with the translation of shuttle **28** to the distal end of tubular body **24**. Also, as seen in the exemplary embodiment shown in FIG. 2, end cap **25** includes a barbed fitment **16** for airtight attachment of the proximal end of flexible extension tube **36** to end cap **25**. The distal end of extension tube **36** is secured to a similar barbed fitment at the proximal end of quick disconnect fitment **38**. Such a quick disconnect fitment is available from Colder Products Company, Minneapolis, MN.

[0078] By way of example with respect to the embodiments shown in FIGS. 1 and 2, said extension tubing **36** is a biocompatible flexible vinyl tubing having an inside diameter of 0.187 inch and length of 48 inches (Cole-Parmer, Vernon Hills, IL). The inside diameter of extension tubing is selected to be (a) large enough to enable sufficient air flow and associated rapid evacuation of air from the distal end of tubular body **24** when piston **94** of solenoid-driven vacuum/pressurization assembly **80** is rapidly withdrawn by energized solenoid **84** and (b) small enough that the interior volume of extension tubing **36**, in combination with the interior volume of interior tubing set **100** and the end of tubular body **24** distal to shuttle **28**, are sufficiently small to enable an adequate negative pressure within combined total interior volume to force translation of shuttle **28** when said solenoid **84** in solenoid-driven

vacuum/pressurization assembly **80** is energized.

[0079] An assembly view of an exemplary embodiment of the mouthpiece assembly **20** is depicted in FIG. **3** and FIG. **4** following the placement of shuttle **28** within tubular body **24** and attachment of end cap **25**. A compliant sleeve **162** (e.g., biocompatible foam rubber) surrounds and is secured to tubular body **24** and end cap **25** to facilitate grasping of mouthpiece assembly by hand **6** of patient **8** as seen in FIGS. **1**, **3** and **4**. Also revealed in FIGS. **3** and **4** is noise dampening elastomeric washer **30** mounted on proximal interior surface of end cap **25**. An exemplary embodiment of end cap **25** may be injection molded using a suitable biocompatible plastic. By way of example, a suitable injection moldable plastic for end cap **25** is acrylonitrile butadiene styrene (ABS) or blends containing ABS, such as those manufactured by Bayer AG (distributed through Bayer USA, Pittsburgh, PA).

[0080] Referring now to FIG. **3**, shuttle **28** is seen in its initial proximal position in preparation for the start of the Valsalva maneuver. In this proximal position, the shuttle **28** remains stationary during the pressure exertion period of the Valsalva maneuver and blocks air flow access to one or more vents **26** so that patient **8** is able to perform Valsalva maneuver by exerting exhalation pressure of about 40 mm Hg from his or her lungs into ergonomic tube **22** and into the essentially closed volume at the end of the tubular body **24**, extension tubing **36** and internal tubing assembly **100**. A small leak hole **29** is located proximal to first shuttle O-ring **14a** to allow a small flow rate of air to escape from mouthpiece assembly **20** during the Valsalva maneuver.

[0081] By way of example and through clinical testing with human subjects, it has been determined that a leak rate of about 20 to 25 cubic centimeters per second under an applied exhalation gauge pressure of 40 mm Hg is (a) large enough to ensure that the exhalation pressure must be exerted by the lungs of patient **8** and not through the use of contraction of distended cheek muscles and (b) small enough to enable an adult to maintain an exhalation pressure of about 40 mm Hg for a period of at least 5 seconds without depleting their natural lung volume capacity. Also, FIG. **3** reveals enlarged entrance hole **17** and pressure equalization channel **18** within shuttle

28, which enables exhalation pressure exerted during the Valsalva maneuver by patient **8** to be dynamically measurable by pressure sensor **110** (see FIG. 1) by virtue of the air column between the mouthpiece assembly **20** and pressure transducer **110**.

5 **[0082]** Referring now to FIG. 4, the shuttle is seen at its most distal position corresponding to the period immediately following the negative pressure induced by the retraction of piston **94** in the solenoid-driven vacuum/pressurization assembly **80** (see also FIG. 1). As seen in FIG. 4, the translation of shuttle **28** to its most distal position exposes one or more vents
10 **26** to the surrounding atmospheric pressure conditions. Immediately following the exposure of the vents and the associated low air flow resistance pathway between ergonomic tube **22** and one or more vents **26**, the exhalation exertion by patient **8** ends with the rapid expiration of all pressurized air within the lungs. The rapid expiration of all pressurized air within the lungs thereby
15 ensures the end of the Valsalva maneuver at the precise time interval, T_{in} selected by the operator at time interval control unit **72**.

[0083] Referring to FIGS. 2, 3 and 4, the shape of the opening of said one or more vents **26** may be of various shape, such as circular, trapezoidal or square. In an exemplary embodiment, the shape of the opening of six vents
20 **26a-26f** may be circular or trapezoidal to minimize the friction between the proximal shuttle O-ring **14a** as it traverses the perimeter edges of vents **26a-26f**. Also, to ensure acceptably low static and dynamic friction to enable translation of the shuttle from its proximal position as seen in FIG. 3 to its distal position as seen in FIG. 4, a biocompatible lubricant (Dow Corning
25 Silicone 360 Lubricant, Midland, MI) is preferably applied (not shown) to the inner smooth walls of tubular body **24** and shuttle O-rings **14a** and **14b**.

[0084] Referring now to FIGS. 5A through 5D, shuttle **28** is seen in a side view, cross-sectional view and perspective views. As can be seen in the side view of FIG. 5A, shuttle **28** includes shuttle O-ring grooves **13a** and **13b**. The
30 cross-sectional view seen in FIG. 5B reveals elastomeric shuttle O-rings **14a** and **14b** positioned in shuttle O-ring grooves **13a** and **13b**. By way of example, shuttle O-rings **14a** and **14b** may be Size No. 20, Buna-N material,

0.864 inch ID x 0.070 inch wide (available Parker Hannifin Corporation, Lexington, Kentucky). As also seen in FIG. 5B, both a larger and smaller hole extend across the full length of shuttle **28**. The larger entrance hole **17** (e.g., 0.18 inch diameter by 0.56" long) provides a low resistance to air flow
5 between the proximal surface of shuttle **28** and the start of the smaller diameter pressure equalization hole **18** as seen in FIG. 5B. The larger entrance hole **17** also minimizes the possibility that any fluid that might be ejected from the mouth **4** of patient **8** results in the occlusion of the pressure equalization channel **18**. An exemplary embodiment of shuttle **28** of the
10 invention includes a pressure equalization channel having a diameter of 0.026 inches and a length of 0.44 inches. Perspective views of shuttle **28** are seen in FIGS. 5C and 5D, revealing an opening of larger entrance hole **17** and pressure equalization channel **18**, respectively.

[0085] An assembly view of the exemplary solenoid-driven vacuum/pressurization assembly **80** is illustrated in FIG. 6, which comprises
15 vacuum/pressurization subassembly **87**, solenoid **84**, solenoid drive rod **86** and platform **82**. Said vacuum/pressurization subassembly **87** seen in FIG. 6 comprises vacuum/pressurization tube **88**, piston **94**, compression spring **120** and first and second tube support endplates **90** and **92**.

[0086] By way of example, an exemplary embodiment of the solenoid-driven vacuum/pressurization assembly **80** employs a Ledex 150 pull-type tubular solenoid (Johnson Controls, Vandalia, Ohio) for solenoid **84**, providing a maximum stroke length of 0.7 inches and a pull-force of about 5 to 7 pounds. Still referring to FIG. 6, compression spring **120** of the exemplary
20 vacuum/pressurization subassembly **87** may be, by way example, a stainless steel spring, having a 1.218 inch OD, a 0.063-inch wire diameter, and an overall free length of 1.75 inches (available from, e.g., Lee Spring, Bristol, CT). Also by way of example, vacuum/pressurization tube **88** may be machined from a plastic having a low coefficient of friction, such as acetal resin (e.g., Delrin, DuPont, Parkersburg, WV), to enable reliable translation of
25 the piston **94** within vacuum/pressurization tube **88** during alternating evacuation and pressurization cycles.

[0087] The inner circular walls of vacuum/pressurization tube **88** are preferably machined and polished to a smooth finish in order to minimize static and dynamic friction between first and second piston O-rings **93a** and **93b** and the inner wall of vacuum/pressurization tube **88** during the cyclic translation of piston **94**. In addition, a lubricant is preferably applied to the inner walls of the vacuum/pressurization tube **88** in order to further minimize static and dynamic friction during the cyclic translation of the piston. By way of example, said lubricant (not shown) may be Super-O-Lube (Parker Hannifin Corporation, Lexington, Kentucky).

[0088] As seen in FIG. 6, first and second tube support end plates **90** and **92** are attached at either end of vacuum/pressurization tube **88** with an airtight sealing adhesive used at the interface between the vacuum/pressurization tube **88** and second tube support end plate **92**. A barbed fitment **91** is attached to the exterior side of second tube support end plate **92** to provide for secure and airtight connection to first tubing member **98**. Tubing member **98** extends to and is secured with an airtight seal to a “T” shaped barbed fitment (not shown) with (a) first remaining branch of the “T” extending to pressure sensor **110** via second tubing member **106** with airtight seals at both ends of tubing member **106** and (b) second remaining branch of the “T” extending to a quick-disconnect front panel receptacle **104** via third tubing member **105** with airtight seals at both ends of tubing member **105** (also refer to FIG. 1). Also seen in FIG. 6 is solenoid pull rod **86** with a movement vector **142** illustrating translation of solenoid pull rod **86** during alternating evacuation and pressurization cycles. The vacuum/pressurization subassembly **87** and solenoid **84** are mounted (e.g., mechanically attached using machine screws and nuts) on platform **82** to maintain and stabilize their relative positions during alternating evacuation and pressurization cycles. Still referring to FIG. 6, a noise dampening elastomeric disk **122** is positioned at the distal end of vacuum/pressurization tube **88** to dissipate the kinetic energy and force associated with the translation of piston **94** by compression spring **120** immediately following de-energizing of solenoid **84**, thereby reducing the noise associated with the return of piston **94** to the distal end of

vacuum/pressurization tube **88**.

[0089] An exploded view of vacuum/pressurization subassembly **87** is seen in FIG. 7 providing addition details of an exemplary embodiment of its construction. Flat-head machine screw **152** extends through piston **94** and is threaded into piston attachment cap **154**. Piston attachment cap **154** is mechanically secured to solenoid pull rod **86** at first drive rod coupling **156a**. Second drive rod coupling **156b** is mechanically secured to plunger (not shown) of solenoid **84**.

[0090] By way example, solenoid pull rod **86** comprises a flexible cable with drive rod couplings **156a** and **156b** secured at either end through mechanical swaging of couplings onto flexible cable. The use of a flexible cable in solenoid pull rod **86** compensates for any misalignment that may exist between the central axis of translation of piston **94** and the central axis of translation of the plunger in solenoid **84**. See for example commercially available Flexible Drive Shaft (Stock Drive Components/Sterling Instrument, New Hyde Park, New York).

[0091] Referring now to FIG. 8A and 8B, piston **94** is shown in a cross-sectional view and perspective view, respectively. As seen in the cross-sectional view of piston **94** in FIG. 8A, piston O-rings **95a** and **95b** (e.g., Buna N, Parker Hannifin Corporation, Lexington, Kentucky) are positioned in piston O-ring grooves **93a**, **93b**. Counter bore **158** in piston **94** receives piston attachment cap **154** at the proximal end of piston **94**. Drilled and counter bored hole **159** receives piston attachment flat head machine screw **152**.

[0092] Three of the components of the exemplary embodiment of the vacuum/pressurization subassembly **87** seen in FIG. 6 are shown in greater detail in FIGS. 9, 10A, 10B, 11A and 11B. By way of example and referring first to FIG. 9, vacuum/pressurization tube **88** is shown along with defining dimensional parameters of a circular cross-section tube machined from a low coefficient of friction material (e.g., Delrin). The inner bore **160** is preferably polished to reduce the static and dynamic friction relative to piston O-rings **95a** and **95b** during the translation of piston **94** during the evacuation and pressurization cycles (see also FIG. 8A).

[0093] First tube support end plate **90** is seen in FIG. **10A** showing circular channel **151** sufficiently large to accommodate passage of solenoid drive rod **86** and its end fitments **156a** and **156b** to effect a linkage between a plunger (not shown) in solenoid **84** and piston **94** (see also FIG. 7). By way of example and referring next to cross-sectional and perspective views seen in FIGS. 10A and 10B, additional vent holes **150** are machined through first tube support end plate **90** to provide a low resistance pathway for air flow into or out of vacuum/pressurization tube **88** during the translation of piston **94** associated with the evacuation and pressurization cycles (see also FIGS. 6 and 7).

[0094] By way of example and referring next to the cross-sectional and perspective views seen in FIG. 11A and 11B, second tube end plate support **92** is covered with noise dampening elastomeric disk **122** to dissipate the kinetic energy of and force applied to piston **94** as it is translated to its most distal position by compression spring **120** following the de-energizing of solenoid **84**. Threaded hole **163** is machined through the full thickness of second tube end plate support **92** to receive the threaded end of vacuum/pressurization barbed fitment **91** (see also FIGS. 6 and 7).

[0095] By way of example, the dimensions of the components of one exemplary embodiment of mouthpiece assembly **20** and solenoid-driven vacuum/pressurization assembly **80** are summarized below, in units of inches, with the identification of these dimensions seen in FIGS. 4, 5B, 6, 8A, 9, 10A and 11A. The dimensions listed below are provided merely for illustration and not limitation, as a wide range of possible dimensions would enable a functioning device as long as the vacuum and pressurization parameters as well as pressure equalization flow parameter required for reliable translation of shuttle **28** are achieved.

TK = 0.05 to 0.20

D1 = 0.98

30 D2 = 0.18

D3 = 0.026

D4 = 1.235

$$D5 = 1.25$$

$$D6 = 1.71$$

$$D7 = 1.229$$

$$L1 = 1.02$$

5 $L2 = 0.44$

$$L3 = 3.00$$

$$L4 = 1.65$$

$$L5 = 1.53$$

$$L6 = 1.00$$

10 $L7 = 2.75$

$$L8 = 0.50$$

$$L9 = 0.50$$

$$L10 = 2.50$$

[0096] A general flow chart of the operation of an exemplary embodiment of the system is collectively represented by FIGS. 12A-12E. These figures are combined as labeled thereon to provide a single flow chart describing the exemplary system and method for the performance of a Valsalva maneuver as one of the steps of a procedure for the detection of a right-to-left cardiac shunt. The specified system for performing a Valsalva maneuver and detection of a cardiac right-to-left shunt can utilize the following protocol without extensive experimentation. The system, apparatus and method for detection of a cardiac right-to-left shunt are also described in PCT application No. PCT/US11/31433 and U.S. Patent Application Serial No. 12/754,888, as mentioned previously.

25 **[0097]** Beginning as represented by symbol **200** and continuing as represented by arrow **202** to block **204**, the controller carries out system initialization with the establishment of default parameters. First Time Interval, TI_1 is selected, procedure count parameter, PFLAG is set to a value of 1 and the elapsed time, t_1 is set to zero. Next, as represented at arrow **206** and block **208**, the program continues where the indicator solution for injection is prepared, for example by mixing a known weight of indicator, e.g., ICG dye, with a predetermined volume of sterile water. A predetermined volume of that

30

mixed indicator is withdrawn into a first syringe. Such a syringe is shown as **45** in FIG. 1.

[0098] The program continues as represented at arrow **210** to block **212**. Block **212** 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 patient. As represented at arrow **214** to block **216** of FIG. 12B, 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. 1. As represented at block **216**, 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.

[0099] Still referring to FIG. 12B, the program continues as represented at arrow **218** to block **220** to provide for placing the vein access catheter in a peripheral vein, preferably in the antecubital vein **5** of one of the arms **3** of the patient **8** as seen in FIG. 1. The flow sensor is also attached at block **220** between the proximal terminus of the extension tubing and the three-way valve as seen at **44** in FIG. 1. The three-way valve is turned off in the direction of the flow sensor.

[00100] One or more indicator sensors **182** are then positioned at a blood vessel site at arrow **222** to block **224**. For example, as seen in FIG. 1, a first indicator sensor **182a** may be positioned at the surface of the scaphoid fossa of the left ear **180a** of patient **8** and a second indicator sensor **182b** (not shown) may be positioned at the surface of the scaphoid fossa of the right ear **180b** (not shown) of patient **8**.

[00101] The program continues as represented at arrow **225** to block **226** to provide for placement of mouthpiece assembly in the hand of the patient and instructs the patient to place the ergonomic tube **22** in his or her mouth **4** as seen at **20** in FIG. 1. Still referring to FIG. 12B, from block **226**, arrow **228**

leads to the "Start of Test " indication at block **230**.

[00102] Arrow **232** reappears in FIG. 12C extending to block **234**, to provide for initialization of the shuttle location in the mouthpiece assembly by activating one evacuation cycle followed by one pressurization cycle to position shuttle in the initial "home" position within the tubular body of the mouthpiece assembly. Next, the program starts measurement as represented at arrow **236** extending to block **242**, wherein instructions are provided to the patient to begin the Valsalva maneuver by exhaling into the ergonomic tube of the mouthpiece assembly, as seen in FIG. 1, to reach and maintain the target pressure level until the monitor terminates the Valsalva maneuver automatically after the specified Time Interval, TI_1 has elapsed.

[00103] Generally, the Valsalva maneuver procedure is accompanied by some form of display on monitor **10**. By way of example, turning momentarily back to FIG. 1, a line graph **123** is provided along with a minimum exhalation pressure level **125**, represented as a solid line, giving the patient the actual real-time measurement of the pressure being exerted by the patient during the Valsalva maneuver. The graph display **124** shows exhalation pressure versus elapsed time. In FIG. 1, the patient's Valsalva exhalation pressure has just been released automatically by the combined operation of the solenoid-driven vacuum/pressurization assembly and mouthpiece assembly seen at release time point **129** in FIG. 1. As seen at display screen **124** of FIG. 1, the Valsalva maneuver was properly ended with the graph **123** displaying that the patient held the proper pressure (with some acceptable variation) during the duration of the Valsalva maneuver.

[00104] Returning to Fig. 12C, as represented at arrow **244** to block **246**, the exhalation pressure created by the patient during the Valsalva maneuver is continuously measured and displayed on the monitor, as explained in connection with FIG. 1, and is compared to the ideal Valsalva curve or required minimum exhalation pressure level. As represented by arrow **248** to block **250**, the exhalation pressure is queried and it is determined whether it falls within a measurable range, for example from 0-4000 analog-to-digital converted (ADC) units. If not, arrow **252** is followed to block **254**, wherein a

system fault is displayed and the test is ended. If the measured exhalation pressure is within an expected range, arrow **256** is followed to block **258**.

[00105] Still referring to FIG. 12C, block **258** poses the query as to whether the exhalation pressure is above or equal to the targeted pressure, for example 35 mm Hg. In the event that it is not, as represented at arrow **260** and block **262**, the operator is alerted with an audible alarm or visual error message to instruct the patient to increase pressure to meet or exceed the target exhalation pressure level. Where the exhalation pressure is appropriate, the program continues as represented at arrow **264**.

[00106] As represented at arrow **264**, extending from the query at block **258** and leading to block **266**, the Time Interval elapsed time clock, t_1 is set to $t_1 = 0$ and begins the countdown (i.e., count up) to the specified Time Interval value, TI_1 .

[00107] Arrow **268** reappears in Fig. **12D** extending to block **270**, which looks to initiating the start of the measurement of the fluorescence signal level associated with the relative concentration of the injected indicator dye including obtaining the baseline signal level data (i.e., measured background signal level prior to the presence of injected indicator dye in the bloodstream as measured at the indicator sensor location) using one or more indicator sensors as seen at **182a** placed on ear **180a** of patient **8**, as seen in FIG. 1.

[00108] As represented at arrow **272** leading to block **274** in FIG. 12D, the monitor issues a visual and/or audible cue to the operator to start the injection of the indicator (e.g., ICG dye) at TI_1 seconds before the specified end of the Valsalva maneuver. The practitioner may be provided with a visual cue via, for example, an illuminated LED light affixed on or near the flow sensor **44** as seen in FIG. 1, so that the cue may be conveyed without difficulty. By way of example, if the selected Time Interval, TI_1 is 2.60 seconds and the programmed Valsalva maneuver duration is 5.00 seconds, then said visual and/or audible cue to the operator is issued 5.00 seconds less 2.60 seconds, which equals 2.4 seconds after the detected start of the Valsalva maneuver at block **266**.

[00109] Still referring to FIG. 12D, the flow sensor **44** seen in FIG. 1 will

detect the flow of indicator. As seen at arrow to query block **278**, the flow sensor will continue to check for the detection of the start of the flow of the indicator. When said flow of indicator is detected, as represented by arrow **282** to block **284**, time clock t_1 is set to zero at the moment the flow sensor
5 detects the start of the injection of indicator and the countdown (i.e., count up) to the specified Time Interval, TI_1 begins. Then, as represented by arrow **286** to query block **288**, monitor continues to check to determine if the elapsed time, t_1 now equals the selected Time Interval, TI_1 .

[00110] Once the elapsed time, t_1 equals the selected Time Interval, TI_1 as
10 seen at arrow **292**, the program continues to block **294** at which time the solenoid **84**, as seen in FIG. 1, is energized, forcing a rapid retraction of the piston **94** in the vacuum/pressurization subassembly **87** and inducing a vacuum level (i.e., negative pressure level) sufficient to rapidly retract the shuttle in the mouthpiece assembly **20**. Upon the retraction of the shuttle, as
15 seen in FIG. 4, one or more vents **26** in the mouthpiece assembly are in low-resistance, air-flow communication with the mouth **4** and lungs of patient **8** as seen in FIGS. 1 and 4, thereby inducing the immediate expiration of air from the lungs of patient **8** and the corresponding end of the Valsalva maneuver. By this process, the Valsalva maneuver is controllably ended at a precise,
20 predetermined time interval after the detected start of indicator injection and does not depend on the response time of patient **8** to any audible and/or visual cues to initiate their own action to end the Valsalva maneuver.

[00111] Still referring to block **294** of FIG. 12D as well as FIG. 1, within a
25 predetermined time after solenoid **84** is energized and vents **26** "open" (e.g., a time period of about 5.0 seconds), the solenoid is de-energized at which time the restraining force holding piston **94** in the retracted position, as seen in FIG. 1, becomes zero. At this moment, the force exerted by compression spring **120** in its contracted state induces the rapid return of piston **94** to its distal starting position. The rapid return of piston **94** to its distal starting
30 position induces a positive pressure in the internal tubing assembly **100** and extension tubing **36**, thereby forcing the shuttle in the mouthpiece assembly **20** to return to its proximal starting ("home") position as seen in FIGS. 1 and 3.

[00112] Referring next to FIG. 12E, arrow **296** reappears, extending to block **298**, which 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 **300** to block **302**, 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 **304** to block **306**, 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, and the test is ended.

[00113] Where that signal is greater than the minimum required signal, then as represented at arrow **308** and block **310**, the peak amplitude signal for each channel with a premature indicator/dilution curve prior to the normal indicator/dilution curve, or the peak amplitude of 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 premature indicator/dilution curve/inflection signal result is occurring, then as represented at arrow **312** to block **314**, the conductance associated with a right-to-left cardiac shunt is calculated. This can be done using a ratio obtained by dividing the shunt curve/inflection signal peak amplitude by 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.

[00114] Next, as represented at arrow **316** to block **318**, an inquiry is made to whether the procedure count index, PFLAG, is now equal to 2. Where PFLAG is equal to 2, then as represented at arrow **328** to symbol **330**, the test is ended. Where the procedure count index, PFLAG is not equal to 2, then as represented at arrow **320**, the procedure count index, PFLAG is set equal to 2 and the second Time Interval, TI_2 is selected. In this regard, it should be noted that this exemplary embodiment of the invention assumes that a complete test for the presence of a right-to-left cardiac shunt requires that two

tests be performed with two different Time Intervals, TI_n (e.g., 2.60 and 1.60 seconds). For this embodiment, the program then continues as represented at arrow **324** to Node A at **326**. The program is now prepared to proceed to the second of two right-to-left shunt test procedures, which begins at block **242** and ends at block **330**. In this regard, Node A **326** reappears in FIG. 12C in conjunction with arrow **240** extending to arrow **236**.

[00115] A general flow chart of the operation of another exemplary embodiment of a system of the invention is described in FIGS. 13A through 13C. These figures are combined as labeled thereon to provide a flow chart describing the system and method for the performance of a Valsalva maneuver. By way of example, this flow chart of the operation of an embodiment of the invention corresponds to the performance of a Valsalva maneuver required for the detection of a right-to-left cardiac shunt using the Transcranial Doppler (TCD) method, Transthoracic Echocardiography (TTE) method, as well as other methods using indicator dyes to detect the presence of a right-to-left cardiac shunt. The apparatus, system and method used for the performance of a Valsalva maneuver according to this embodiment, are seen in FIGS. 2 through 11, 13A through 13C and 14.

[00116] Beginning as represented by symbol **340** and continuing as represented by arrow **342** to block **344**, the monitor **10** carries out system initialization with the establishment of default parameters. Time Interval, TI is selected and the elapsed time t_1 is set to zero. At this step, mouthpiece assembly **20** is connected to monitor **10** using quick-disconnect fitment **50** at distal end of extension tubing **36** as seen in FIG. 14. The program continues, as represented at arrow **346** and block **348**, to provide for placement of mouthpiece assembly in the hand of patient **8** and to instruct patient **8** to place the ergonomic tube **22** in his or her mouth **4** of as seen at **20** in FIG. 14. Still referring to FIG. 13A, from block **348**, arrow **350** leads to the "Start of Test " indication at block **352**.

[00117] Arrow **354** reappears in FIG. 13B extending to block **356**, to provide for the initialization of the shuttle location in the mouthpiece assembly **20** by activating one evacuation cycle followed by one pressurization cycle to

position shuttle in the initial “home” position within the tubular body of the mouthpiece assembly **20**. Next, the program starts measurement as represented at arrow **358** extending to block **360**, wherein instructions are provided to the patient to begin the Valsalva maneuver by exhaling into the ergonomic tube **22** of the mouthpiece assembly **20**, as seen in FIG. 14, to reach and maintain the target pressure level until the monitor terminates the Valsalva maneuver automatically after the specified Time Interval, TI_1 has elapsed.

[00118] Generally, the Valsalva maneuver procedure is accompanied by some form of display on monitor **10**. Turning momentarily to FIG. 14, a line graph **123** is provided along with a minimum exhalation pressure level **125**, represented as a solid line, giving the patient the actual real-time measurement of the pressure being exerted by the patient during the Valsalva maneuver. The graph display **124** shows exhalation pressure versus elapsed time. In FIG. 14, the patient’s Valsalva exhalation pressure has just been released automatically by the combined operation of the solenoid-driven vacuum/pressurization assembly and mouthpiece assembly seen at release time point **129** in FIG. 14. As seen at display screen **124** of FIG. 14, the Valsalva maneuver was properly ended with the graph **123** displaying that the patient held the proper pressure (with some acceptable variation) during the duration of the Valsalva maneuver.

[00119] Returning to Fig. 13B, as represented at arrow **362** to block **364**, the exhalation pressure created by the patient during the Valsalva maneuver is continuously measured and displayed on the monitor, as explained in connection with FIG. 14, and is compared to the ideal Valsalva curve or required minimum exhalation pressure level **125**. As represented by arrow **366** to block **368**, the exhalation pressure is queried and it is determined whether it falls within a measurable range, for example from 0-4000 analog-to-digital converted (ADC) units. If not, arrow **372** is followed to block **374**, wherein a system fault is displayed and the test is ended. If the measured exhalation pressure is within an expected range, arrow **370** is followed to block **376**.

[00120] Still referring to FIG. 13B, block **376** poses the query as to whether the exhalation pressure level is above or equal to the targeted pressure, for example, 35 mm Hg. In the event that it is not, as represented at arrow **378** and block **380**, the operator is alerted with an audible alarm or visual error message to instruct the patient to increase pressure to meet or exceed the target exhalation pressure level. Where the exhalation pressure is appropriate, the program continues as represented at arrow **384**.

[00121] As represented at arrow **384**, extending from the query at block **376** and leading to block **386**, the Time Interval elapsed time clock t_1 is set to $t_1 = 0$ and begins the countdown (i.e., count up) to the specified Time Interval value, TI_1 . By way of example, at a point in time appropriate to the right-to-left cardiac shunt detection method being used and corresponding to the selected Time Interval, TI_1 the operator injects indicator **404** using syringe **402** into the antecubital vein **5** at arm **3** of patient **8** as seen in FIG. 14. Said indicator **404** in this example may be a contrast agent containing a multiplicity of small air bubbles for detection using ultrasound-based methods (see above-listed References 5 through 8) or a dye detectable by a spectrophotometric method such as pulsed dye densitometry (see above-listed Reference 15).

[00122] Arrow **388** reappears in Fig. 13C extending to query block **390**. Then, as represented by query block **390**, monitor continues to check to determine if the elapsed time, t_1 now equals the selected Time Interval, TI_1 . Once the elapsed time, t_1 equals the selected Time Interval, TI_1 as seen at arrow **394**, the program continues to block **396** at which time the solenoid **84**, as seen in FIG. 14, is energized by power supply (not shown) within controller **60**, forcing a rapid retraction of the piston **94** in the vacuum/pressurization subassembly and inducing a vacuum level (i.e., negative pressure level) sufficient to rapidly retract the shuttle in the mouthpiece assembly **20**.

[00123] Upon the retraction of the shuttle, as seen in FIG. 4, one or more vents **26** in the mouthpiece assembly **20** are in low-resistance, air-flow communication with the mouth **4** and lungs of patient **8** as seen in FIGS. 4 and 14, thereby inducing the immediate expiration of air from the lungs of patient **8** and the corresponding end of the Valsalva maneuver. By this

process, the Valsalva maneuver is controllably ended at a precise, predetermined time interval after the detected start of indicator injection and does not depend on the response time of patient **8** to any audible and/or visual cues to initiate their own action to end the Valsalva maneuver.

5 **[00124]** Still referring to block **396** of FIG. 13C as well as FIG. 14, within a predetermined time after solenoid **84** is energized and vents 26 “open” (e.g., a time period of 5.0 seconds), solenoid **84** is de-energized at which time the restraining force holding piston **94** in the retracted position, as seen in FIG. 14, becomes zero. At this moment, the force exerted by compression spring
10 **120** in its contracted state induces a rapid return of piston **94** to its distal starting position. The rapid return of piston **94** to its distal starting position induces a positive pressure in the internal tubing assembly **100** and extension tubing **36**, thereby forcing the shuttle in the mouthpiece assembly **20** to return to its proximal starting (“home”) position as seen in FIGS. 3 and 14. Finally, as
15 represented at arrow **398** to symbol **400**, the test is ended.

[00125] The present application, by way of U.S. Provisional Application No. 61/696,409 to which it claims benefit, herein incorporates by reference the subject matter of U.S. Patent Application Serial Nos. 12/754,888 filed April 6, 2010 and 12/418,866 filed April 6, 2009; U.S. Provisional Application Nos.
20 61/156,723 filed March 2, 2009 and 61/080,724 filed July 15, 2008; and PCT applications PCT/US09/50630 filed July 15, 2009 and PCT/US11/31433 filed April 6, 2011. All citations referred to therein are also expressly incorporated herein by reference.

[00126] All terms not specifically defined herein are considered to be
25 defined according to Dorland’s Medical Dictionary, and if not defined therein according to Webster’s New Twentieth Century Dictionary Unabridged, Second Edition.

[00127] While certain exemplary embodiments of the invention are described in detail above, the scope of the invention is not to be considered
30 limited by such disclosure, and modifications are possible without departing from the spirit of the invention as evidenced by the following claims:

WHAT IS CLAIMED IS:

1. A Valsalva maneuver control device, comprising:
 - a mouthpiece assembly having a first end for insertion into the mouth of a patient and a second end for connection to a vacuum/pressurization assembly;
 - 5 a solenoid-driven vacuum/pressurization assembly connected, by tubing, to the second end of the mouthpiece assembly;
 - a controller for operating the solenoid-driven vacuum/pressurization assembly to either provide pressure resistance against air exhaled into the mouthpiece assembly by the patient or to allow said air to pass therethrough,
 - 10 the controller including a timer; and
 - a monitor having a display for guiding the patient through performance of the Valsalva maneuver;
 - wherein the controller is operative to actuate the vacuum/pressurization assembly to rapidly discontinue the pressure resistance against air exhaled
 - 15 into the mouthpiece assembly by the patient as directed by the timer so as to end the Valsalva maneuver at a desired time.
2. The Valsalva maneuver control device of Claim 1, further comprising:
 - 20 a catheter set and dye syringe for injecting an indicator dye into the blood stream of patient at a peripheral location, a flush syringe in communication with the catheter set for introducing a second injection of isotonic saline, and a flow sensor for detecting the passage of indicator dye, the flow sensor in electronic communication with the controller;
 - 25 wherein the controller is programmed to cue an operator to initiate the dye injection at approximately 2.4 seconds after the beginning of the Valsalva maneuver.
3. The Valsalva maneuver control device of Claim 2, wherein the
- 30 controller is programmed to actuate the vacuum/pressurization assembly to end the Valsalva maneuver at a particular elapsed time after the detection of dye injection, the elapsed time being equal to a specified time interval of 1.60 or 2.60 seconds.

4. The Valsalva maneuver control device of Claim 1, wherein the mouthpiece assembly includes a plurality of vents, and a reciprocating shuttle that is actuatable by the solenoid-driven vacuum/pressurization assembly to
5 selectively cover or uncover the vents so as to either provide pressure resistance against air exhaled into the mouthpiece assembly by the patient or to allow said air to pass therethrough.

5. The Valsalva maneuver control device of Claim 4, wherein activation of
10 the solenoid-driven vacuum/pressurization assembly will produce a vacuum that will displace the shuttle in a manner that uncovers the mouthpiece vent holes, thereby removing the pressure resistance against air exhaled into the mouthpiece assembly so as to cause a rapid exhalation by the patient that will end the Valsalva maneuver.

15 6. The Valsalva maneuver control device of Claim 1, wherein the monitor display graphically indicates whether the patient is creating a sufficient level of exhalation pressure while performing the Valsalva maneuver and issues a warning if the created pressure drops below a threshold pressure level.

20 7. A mouthpiece for use in performing a Valsalva maneuver, comprising:
a mouthpiece blow tube for insertion into the mouth of a patient, and in fluid connection with a tubular body;
vent holes located in the tubular body;
25 a movable shuttle located in the tubular body, the shuttle alternately reciprocatable between a first position that isolates the vent holes, and a second position that exposes the vent holes; and
an extension tube providing fluid communication between the tubular body and a vacuum/pressurization device;
30 wherein, the shuttle is adapted such that the application of vacuum to the tubular body will cause the shuttle to move to the second position, thereby exposing the vent holes and rapidly de-pressurizing the mouthpiece.

8. The mouthpiece of Claim 7, wherein the tubular body includes baffle plates that are designed and located to direct air exhaled by a patient into the mouthpiece away from the face of the patient when the vents are exposed and air is allowed to be rapidly expelled from the patient's lungs.

5

9. The mouthpiece of Claim 7, wherein the shuttle is adapted to remain in its current position when a negative pressure or positive pressure is initially applied to the tubular body, but to move to the alternative position when the negative pressure or positive pressure is reversed.

10

10. The mouthpiece assembly of Claim 7, further comprising a pair of O-rings and a biocompatible lubricant in contact with inner walls of the tubular body to further enable the movement of the shuttle upon application of a negative pressure or positive pressure to the tubular body.

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11. The mouthpiece assembly of Claim 7, further comprising a small diameter hole in the tubular body, the hole providing a sufficiently large flow factor so as to enable pressure equalization and dynamic exhalation pressure measurement, and simultaneously a sufficiently small flow factor to enable negative pressures or positive pressures rapidly created within the tubular body to induce rapid movement of the shuttle from a vents closed position during a Valsalva maneuver to a vents open position at the moment of an intended Valsalva maneuver release.

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12. A Valsalva maneuver control method, comprising:

providing a mouthpiece assembly having a first end for insertion into the mouth of a patient and a second end for connection to a vacuum/pressurization assembly;

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providing a solenoid-driven vacuum/pressurization assembly connected, by tubing, to the second end of the mouthpiece assembly;

providing a controller for operating the solenoid-driven vacuum/pressurization assembly to either provide pressure resistance against air exhaled into the mouthpiece assembly by the patient or to allow said air to pass therethrough, the controller including a timer;

providing a monitor having a display for guiding the patient through performance of the Valsalva maneuver;

initiating the Valsalva maneuver;

using the timer of the controller to determine when to terminate the
5 Valsalva maneuver;

at the determined time of Valsalva maneuver termination, using the controller to actuate the vacuum/pressurization assembly to create a vacuum that rapidly discontinues the pressure resistance against air exhaled into the mouthpiece assembly by the patient, thereby causing a rapid exhalation by
10 the patient and release of the Valsalva maneuver at the desired time.

13. The method of Claim 12, further comprising:

providing a catheter set and dye syringe for injecting an indicator dye into the blood stream of patient at a peripheral location, a flush syringe in
15 communication with the catheter set for introducing a second injection of isotonic saline, and a flow sensor for detecting the passage of indicator dye, the flow sensor in electronic communication with the controller;

injecting dye and, subsequently saline, into the patient via the catheter set;

20 programming the controller to end the Valsalva maneuver at 1.60 or 2.60 seconds after dye injection; and

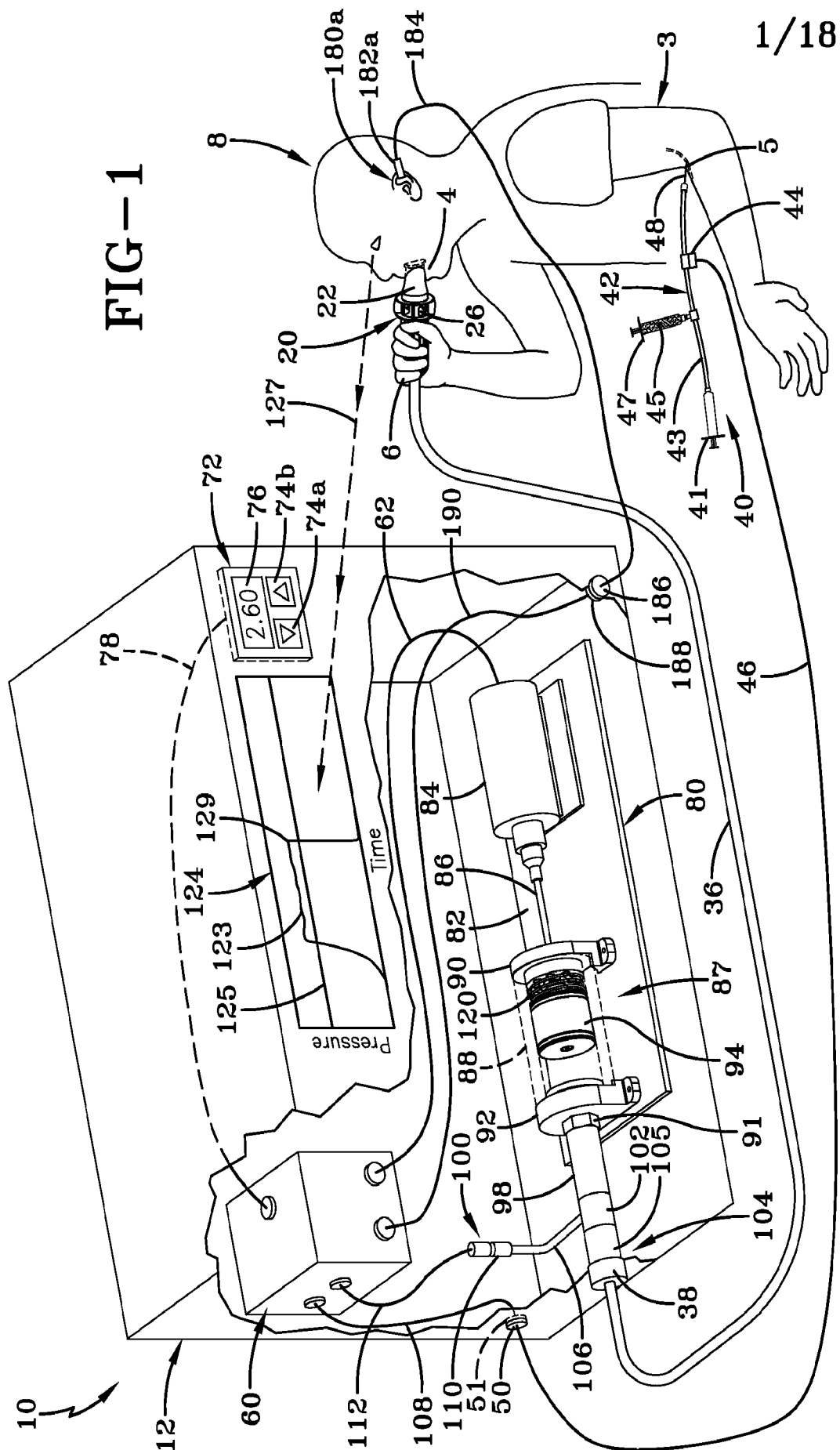
using the Valsalva maneuver control method in conjunction with the dye injection for the purpose of detecting a cardiac shunt in the patient.

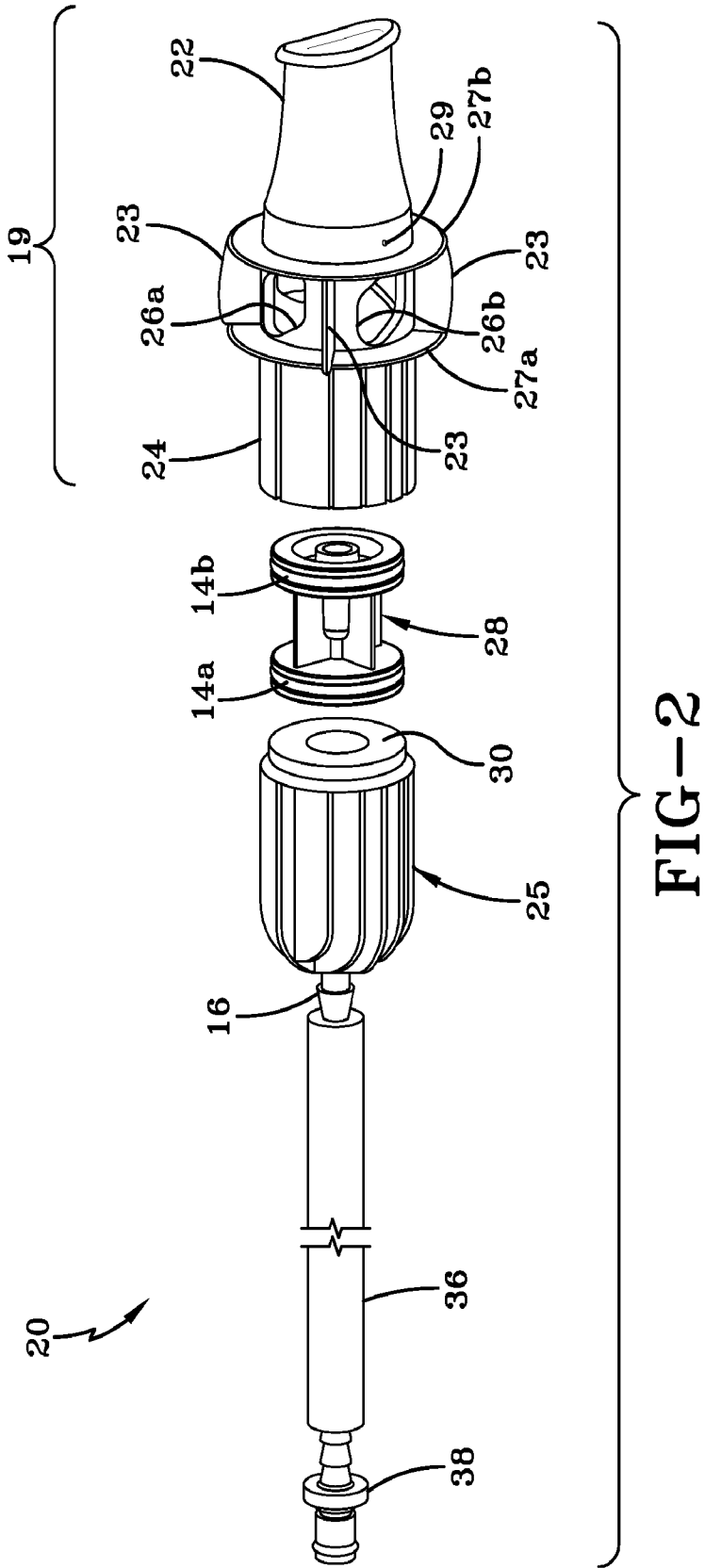
25 14. The method of Claim 12, further comprising providing on the monitor display a graphical indication as to whether the patient is creating a sufficient level of exhalation pressure while performing the Valsalva maneuver, and issuing a warning if the created pressure drops below a threshold pressure level.

30

15. The method of Claim 12, further comprising providing a controlled leak in the mouthpiece assembly that forces a patient to create the required

Valsalva maneuver pressure using their diaphragm and not their cheek muscles.





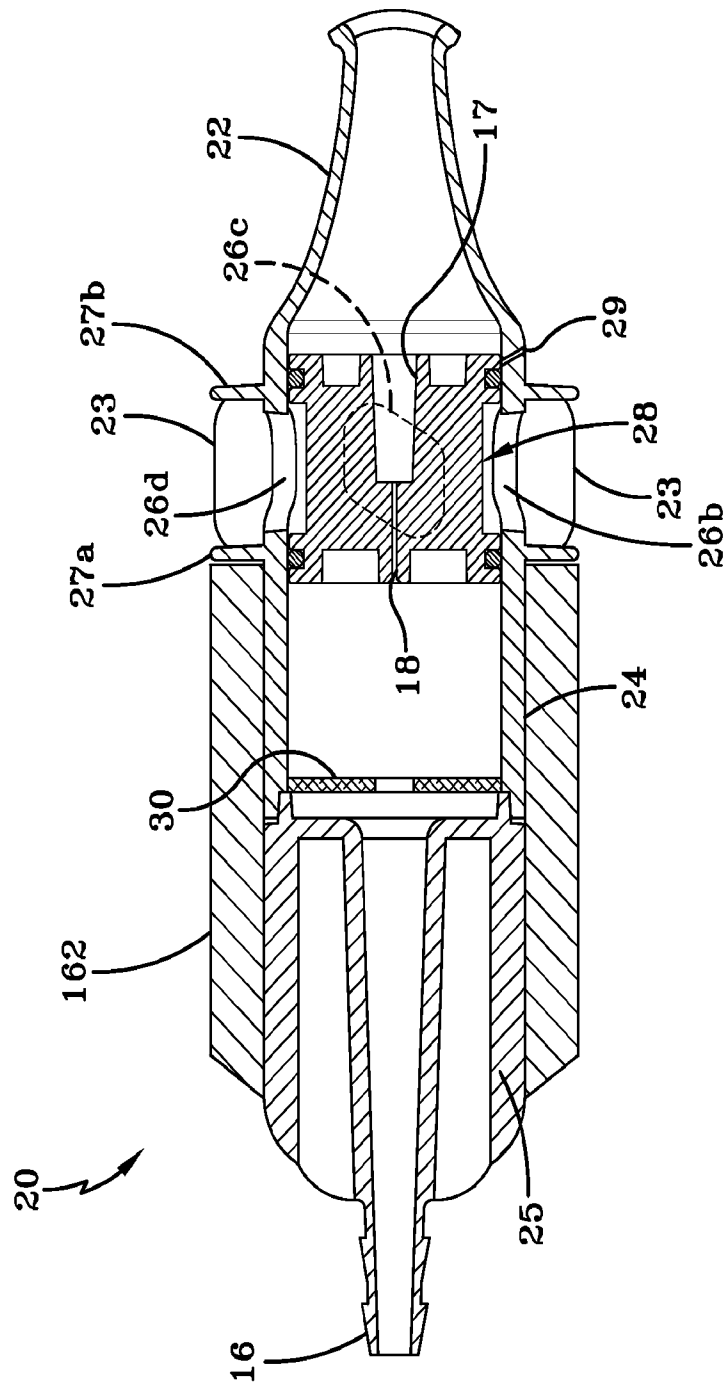


FIG-3

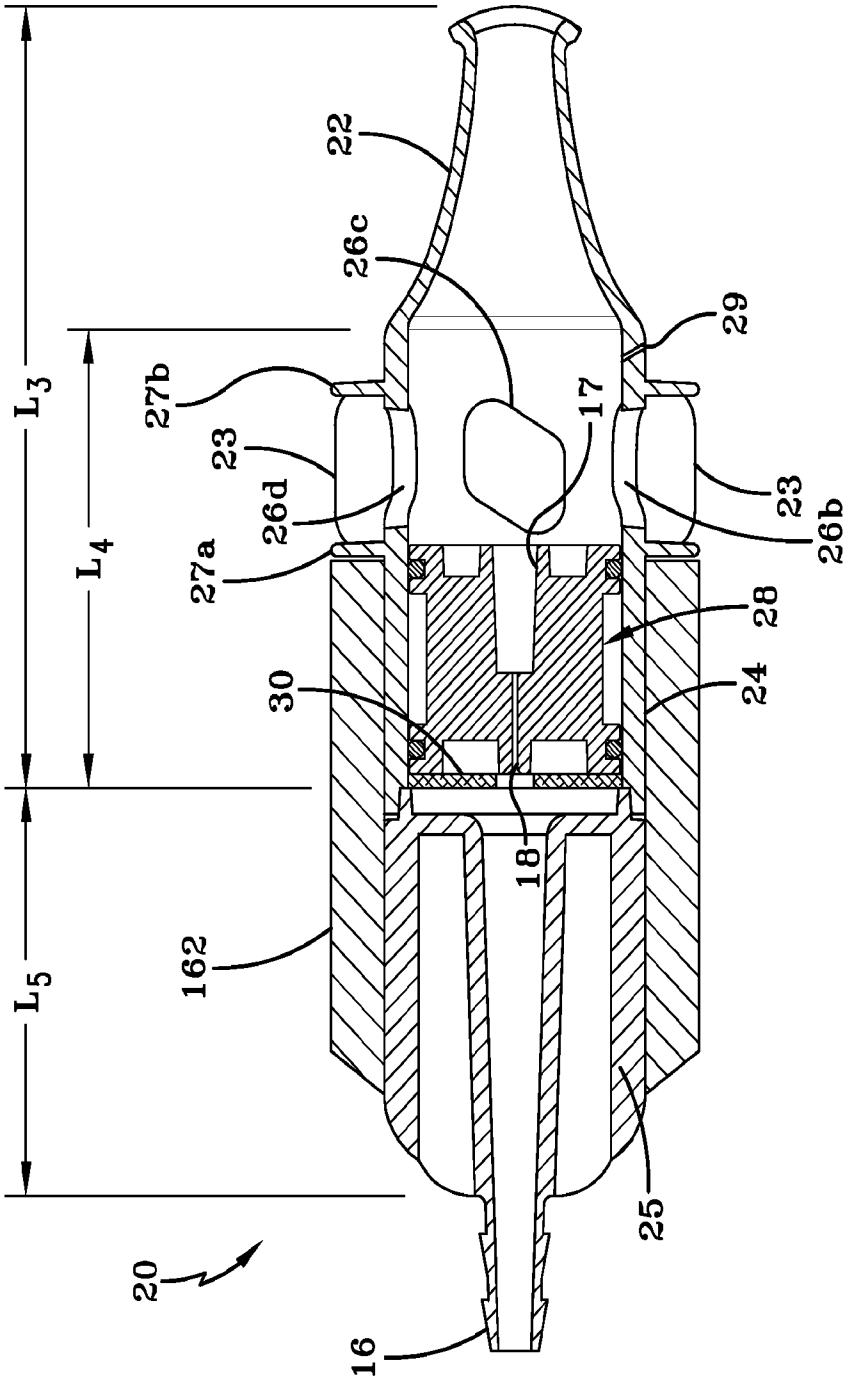
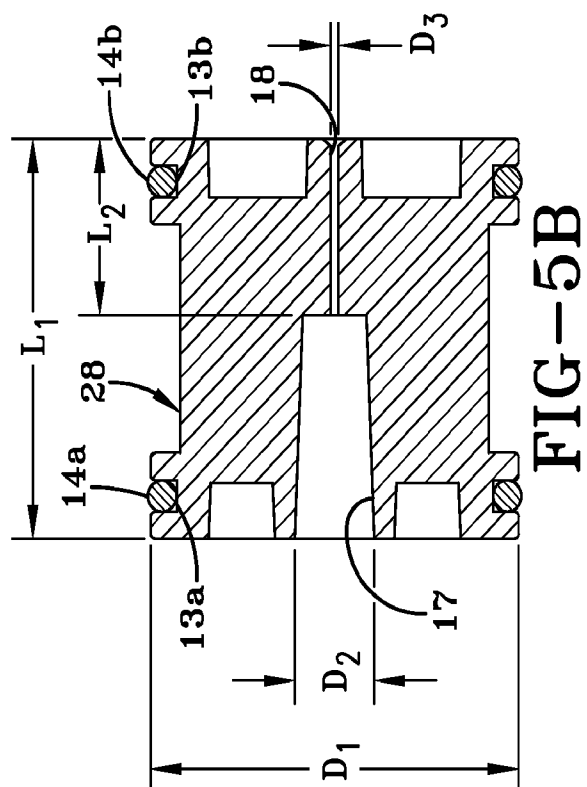
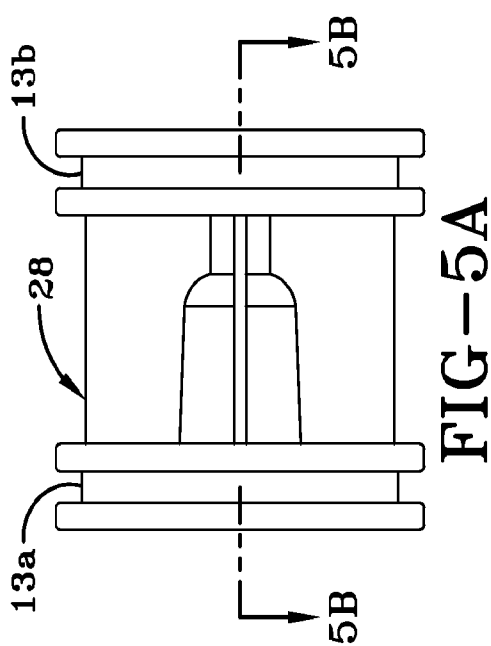
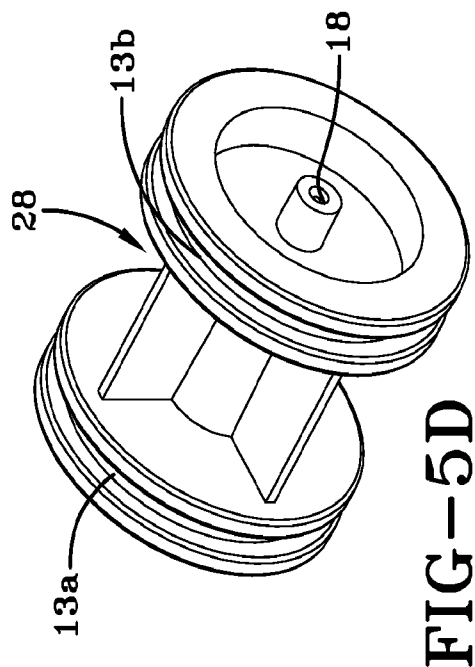
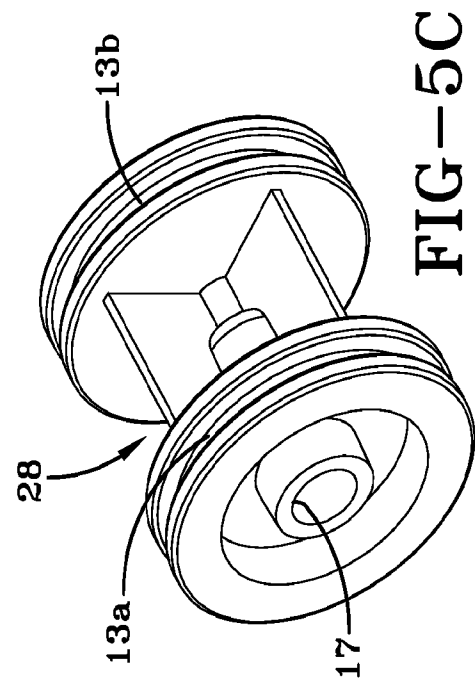


FIG-4



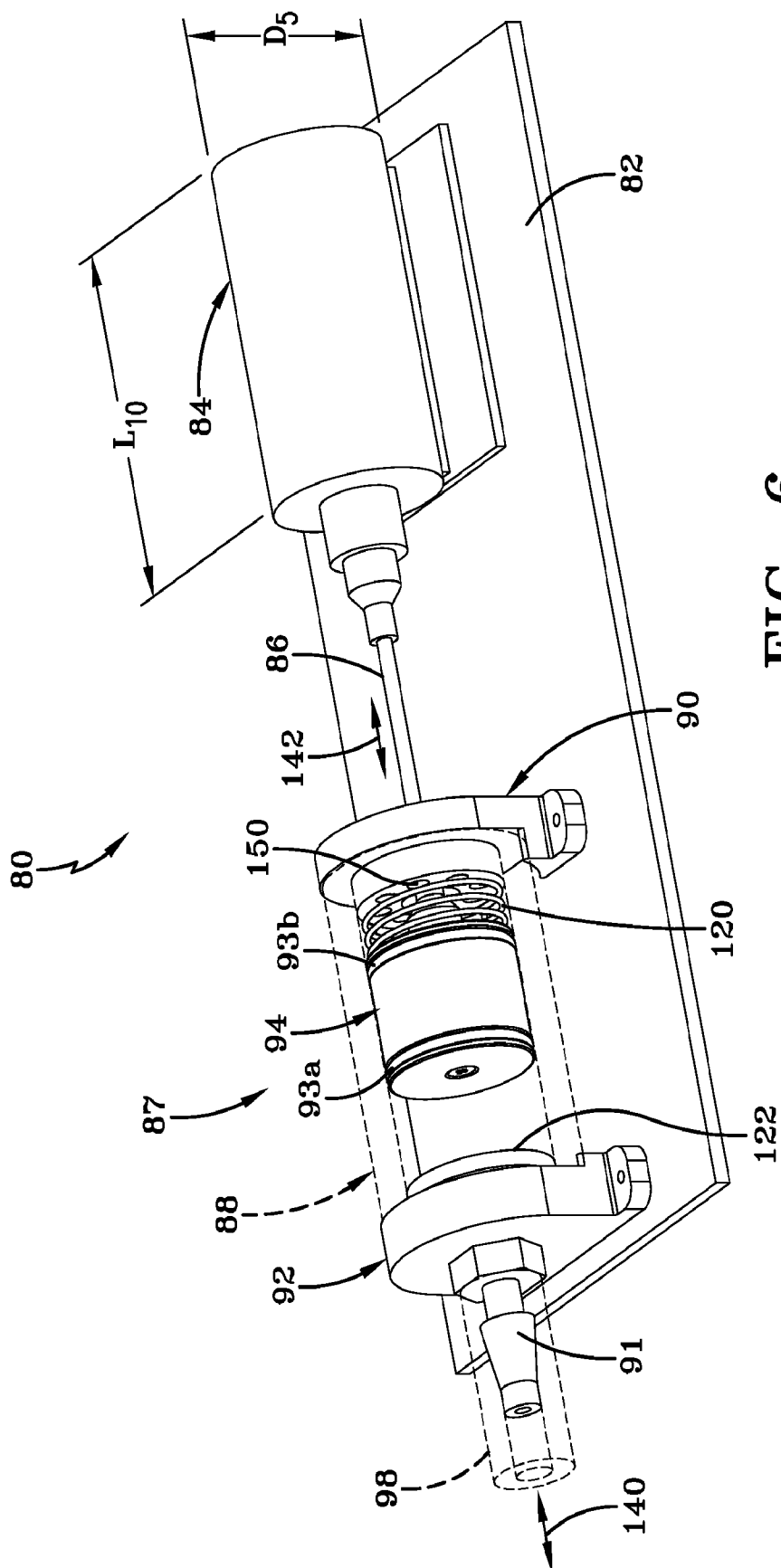
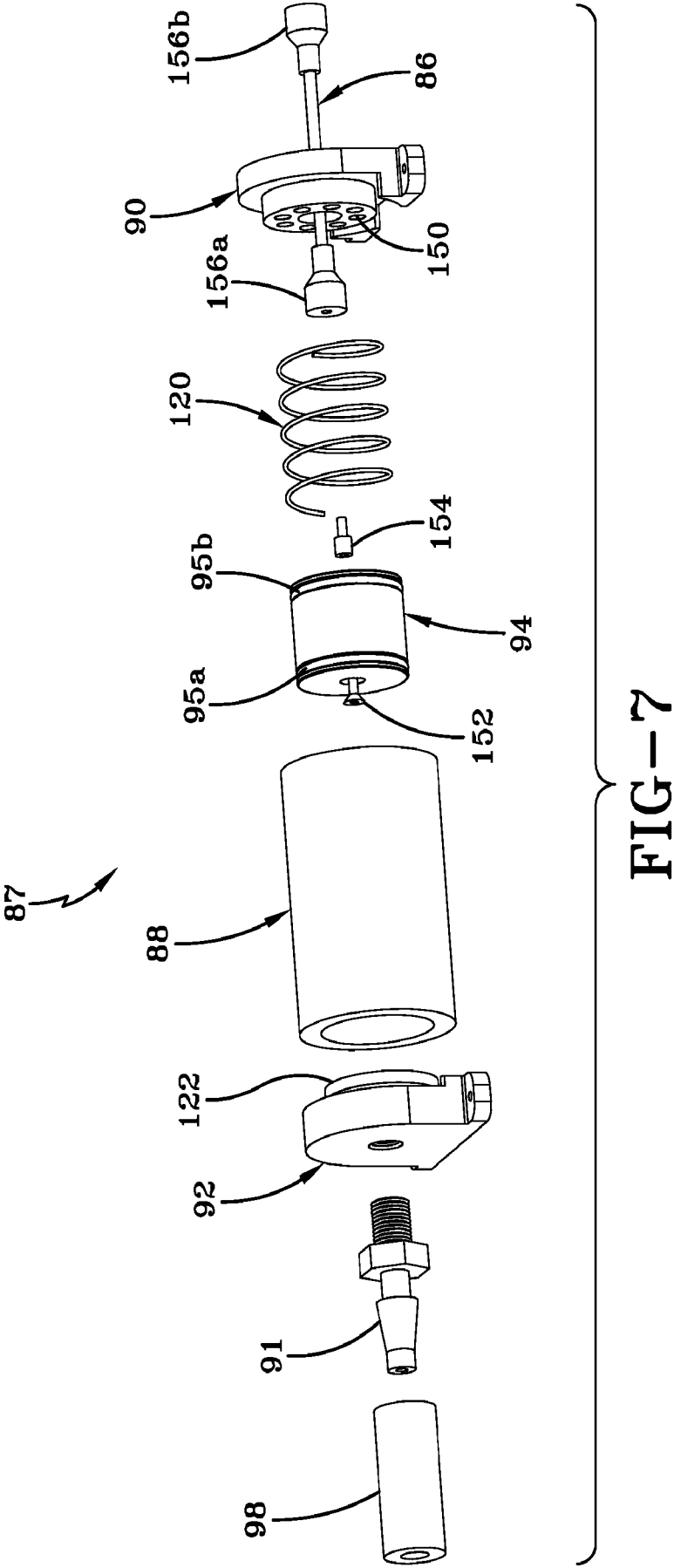


FIG-6

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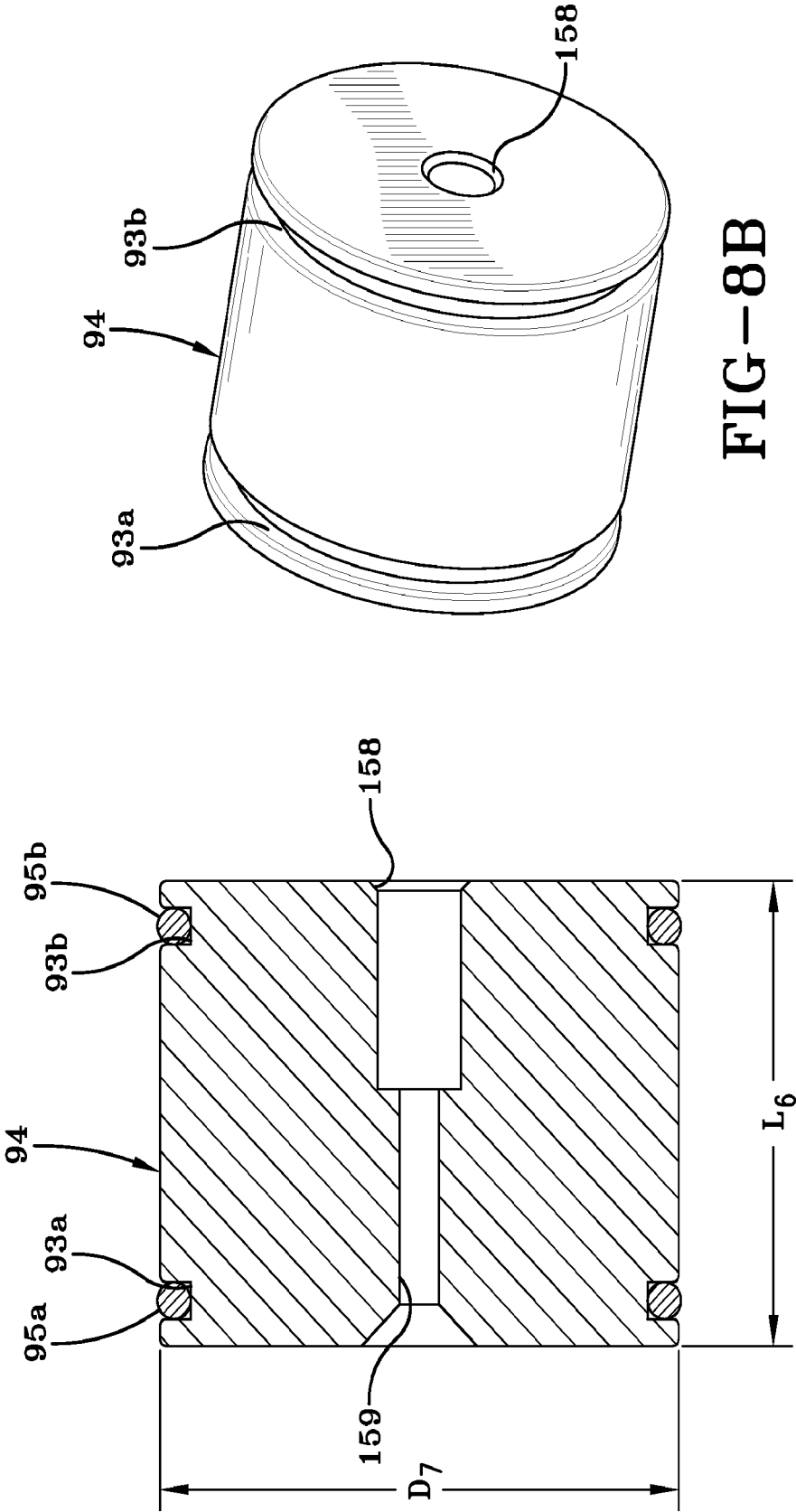


FIG-8B

FIG-8A

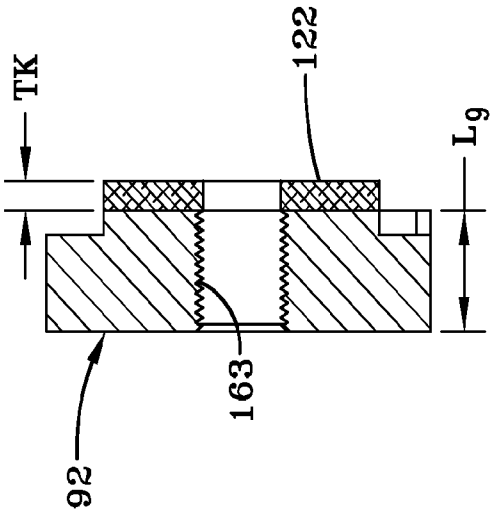


FIG-11A

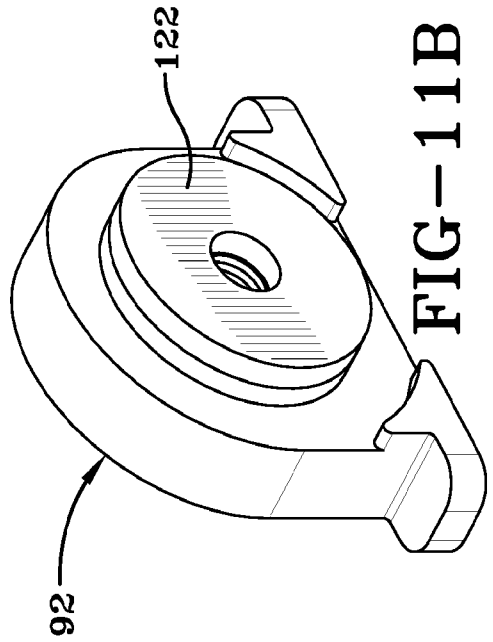


FIG-11B

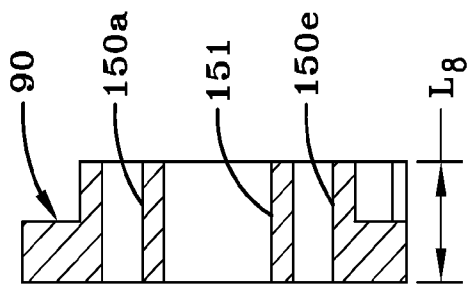


FIG-10A

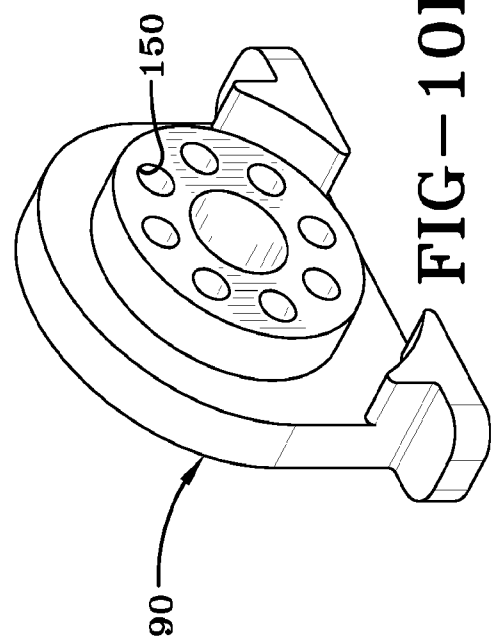


FIG-10B

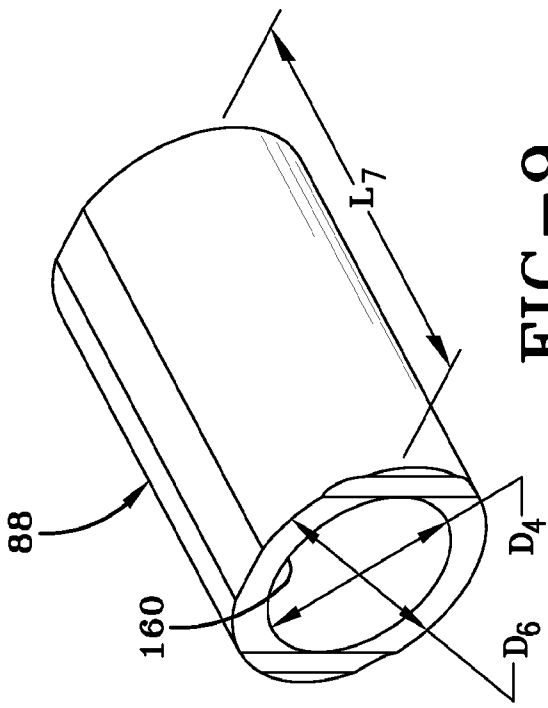


FIG-9

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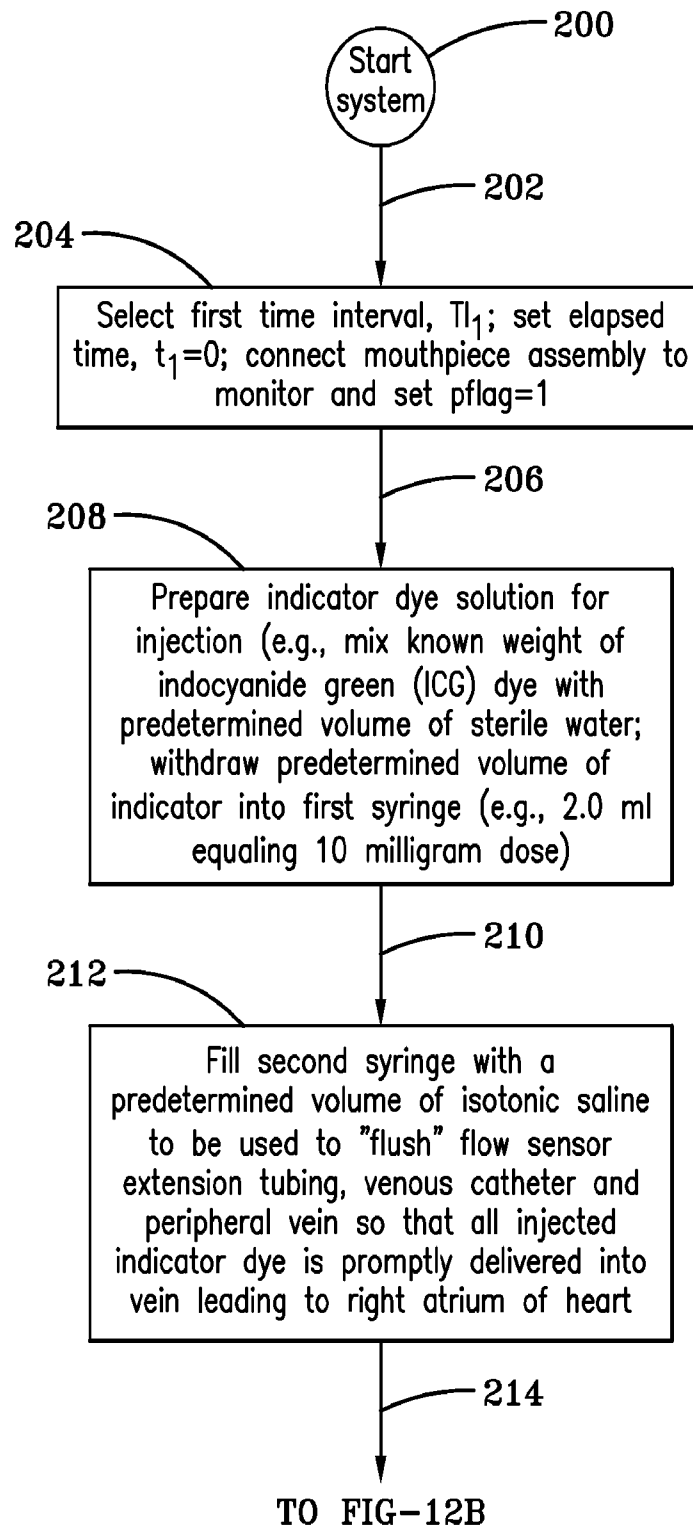


FIG-12A

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FROM FIG-12A

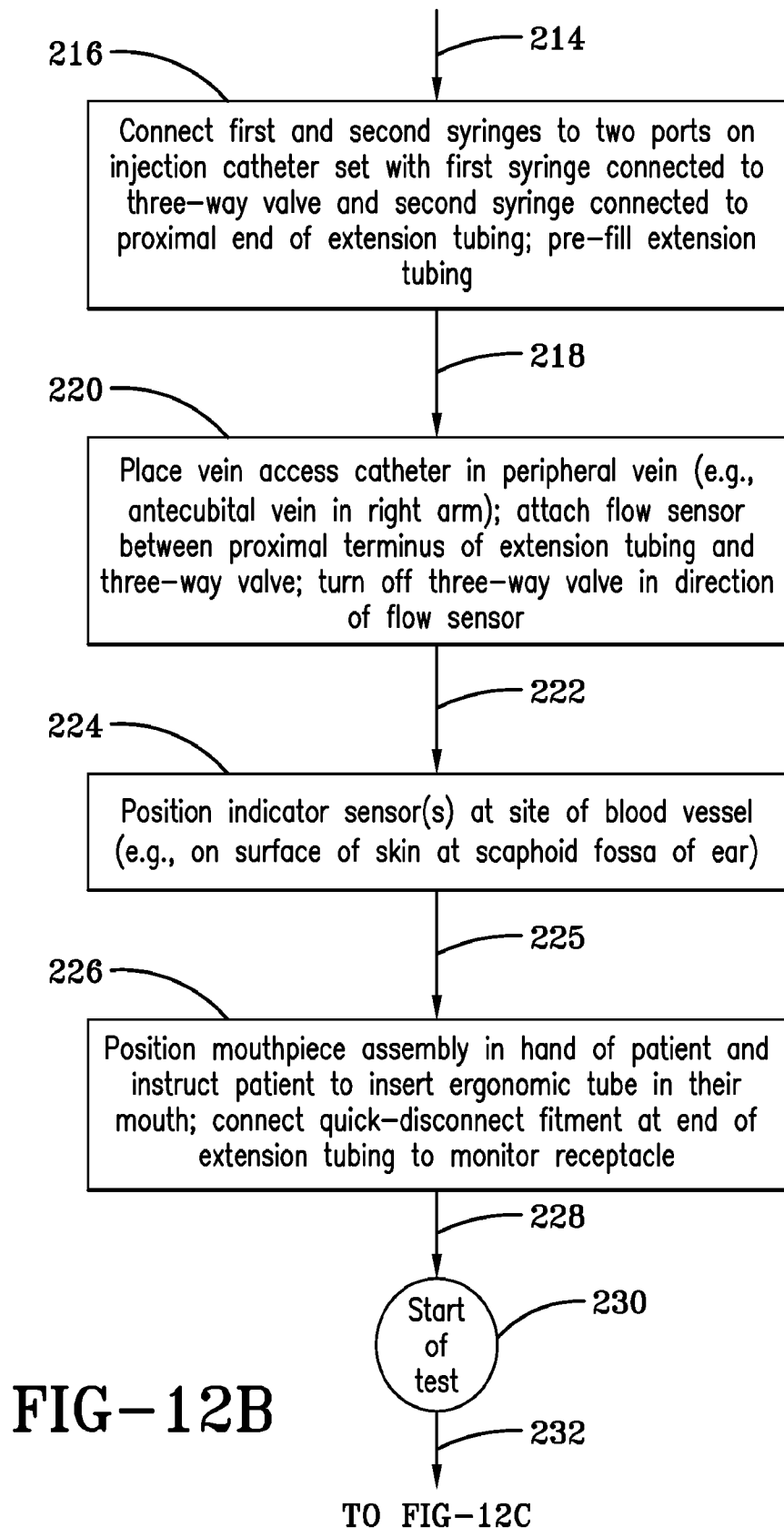


FIG-12B

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FROM FIG-12B

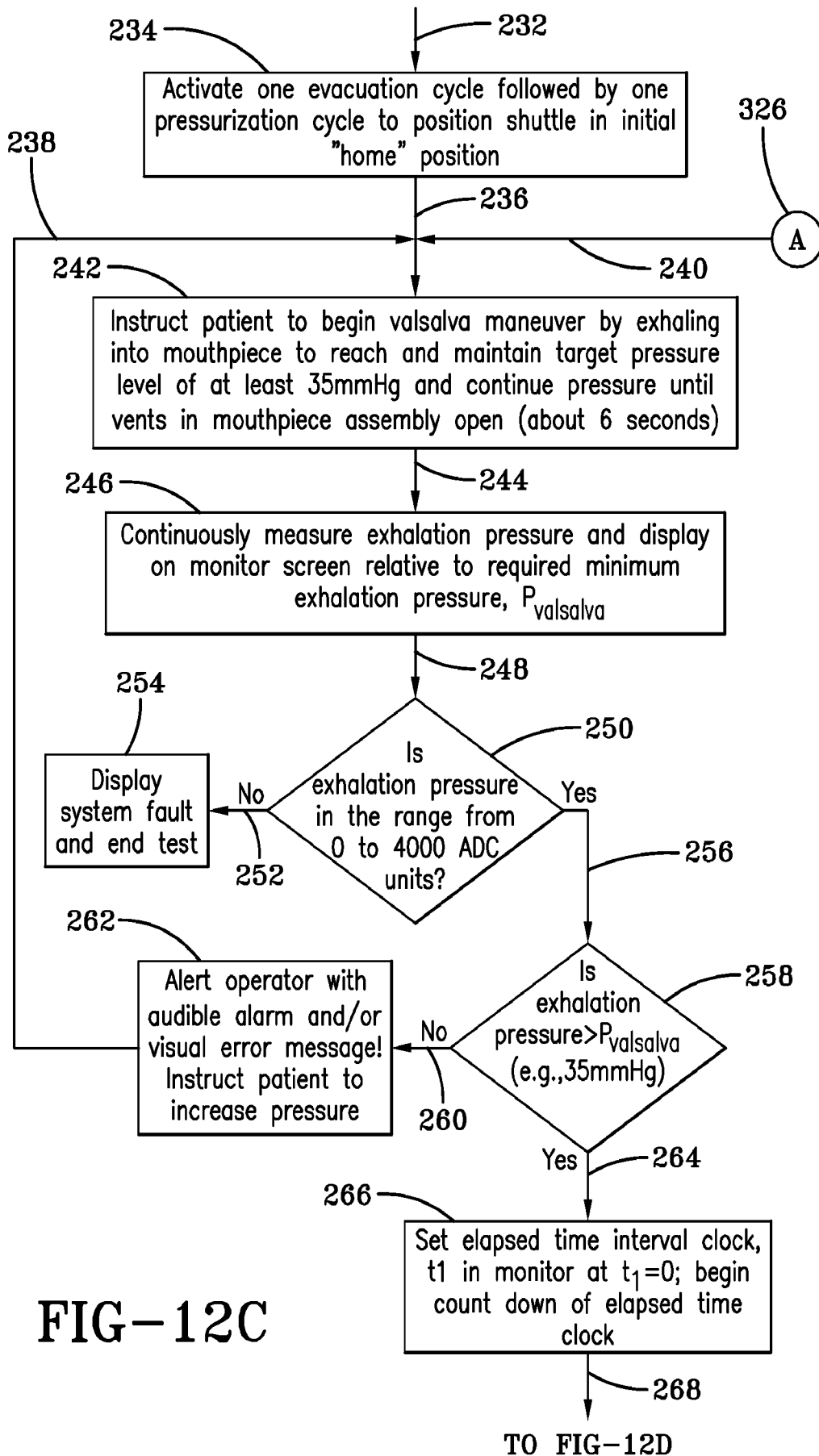
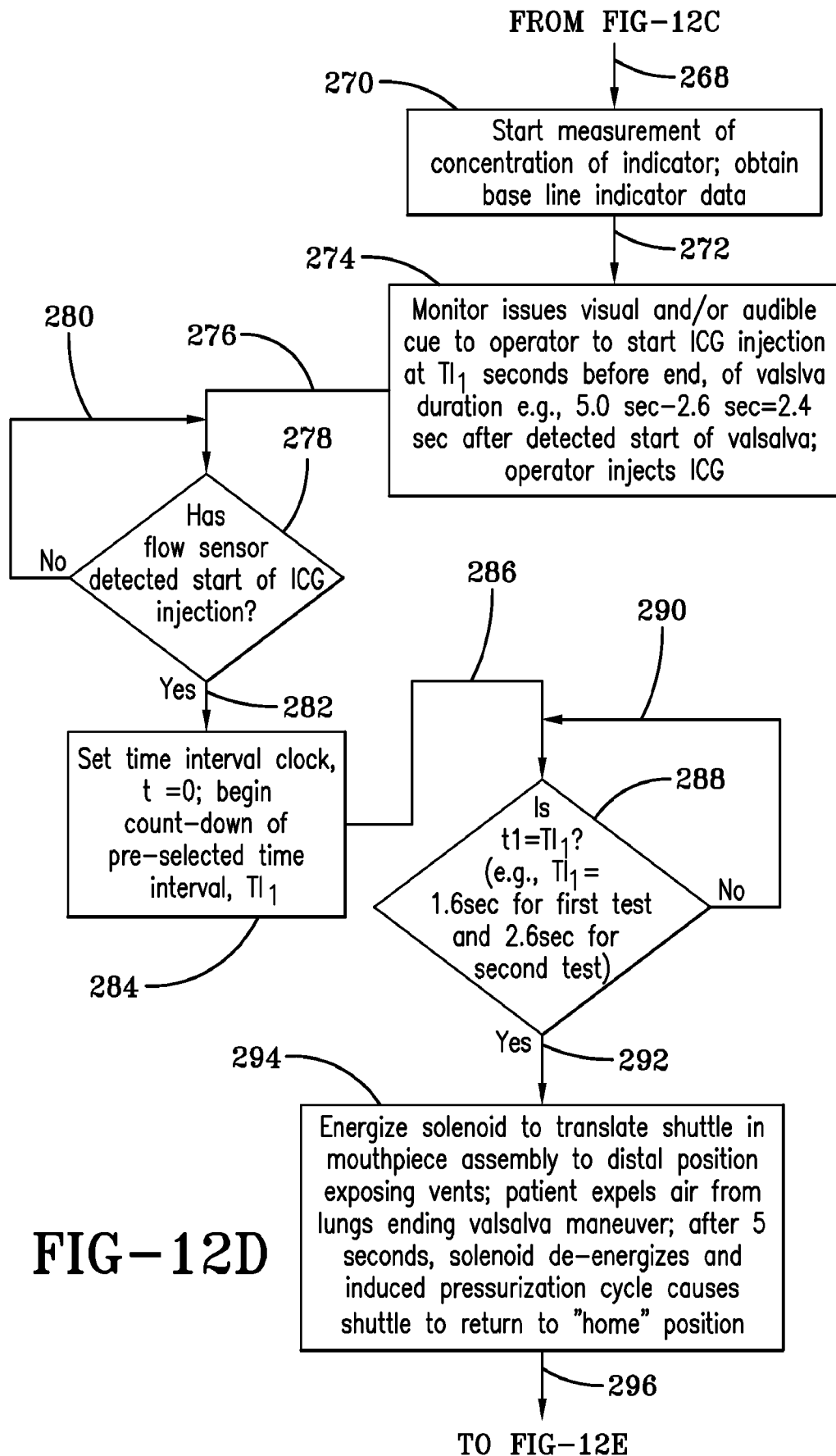


FIG-12C

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FROM FIG-12D

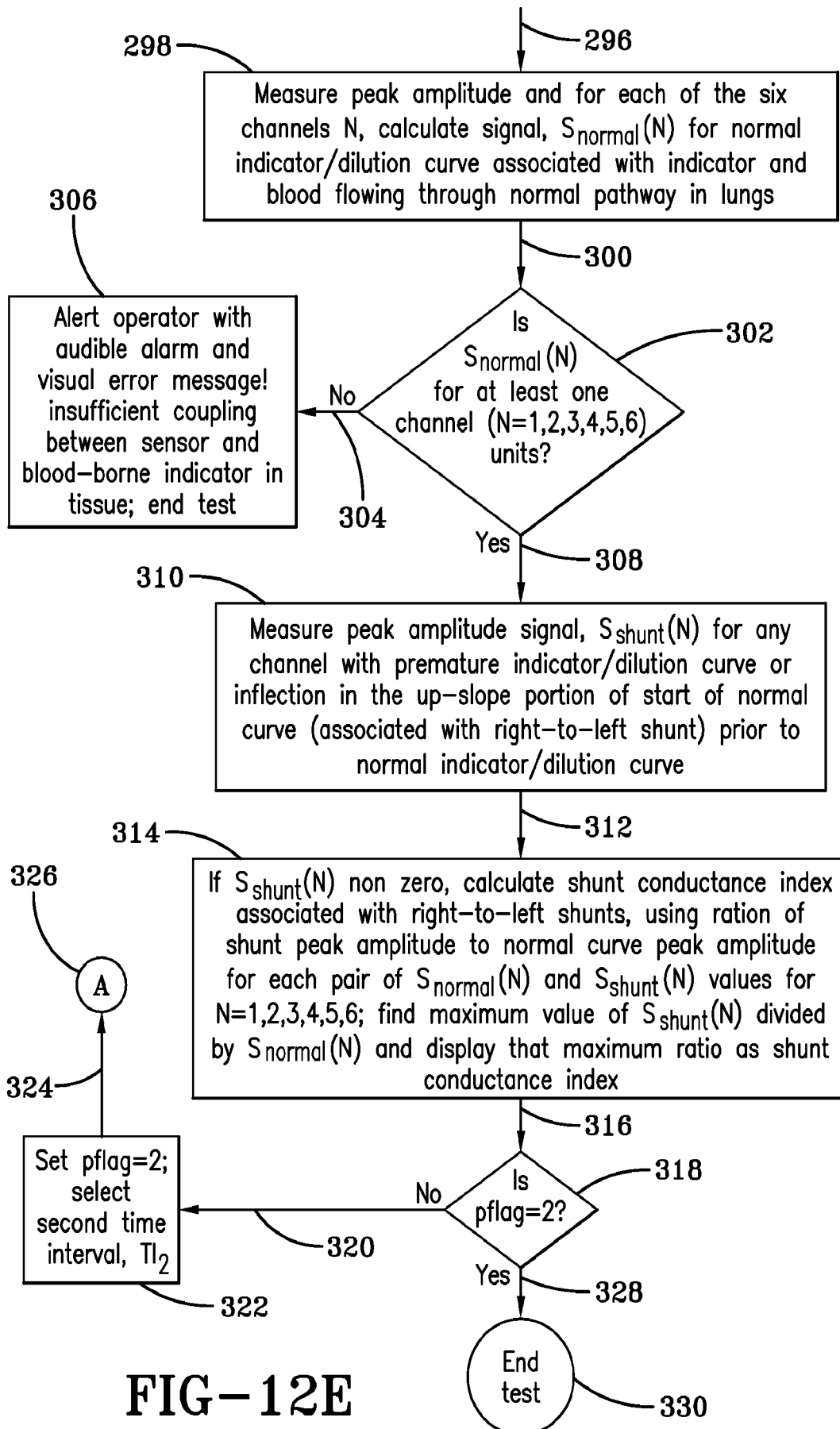


FIG-12E

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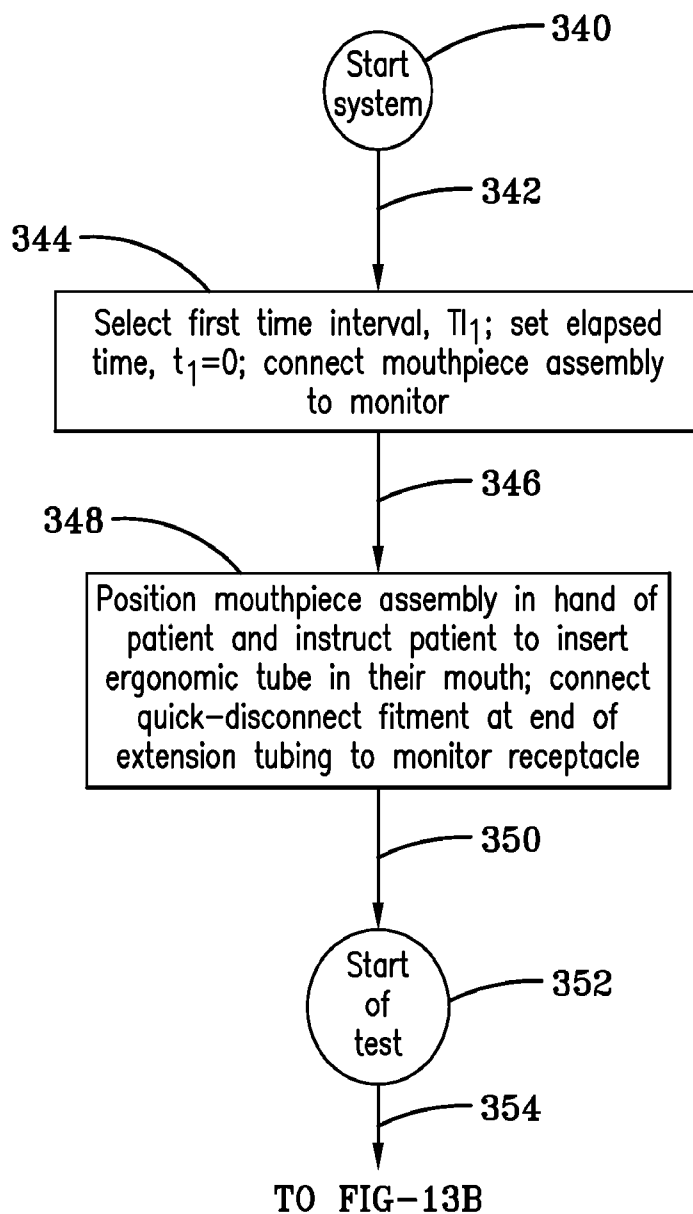


FIG-13A

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FROM FIG-13A

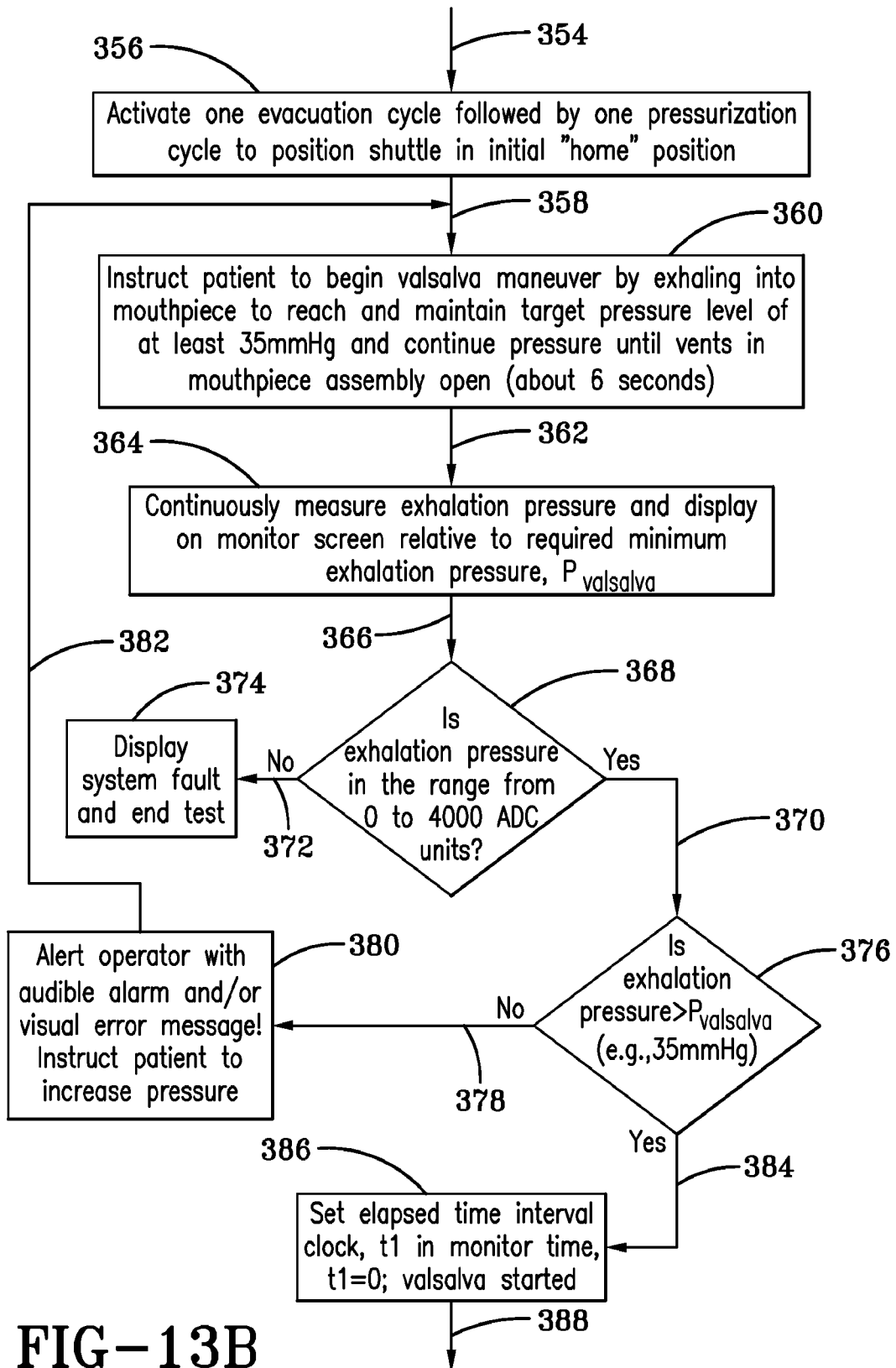


FIG-13B

TO FIG-13C

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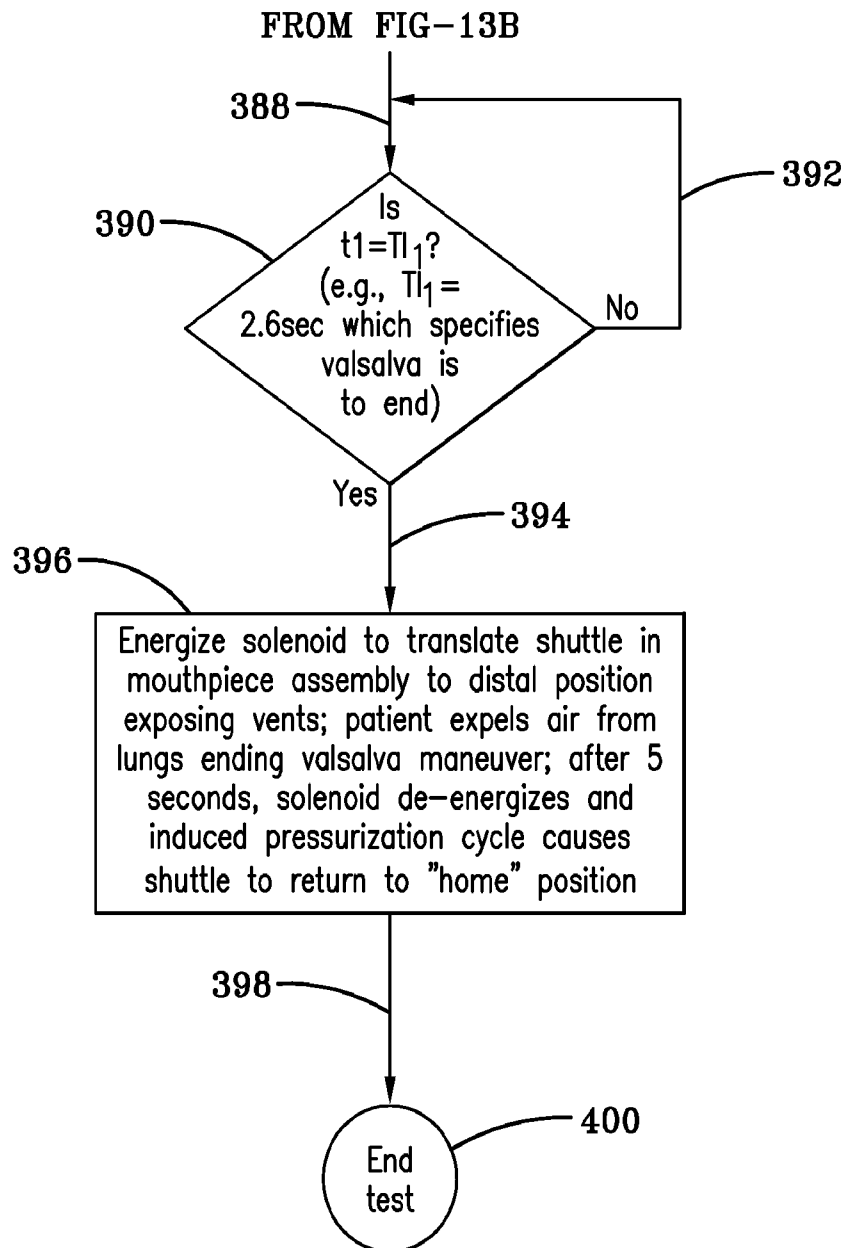
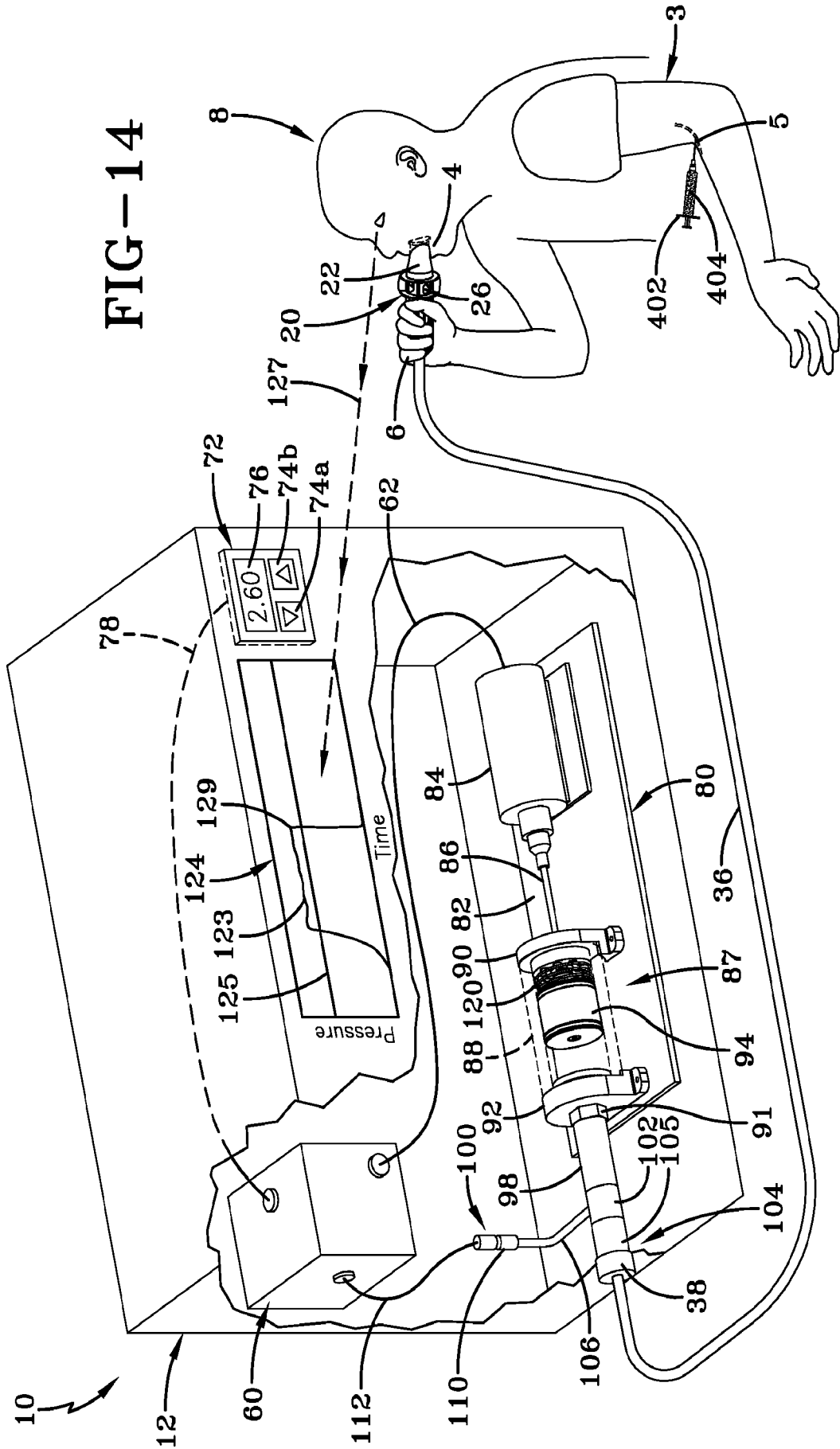


FIG-13C

FIG-14



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/058085

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 5/0215 (2013.01)

USPC - 600/454, 532

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61B 5/02, 5/021, 5/0215, 5/08, 8/06 (2013.01)

USPC - 600/303, 431, 454, 508, 513, 532, 587, 590

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC - A61B 5/02028, 5/026, 5/082, 5/682, 8/0883, 8/481 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0245662 A1 (EGGERS et al) 06 October 2011 (06.10.2011) entire document	12-14
Y		1-3, 6, 15
Y	US 2011/0082373 A1 (GURLEY et al) 07 April 2011 (07.04.2011) entire document	1-3, 6
Y	WO 2011/127184 A1 (EGGERS et al) 13 October 2011 (13.10.2011) entire document	15
A	COOPER et al. "Effects Of Simulated Obstructive Sleep Apnoea On The Human Carotid Baroreceptor-Vascular Resistance Reflex"; The Journal of Physiology Vol. 557.3 (2004): pages 1055-1065.	1-15

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

05 December 2013

Date of mailing of the international search report

12 DEC 2013

Name and mailing address of the ISA/US

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Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

专利名称(译)	用于执行Valsalva机动的方法，装置和系统		
公开(公告)号	EP2919645A4	公开(公告)日	2016-11-23
申请号	EP2013835896	申请日	2013-09-04
[标]申请(专利权)人(译)	卡迪奥克斯公司		
申请(专利权)人(译)	CARDIOX CORPORATION		
当前申请(专利权)人(译)	CARDIOX CORPORATION		
[标]发明人	EGGERS PHILIP E EGGERS ANDREW R MAYERCHAK MARK A		
发明人	EGGERS, PHILIP, E. EGGERS, ANDREW, R. MAYERCHAK, MARK, A.		
IPC分类号	A61B5/0215 A61B5/00 A61B5/02 A61B5/03 A61B5/087 A61M5/00 A61M5/178 A61M15/00		
CPC分类号	A61B5/4884 A61B5/02028 A61B5/03 A61B5/087 A61B5/742 A61B2562/0247 A61M5/007 A61M5/178 A61M15/0098 A61M2016/0027		
代理机构(译)	WILSON , GLEN		
优先权	61/696409 2012-09-04 US		
其他公开文献	EP2919645A1		
外部链接	Espacenet		

摘要(译)

用于精确控制Valsalva操纵及其定时的方法，装置和系统结合测试患者进行心脏分流，并确保执行Valsalva操作的患者使用他们的隔膜产生所需压力。还公开了Valsalva操纵吹嘴组件的实施例，用于本发明的方法，装置和系统。接口管组件适于在产生对患者的呼气压力进入接口管的阻力的状态和快速去除耐压性的状态之间选择性地操作，从而导致患者肺部的空气不自主地呼气。期望Valsalva机动释放的时间。