(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 August 2012 (09.08.2012)

(10) International Publication Number
WO 2012/104848 A1

(51) International Patent Classification:
A61M 1/36 (2006.01) *A61F 2/06* (2006.01) *A61B 17/12* (2006.01)

(21) International Application Number: PCT/IL2012/050022

(22) International Filing Date: 24 January 2012 (24.01.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/438,978 3 February 2011 (03.02.2011) US
2007134 18 July 2011 (18.07.2011) NL

(71) Applicant *(for all designated States except US)*: **GEVA SOL BV** [NL/NL]; Nijverheidsweg 22, NL- 2215 MH Voorhout (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KRITZMAN KADRON, Amnon** [IL/IL]; 18 ZAFRIRIM ST., 30700 Pardes Hannah Karkur (IL). **SCHER, Menachem** [IL/IL]; Moshav Habonim, 30845 Harhava (IL).

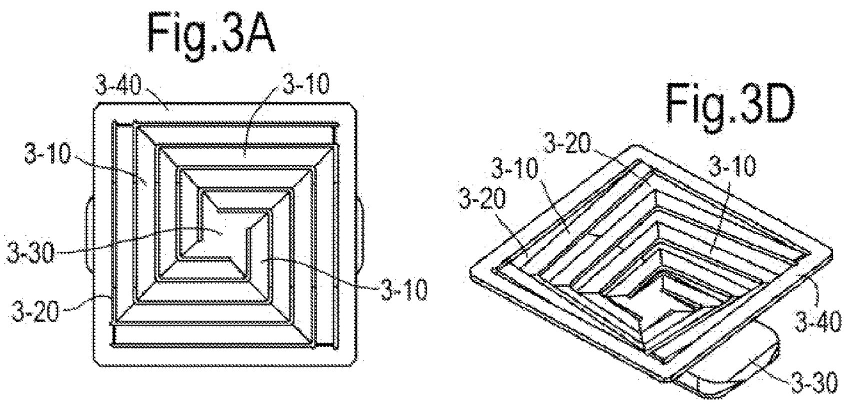
(74) Agent: **TEITELBAUM, Rachel**; Wolff Bregman And Goller, P.O.Box 1352, 91013 Jerusalem (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: CONTROLLABLE FLOW REGULATOR SYSTEM



(57) **Abstract**: This invention is directed to an implantable controllable displacement regulator system enabling vessel wall displacement and/or total or partial luminal occlusion, which when implanted in a subject, provides for a defined luminal flow and pressure. Methods of use thereof are described, as well.

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CONTROLLABLE FLOW REGULATOR SYSTEM

FIELD OF THE INVENTION

[001] This invention is directed to an implantable controllable displacement regulator system enabling vessel wall displacement and/or total or partial luminal occlusion, which when implanted in a subject, provides for a defined luminal flow and pressure. In some aspects, the flow is substantially laminar or pulsatile.

BACKGROUND OF THE INVENTION

[002] Any number of organs in the human body relies on nutrient or fluid transport within and waste removal out of the organs for maintaining homeostasis. For example, chronic renal failure in a subject results in an inability to filter the blood and remove waste substances. The most common treatment for chronic renal failure is hemodialysis, using a dialysis machine that replaces the failing kidneys. Effective hemodialysis entails the filtering of large volumes of blood and necessitates a connection of the dialysis machine to the subject's circulatory system. The primary methods used to gain access to the blood: of the afflicted subject is via an arteriovenous (AV) shunt called fistula or a synthetic or native graft, both methods which rely upon the joining of an artery and a vein in the subject either directly or via an artificial or native vessel, done subcutaneously in the subject. The type of access is influenced by factors such as the expected time course of a patient's renal failure and the condition of his or her vasculature. Typically an arteriovenous graft is placed subcutaneously in the subject which in turn, is connected to the dialysis machine, where blood removed from the subject is circulated through the dialysis machine, filtered and returned to the patient. Typically, subjects undergo hemodialysis approximately four hours a day, three days a week.

[003] The arteriovenous shunt for hemodialysis is accompanied by numerous complications, including ischemia, steal syndrome, thrombosis, stenosis, aneurysm formation, intimal hyperplasia, heart failure and others.

[004] The circulatory, respiratory, digestive, urinary, and reproductive organs rely on material transit through active lumens whether such movement is of fluids, solids, air, etc., for which appropriate transit and proper functioning is necessary for optimal performance and survival.

[005] While various access systems have been developed, including valve or control flow devices, which reduce some of the complications listed hereinabove, nonetheless such systems are not ideal for example, certain uses of such systems result in significant flow turbulence, contributing to complications.

[006] An ideal implantable controllable displacement regulator system, which regulates flow and pressure, providing optimal performance, and for example, without causing turbulence, has not

as yet been identified.

SUMMARY OF THE INVENTION

[007] In one embodiment, the present invention provides an implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined flow and pressure within said vessel, which piston is magnetically or electromagnetically or electrically (by induction) actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material.

[008] In some embodiments, the regulator system specifically controls liquid transit through a body vessel. In some embodiments, according to this aspect, the regulator system functions as a controllable arteriovenous graft system and in some embodiments, the regulator system functions such that fluid flow through said body vessel is substantially laminar or pulsatile.

[009] In some embodiments, according to this aspect, when the piston is in the extended form, occluding or partially occluding a proximally located vessel, flow through the vessel exhibits minimal shear stress, minimal turbulence, minimal stagnation points or a combination thereof.

[0010] In some embodiments, the piston is of a length that correlates with a desired flow rate, pressure rate or combination thereof in said vessel, which in some embodiments, therefore exhibits minimal shear stress, minimal turbulence, minimal stagnation points or a combination thereof.

[0011] In some embodiments, the piston is a composite of a single part made of ferromagnetic alloy. In some embodiments, the piston is a composite of at least two materials.

[0012] In some embodiments, the piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material, present as a hollow layer and additional layers of the piston collapse within the hollow layer when the system is subjected to a magnetic or electromagnetic field. According to this aspect and in one embodiment, when the system is no longer subjected to a magnetic or electrical field, the piston is present in an extended form.

[0013] This invention provides, in some embodiments, an implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a body vessel, which may displace or occlude said vessel, wherein the valve comprises a controllable, extendible spring structure which may exist in an extended and compact form, which spring when in an extended form provides for a defined flow and pressure within said vessel, which flow is substantially laminar or pulsatile and which spring is magnetically or electromagnetically actuated.

[0014] According to this aspect and in some embodiments, the spring structure further comprises a base and a pressure plate, wherein said pressure plate has a substantially rectangular profile and wherein during extension the base is distal to the pressure plate. In some embodiments, at least the pressure plate is comprised of a magnetic, paramagnetic or superparamagnetic material. In some embodiments, according to this aspect, the device further comprises a solenoid whose long axis is positioned substantially perpendicularly to that of the pressure plate wherein generation of a magnetic field by the solenoid results in the pressure plate being drawn proximal to the base and minimal electromagnetic radiation is lost as a result of the diminished gap between the pressure plate and the base In some embodiments, when the system is no longer subjected to a magnetic field, the spring structure is present in an extended form.

[0015] This invention also provides implantable controllable displacement regulator systems, which further comprise a sensor or indicator, which sensor or indicator denotes when said spring is in an extended versus a collapsed form, said sensor or indicator denotes positioning of said spring.

[0016] This invention also provides an indicator unit, which facilitates the identification of the location of the implanted valve device or devices, and optionally an activator which renders the device operational once the indicator is positioned at an ideal location with respect to the device. In some embodiments, the indicator unit identifies the location of the valve, the orientation of the valve or a combination thereof.

[0017] All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of a conflict between the specification and an incorporated reference, the specification shall control. Where number ranges are given in this document, endpoints are included within the range. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges, optionally including or excluding either or both endpoints, in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. Where a percentage is recited in reference to a value that intrinsically has units that are whole numbers, any resulting fraction may be rounded to the nearest whole number.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Fig. 1A schematically depicts the flow simulation system mimic human hand vascular system, and Figure 1B depicts the simulation branches constructed to test circular and rectangular flow simulation modules.

[0019] Figs. 2 presents the ultrasound flow profiles obtained for circular and rectangular flow simulation modules described by Figure 1.

[0020] Fig. 3 schematically depicts embodiments of valve device of this invention comprising a substantially rectangular piston..

[0021] Fig. 4 schematically depicts embodiments of valve device of this invention comprising a controllable spring structure.

[0022] Figure 5 schematically depicts solenoid structure positioning proximally to a valve device of the invention. According to this aspect, and representing one embodiment, the system may further comprise a location indicator, which provides a signal which in turn advises when optimal positioning occurs for minimum electromagnetic radiation loss and optimal device functioning.

[0023] Figure 6 schematically depicts embodiments of the valve devices of this invention located within a casing. Figure 6A depicts an embodiment of a rectangular casing, to accommodate embodiments of the valves of this invention comprising a substantially rectangular piston. Figure 6B depicts an embodiment of a disk-shaped casing, to accommodate embodiments of a valve device of this invention comprising a controllable spring structure. Figures 6C and 6D provide side and transverse views of the device in Figure 6B.

[0024] .Figure 7 schematically depicts additional views of a valve device of this invention comprising a controllable spring structure and its containment within a casing.

[0025] Figure 8A depicts an embodied regulator system of the invention, wherein a cylindrically-shaped piston is extended or compacted, thereby regulating luminal flow in a vessel.

[0026] Figure 8B depicts an embodied regulator system of the invention, wherein the system comprises a magnetic, paramagnetic or superparamagnetic lever which can be raised or lowered, thereby regulating luminal flow in a vessel.

[0027] Figure 9 depicts an embodied implantable controllable displacement regulator system of this invention making use of an electro-active polymer or magneto polymer, wherein the power supply is located above (A, B) or beneath (C, D) the skin. Figure 9E depicts another embodied implantable controllable displacement regulator system of this invention making use of a flat coil transformer for either the internal or external power supply, located beneath and above the skin, respectively.

[0028] Figure 10 depicts an embodied implantable controllable displacement regulator system of this invention making use of a solenoid, wherein the power supply is located above (A, B) or beneath (C, D) the skin.

[0029] Figure 11 depicts an embodied flat coil for incorporation within the implantable controllable displacement regulator systems of this invention.

[0030] Figure 12 depicts an embodied volumetric coil for incorporation within the implantable controllable displacement regulator systems of this invention.

[0031] Figure 13 is a block diagram showing incorporation of a device of this invention within a hemodialysis scheme of operation.

[0032] Figure 14 depicts an embodied implantable controllable displacement regulator system showing a "duck bill" configuration showing the passive closed configuration (Figure 14A) and the active open configuration (Figure 14B) following application of an electric, magnetic or electromagnetic field, as herein described.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0033] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as not to obscure the present invention

[0034] In one embodiment, the present invention provides an implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion or partial occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined flow and pressure within said vessel, which piston is magnetically or electromagnetically actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material.

[0035] The systems of this invention are useful for regulating any luminal transit in a body vessel. In some embodiments, the term "luminal transit" refers to movement of a material down a length of a vessel. In some embodiments, such material can be liquid, gas, or semi-solid. In some embodiments, such vessels may be endogenous body vessels, or artificial vessels, which interface with a body region or organ, or body vessel, etc., as will be appreciated by the skilled artisan. At least a portion of such vessels for which regulated luminal transit is desired and which is therefore affected by the regulated systems of this invention are located internally, within a body of a subject.

[0036] Luminal transit may be affected by a number of parameters. For example, perfusion by the cardiovascular system relies on the basic principle, that the higher the pressure exerted by the left ventricle of the human heart, the faster the blood will flow through the vascular system. This is an example of a direct or proportional relationship between two quantities.

[0037] Blood flow is also affected, however, by the inherent resistance of the blood vessels, which is a function of the width of the vessels or in another word to blood vessels cross section. Thus, an inverse relationship between blood vessel resistance and the blood flow rate exist, such that the higher the resistance, the slower the flow rate.

The relationship is expressed as follows:

$$\text{Blood flow rate} = \frac{\text{pressure difference}}{\text{resistance}}$$

$$\begin{matrix}\text{Volume}\\\text{Flowrate}\end{matrix} = \mathcal{F} = \frac{P_1 - P_2}{\mathcal{R}}$$

Therefore:

$$\text{Pressure difference}\ P_1 - P_2 = \begin{matrix}\text{Volume}\\\text{Flowrate}\end{matrix} \cdot \mathcal{R} \begin{matrix}\text{Resistance}\\\text{to Flow}\end{matrix}$$

[0038] Typical pressure differences between the left and right ventricles are about 100 mmHg. The normal cardiac output is about 5 liters/minute, therefore the total peripheral resistance is about 20 (mmHg*min/liters).

[0039] The resistance to flow of a fluid and the resistance to the movement of an object through a fluid are usually stated in terms of the viscosity of the fluid. Experimentally, under conditions of laminar flow, the force required to move a plate at constant speed against the resistance of a fluid is proportional to the area of the plate and to the velocity gradient perpendicular to the plate. The constant of proportionality is called the viscosity.

[0040] Thus, the formula $F_{viscous} = \eta A \frac{\Delta vx}{\Delta y}$

where the units of viscosity η are N s/m^2 or Pa·s. The CGS unit is dyne sec/cm^2 which is called Poise. The viscosity of water at 20 °C is 0.01 Poise. The viscosity of blood at body temperature is about 0.03 Poise. The Pa·s is called a Poisuille and is equal to 10 Poise.

[0041] In the case of smooth flow (laminar flow), the volume flow rate is given by the pressure difference divided by the viscous resistance.

[0042] This resistance depends linearly upon the viscosity and the length, but the fourth power dependence upon the radius is dramatically different.

[0043] Poiseuille's law is found to be in reasonable agreement with experiment for uniform liquids (called Newtonian fluids) in cases where there is no appreciable turbulence.

[0044] Poiseuille's law gives insight into the complex task of regulating blood flow to different parts of the body. In response to demand, the body must direct more oxygen and nutrients to one region of the body, and if necessary temporarily curtail the supply to a less essential region. Since the flow resistance depends upon the fourth power to the interior radius of a vessel or to the blood vessels surface area, the processes of vasodilatation and vasoconstriction offer powerful control mechanisms.

[0045] In the case of smooth flow (laminar flow), the volume flow rate is given by the pressure difference divided by the viscous resistance.

[0046] This resistance depends linearly upon the viscosity and the length, but the fourth power dependence upon the radius is dramatically different. Poiseuille's law is found to be in reasonable agreement with experiment for uniform liquids (called Newtonian fluids) in cases where there is no appreciable turbulence.

[0047] Suppose that for a circular tube having a Length L, with a Resistance to flow R and a radius r, and a pressure across the length of the tube drops, and is reflected by P_1 and P_2, having a volume flowrate of F, where the original flowrate is 100 cm^3/sec. The effect of changes in the parameters, when all other parameters are held at their original value is as follows:

Double length 50 cm3/sec; double pressure 200 cm3/sec; double radius 1600 cm3/sec; when

$$R = \frac{8\,\eta L}{\Pi r^4}$$

when η is the viscosity, and the volume flowrate is $\frac{P_1-P_2}{R}$

[0048] Surprisingly, Applicants found that turbulence can be appreciably diminished, however, as a consequence of regulating the partial occlusion over a length of the blood vessel using a rectangular profile for such occlusion, as opposed to effecting occlusion in a partial manner, using a circular profile.

[0049] A Flow Experimental System (FES) was designed and developed to provide a system for the simulation of the circulation of the Human Body vascular system.

[0050] The system design allowed actual mimicking of major flow types parameters such as Steady State flow (s.s), Pulse Flow (p.f), pressure gradients, velocity, turbulent and laminar flow. The flexibility and versatility of the design allowed for the addition, subtraction and isolation of different flow variables and parameters, and the ability to concurrently examine them individually for velocity, pressure, viscosity, elasticity and other values, to produce real time XY XZ planar cross section visualization.

[0051] The system consisted of closed loop circulating synergistic system constructed from several individual elements joint together to produce predetermines designated flow parameters. At the heart of the system there are two types of pumps responsible to the circulation of fluid within the

FES, a Pulse Flow Pump (1-30) and a "Steady State" Flow Pump (1-10). Both were connected to the compliance Tank (1-60), Experiment module (1-280; 1-310) and 2 reservoir containers (1-160; 1-170), description of the rule of each segment will be further elaborated.

[0052] As can be seen in Figure 1A, a compliance tank 1-160 simulates the blood vessel responsiveness. The tank is a closed vessel containing fluids, and during pulsatile flow, during the systolic stage, liquid entry within the tank results in an increase in the volume of liquids in the tank and thereby an increase in air pressure within the tank. During the diastolic stage, the pressurized air propels the liquids to exit the tank.

[0053] A simulation chamber 1-130 is also present as designated in Figure 1A, and is a container holding liquid and is where the sample testing occurs. The system includes three resistors, R_0 1-20, R_1 1-100 and R_2 1-110, where the resistance may be regulated thereby. The system contains three closures, S_0 1-40, S_1 1-80 and S_2 1-90 and via these closures, flow may be regulated. Pressure is measured via the P_c 1-70 and P_{out} 1-150 meters, which are located as indicated in Figure 1A.

[0054] Flow is measured as follows: The system contains two transducers Q_0 1-50 and Q_1 1-120, which are connected to a switch box. When the switch is in position 1, a signal is transferred from transducer Q_0 1-50; when the switch is in position 2, a signal is propagated from switch Q_1 1-120. The signal reaches a flow meter, and is then delivered to a channel box, where channel 2 represents Q_0 and channel 3 represents Q_1. The measurement itself is based upon ultrasound principles: an ultrasound beam [from 1-140] is sent from one side of the transducer to the other, where it is reflected by a mirror and returned. The delay between the incident beam and the reflected beam is relative to the supply and can be calculated.

[0055] The FES two major modes of operations are Pulsatile or Steady state. In order to mimic the human body vascular system and responses for each flow profile two sets of "controlled occlusions" and "valves" were installed into the system to allow maximum maneuverability and isolation of the different flow parameters.

[0056] The designed system can work with variety of fluids; the tubes connecting the different segments of the system are simple compliance silicon/plastic based tubes to allow room of maneuverability and the occlusions to take place.

[0057] Simulation Branches are depicted in Figure 1B, where branch 1-2 represents the simulated modules, branch 4 provides for ultrasound visualization and branch 3 represents simulating the hand Artery flow. A circular flow simulation module and a rectangular flow simulation module was tested in comparison, as depicted in Figure 2. Flow 1-180, 1-230; and pressure points are depicted 1-190; 1-200; 1-220; 1-300; 1-320, and 1-330; as are valves [1-210, 1-240, 1-250, 1-270 and 1-290] and resistance [1-260] modules. Simulation points/experimental models are depicted, as well 1-280; 1-310.

[0058] The FES thus provides a means of acquiring the appropriate information to determine the influence of different Shunts with various cross section and profiles on individual or overall biological flow 1-340.

[0059] Figure 1 depicts flow simulation modules tested to determine the effect, if any; the flow regulator profile has upon blood flow through the vessel partially occluded thereby. A flow simulation system mimics the human hand vascular system was constructed containing a steady state flow pump, a pulse flow pump, a compliance tank and a simulation system (Figure 1A). A Harvard pump l was used for effecting flow in this system. The pump approximates that of the heart, and mimics the stages of diastolic and systolic pressure, generated by the heart. The pump includes two single-way valves. Fluid is drawn via a first valve and propelled via the second valve. The flow pulse may be regulated i.e., via the R.P.M. rate. Similarly, the length of systole versus diastole may be regulated, i.e. via the Output Phase Ratio. The stroke volume may also be regulated by this pump.

[0060] The flow rate and perfusion along the Hand branch were measured, in accordance with this aspect. Av shunts create a “shortage” of the vascular system that in naturally connected through the capillary system. Avoiding the hand capillary system by diverting 95% of the artery flow into the vein creates “blood steel” from the hand capillary system as well as “export” of artery flow regime into the fragile vein system.

[0061] Partial occlusion of the AV shunt of around 30% of the original full cross section of the AV Shunt enables diversion into the hand capillary system and dramatic reduction of the export of the flow regime from the artery to the vein system.

[0062] A direct correlation was evident between the various rate of the partial occlusion to the revival of flow in the capillary and reduction in flow rate and pressure in the AV graft.

[0063] Table I depicts the results of the simulation studies.

Table I:

Model	Hand Artery System		AV Graft to vein	
	% Flow	% Pressure	% Flow	% Pressure
Hand Artery – Base Line	100	100		
Graft only –				
6mm diameter	28	5	72	95
Gradual controlled occlusion of graft				
Circular Occlusion - Cross section reduction				
Diameter From 6 to 2.2mm	56	38	44	62

Semi-Rectangular - Cross section reduction				
Reduction to 1.7mm in height	44	24	56	76
Reduction to 1.5mm in height	63	52	37	48
Reduction to 1.2mm in height	81	75	19	25

[0064] Ultrasound flow profile studies were conducted. Flow was set to a steady state of ~120mmHg. The circular and rectangular profile models were submerged within a water tank to enhance acoustic resonance detection and measurement. The fluid (water) movement through the tube was induced with air bubbles to achieve a clear image. Ultrasonic consecutive static cross-section images were taken over a period of several seconds. Ultrasonic consecutive dynamic cross-section images were taken over a period of several seconds while running through a data analysis mode to detect and "paint" the boundary flow conditions (Turbulent\Laminar).

[0065] In an experimental flow simulation study (data not shown), the reduction of the fistula cross section over a prescribed length dramatically improved blood flow and pressure as detected in a hand Artery system. The flow simulation profile using the circular flow module, provided a non-uniform flow and turbulence. In contrast, the flow simulation profile using the rectangular flow module, yielded uniform flow and lack of turbulence is evident.

[0066] Full opening of the AV graft cross section reduced the flow into the hand capillary system by 95% as well on pressure by72%.

[0067] Partial occlusion using Device I containing a "circular partial occlusion" that reduced the diameter from 6mm to 2.2 enhanced the flow in the hand artery system leading on to the capillary system from 28% in full opening to 56% with a perfusion increase from 5% to 38%.

[0068] Partial occlusion using Device II containing a "semi-rectangular occlusion" reduced the inner diameter from 6mm to 1.7mm while enhancing the flow in the hand artery system leading in to the capillary system from 28% to 44% (57% improvement) with perfusion increase from 5% to 24% (380% improvement). Concordantly, further reduction of the inner diameter using Device II to 1.5mm corresponded with further flow rate improving from 28% to 63% (125% improvement) and perfusion increased to up to 52%. A final reduction of the inner diameter to 1.2mm enhanced the flow rate to the hand capillary system up 81% (189% improvement) and perfusion up to 75% from initial healthy patient hand flow regime.

[0069] Semi-rectangular partial occlusion provided optimum results, in terms of the clearly reduced flow speed, pressure and/or presence of lower vessel shear stress, and therefore the occlusion profile geometry reduces turbulence and stagnation points within the affected vessel.

[0070] The two flow profiles containing circular and semi-rectangular profiles were assessed and each exhibited an improvement in terms of the flow rate and vascular pressure obtained. The device containing a circular aperture and having an inner diameter of 2.2mm, exhibited an improvement of over 100% at flow rate and 600% of vascular pressure, and the device containing a semi-rectangular dynamic aperture: exhibited an improvement of over 180% at flow rate and 1500% of vascular pressure.

[0071] The invention therefore provides an implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined flow and pressure within said vessel, which piston is magnetically or electromagnetically actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material.

[0072] The invention also provides an implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a body vessel, which may displace or occlude said vessel, wherein the valve comprises a controllable, extendible spring structure which may exist in an extended and compact form, which spring when in an extended form provides for a defined flow and pressure within said vessel, which flow is substantially laminar or pulsatile and which spring is magnetically or electromagnetically actuated.

[0073] In one embodiment, the implantable controllable displacement regulator system is a controllable, arteriovenous graft system wherein when the piston is in an extended form, the system provides for a defined blood flow and pressure within a blood vessel, which blood flow is substantially laminar or pulsatile and which piston is magnetically or electromagnetically actuated.

[0074] The systems of this invention are controllable or regulatable.

[0075] In some embodiments, "controllable" or "regulatable" refers to an ability or means of modulating the systems as herein described. In some embodiments, the modulation of the described systems entails modulating the flow and pressure through a vessel to which the systems of this invention are located proximally thereto, such that fluid, gas or food flow and pressure, etc., may be hampered, stopped or augmented through the vessel as a consequence of the operation of the systems of this invention.

[0076] In some embodiments, flow and pressure through a vessel to which the systems of this invention are placed proximally thereto, may be controlled such that such flow and/or pressure are at a desired flow and/or pressure rate, as a consequence of the operation of the systems of this invention.

[0077] The valve devices which comprise and are used in accordance with the systems of this invention are suitable for deployment proximal to a body vessel as herein described and defined. In some embodiments, the term "suitable for deployment proximal to a vessel" indicates that the valve is constructed of a material, which is biocompatible and provides minimal to no inflammatory or cytotoxic response in the subject in which such devices are deployed. In some embodiments, the term "suitable for deployment proximal to a vessel" indicates that the valve is constructed of a material, which does not damage the vessel to which it is positioned proximally thereto. It will be appreciated by the skilled artisan that the valve can be constructed of any known material, and may include composites, which are biocompatible and which satisfy the requirements for appropriate deployment, as described herein.

[0078] In some embodiments, the systems of this invention provide for the constriction/occlusion or partial constriction/occlusion of the proximal vessel, which in some embodiments, prevents or mitigates the formation of an obstruction in the treated vessel. For example, and representing certain embodiments, when the vessel is a blood vessel, thrombosis is prevented in the treated subject. For example, and representing certain embodiments, when the vessel is a feeding tube, such as a gastric tube, tubal occlusion is prevented, and the feeding tube is likely to be maintained for a longer period of time in the treated subject. In some embodiments the occlusion effected by the systems/valves of this invention are up to about 70 percent of the vessel cross section.

[0079] The terms "constriction" and "occlusion" and grammatical forms thereof are to be construed as synonymous herein, referring to a controllable effect on a proximally located vessel on behalf of the valve devices of this invention, whereby the vessel cross section is reduced and/or enlarged as a consequence of the activation of the valve devices of this invention.

[0080] Figure 3 depicts embodiments of a valve device of this invention. Figure 3A presents a top view of an embodiment of a valve device comprising a substantially rectangular piston, as herein described. The piston is in the collapsed position in this view. According to this aspect, in the collapsed position, at least part of the collapsible components of the piston are nested within a base frame profile. In some embodiments, the piston may comprise a series of expanding profiles, which in some embodiments, may have a width of 1.35 mm, for example 3-10, which are spaced apart from a previous layer profile, for example by a spacing of 0.3 mm, 3-20. Figure 3B depicts a side view of an embodiment of the piston device when in an extended conformation. According to this aspect, expanding profiles 3-10 form a tiered arrangement such that most of the extended layers may collapse within a preceding layer.

[0081] According to this aspect, and in some embodiments, the most extended surface 3-30 comprises a magnetic, paramagnetic or superparamagnetic material, such that upon application of a source of a magnetic field, located proximally to the base frame profile 3-40 results in the attraction of the most extended surface toward the source, thereby causing the collapse of the collapsible structure.

[0082] In some embodiments, the substantially rectangular collapsible pistons of this invention may have dimensions such that the collapsible piston, when extended will have a profile that is wider than a fistula, i.e., since most fistulas have a width of 6-8 mm, the pistons of this invention will have a width of between 6-40 mm, when in extended form i.e. 3mm – 60 mm. In some embodiments, the substantially rectangular collapsible pistons of this invention may have a length of between 5 and 50 mm, or in some embodiments the collapsible pistons of this invention may have a length of between 10 and 20 mm. The skilled artisan will appreciate that the substantially rectangular collapsible pistons of this invention may have a length that is appropriate to the specific locale and application of the systems of this invention, and sizes in ranges beyond those described hereinabove, are envisioned, as well.

[0083] In some embodiments, the pistons of this invention may be arranged as a series of interconnected collapsible boxes, where each surface of said piston may comprise a magnetic, paramagnetic or superparamagnetic material, such that when said device is subjected to a magnetic field, the piston collapses. In some embodiments, at least a terminal surface of the piston, most distally located to a point of application of a magnetic field comprises a magnetic, paramagnetic or superparamagnetic material, which upon application of the magnetic field stimulates the collapse of the piston, thereby removing prior occlusion or partial occlusion of the proximally located vessel.

[0084] In another embodiment, at least a terminal surface of the piston, most proximally located to a point of application of a magnetic field comprises a magnetic, paramagnetic or superparamagnetic material, is so constructed that upon application of the magnetic field and drawing close of the other surfaces of the piston, stimulates the collapse of the piston, thereby removing prior occlusion or partial occlusion of the proximally located vessel.

[0085] In another embodiment, at least a side surface or side surfaces of the piston comprise/s a magnetic, paramagnetic or superparamagnetic material, and is so constructed that upon application of the magnetic field and drawing close of the other surfaces of the piston, stimulates the collapse of the piston, thereby removing prior occlusion or partial occlusion of the proximally located vessel.

[0086] As will be appreciated by the skilled artisan, the springs of this invention may, as well, be constructed such that each surface of said spring may comprise a magnetic, paramagnetic or superparamagnetic material, such that when said device is subjected to a magnetic field, the spring collapses. In some embodiments, at least a terminal surface of the spring, most distally located to a point of application of a magnetic field, or in some embodiments, at least a terminal surface of the piston, most proximally located to a point of application of a magnetic field comprises a magnetic, paramagnetic or superparamagnetic material, which upon application of the magnetic field stimulates the collapse of the spring, via mechanism similar to that described hereinabove with regard to the described pistons, thereby removing prior occlusion or partial occlusion of the proximally located vessel.

[0087] In another embodiment, at least a side surface or side surfaces of the spring comprise/s a magnetic, paramagnetic or superparamagnetic material, and is/are so constructed that upon application of the magnetic field and drawing close of the other surfaces of the spring, stimulates the collapse of the spring, thereby removing prior occlusion or partial occlusion of the proximally located vessel.

[0088] In some embodiments, the spring structures of this invention will have a diameter of between 10-30 mm, or in some embodiments, between 15 -20 mm. In some embodiments, the spring structures of this invention, when extended have a width of between 5-30 mm, or in some embodiments, between 10-20 mm. The skilled artisan will appreciate that the spring structures of this invention may have a diameter that is appropriate to the specific locale and application of the systems of this invention, and sizes in ranges beyond those described hereinabove, are envisioned, as well.

[0089] The pistons and/or springs of this invention may each exist in an extended and compact form, which piston/spring when in an extended form provides for a defined flow within said vessel, which, in some embodiments, may produce a flow that is substantially laminar or pulsatile, and valve devices comprising such piston/spring may partially or entirely occlude a vessel located proximally thereto to which said valve is operationally deployed.

[0090] Referring now to Figure 3C, this aspect depicts another view of this embodiment of the valve of this invention, rotated by 90 degrees as compared to the view depicted in Figure 3B, where the most extended surface 3-30 is of a length that is comparable to or exceeds that of the base frame profile 3-40. In this aspect, upon collapse of the expanding profiles 3-10, the most extended surface covers at least part of the base frame profile 3-40, which can be seen in the top view depicted in Figure 3D.

[0091] Figures 3E and 3H depict top views of a collapsed device depicted in Figures 3A-3D, and Figures 3F and 3G depict side views of the fully collapsed device, which provides an indication of the volume of the collapsed device. Figures 3I-3J depict alternate views including top and side views of semi and fully extended views of the embodied valve device depicted in Figures 3A and

3D. Figures 3I and 3J show side views of extended (panel 1) and collapsed (panel 2) versions of the device, with Figure 3J being rotated 90 degrees with respect to Figure 3I. Some examples of the dimensions of the valve device profile are presented (values are in mm). Figure 3K shows a top view of the embodied device where an example of the dimensions of the most extended surface of the terminal profile is shown. Panels 1 and 2 of Figure 3L show collapsed and extended configurations, respectively, of the valve device, of a top and side view of the embodied device.

[0092] As will be appreciated by the skilled artisan, the valve may be positioned operationally proximal to any vessel of choice, and including shunts or native and artificial vessels, such as blood vessels, artificial urethras, feeding tubes, etc., and as will be suitable for any appropriate application thereof.

[0093] In one embodiment, a solenoid structure is positioned proximally to the valve device as depicted in Figure 3D. In some embodiments, the system may further comprise a location indicator, which provides a signal which in turn advises when optimal positioning occurs for minimum electromagnetic radiation loss and optimal device functioning.

[0094] Figure 4 schematically depicts embodiments of the systems of this invention, which comprise a spring structure as described hereinabove.

[0095] The spring structure is in the collapsed position in this view (Figure 4A). According to this aspect, in the collapsed position, at least part of the collapsible components of the spring structure 4-10 are nested within a base frame profile 4-30. In some embodiments, the spring structure may comprise a series of expanding profiles, which in some embodiments, may have a width of 0.35 mm, for example 3-10, which are spaced apart from a previous layer profile, for example by a spacing of 0.03 mm, for example 3-20. Figure 3B depicts a side view of an embodiment of the spring structure when in an extended conformation. According to this aspect, expanding profiles 4-10 form a tiered arrangement such that most of the extended layers may collapse within a preceding layer.

[0096] According to this aspect, and in some embodiments, the most extended surface 4-30 comprises a magnetic, paramagnetic or superparamagnetic material, such that upon application of a source of a magnetic field, located proximally to the base frame profile 4-40 results in the attraction of the most extended surface toward the source, thereby causing the collapse of the collapsible structure. Figure 4C provides a bottom view of the extended form of the spring structure where the view shows the extension downward of the spring structure.

[0097] As described above with regard to Figure 3, in regard to Figures 4C and 4D, the spring 4-10 is present in its extended form and the vessel located proximally thereto 4-50 to which the device is operationally connected is at least partially occluded thereby, as a consequence of the pressure thereupon exerted by the extended piston. The spring, according to this embodiment, is magnetically or electromagnetically actuated, such that when a magnetic field is applied to the region proximal to the valve device 4-30, the spring collapses such that the occlusion of the vessel is now drastically diminished or removed.

[0098] In some embodiments, a solenoid structure may be positioned proximally to the valve device and in some embodiments, the system may further comprise a location indicator 5-100, which provides a signal which in turn advises when optimal positioning occurs for minimum electromagnetic radiation loss and optimal device functioning (Figures 5A and 5B). The valve device may be implanted beneath the skin (5-70) and proximal to the desired vessel 5-50. According to this aspect, and in one embodiment, the spring structure 5-10 is positioned proximally to the vessel whose controlled constriction is desired, such that the most extended surface of the spring structure 5-30 is proximal to the vessel. The valve device comprising the spring structure may be placed within a casing 5-60, as depicted. The systems of the invention may further comprise a solenoid structure, comprising a magnetic armature 5-80 and magnetic coil, 5-90, which when activated generates a local magnetic field which results in the collapse of the spring, and release of controlled vessel constriction. A location indicator 5-100 may be incorporated within the systems of the invention, which may assist in the determination of the optimal positioning and effect of the application of the magnetic field with regard to the orientation of the valve device for optimal device deployment. Figure 5B depicts comparable use of an electromagnetic actuator 5-110 in place of the solenoid structure.

[0099] In some embodiments, the field strength is controlled as a consequence of the voltage applied to the solenoid structure, which for example, is between 5-30 Volts DC.

[00100] In some embodiments the dimensions of the rectangular piston or spring change as a result of the choice of vessel proximal to which the valve device is implanted. In some embodiments, the length of the rectangular piston, or in some embodiments, the diameter of the spring structure will have a range of about 4mm to 10mm

[00101] The valve devices of this invention may comprise a controllable substantially rectangular collapsible piston or a controllable, extendible spring structure as described herein, which piston and/or spring structures may be contained within a casing, as depicted in Figure 6. Figure 6A depicts a rectangular casing 6-20 which casing accommodates a substantially rectangular collapsible piston, as herein described, by having a rectangular profile within the casing structure, which profile is configured to contain the devices of this invention. The casing may further contain a cylindrical structure or structures 6-30, which accommodate the proximal vessel, whose regulated constriction or occlusion is effected by the proximal placement of the devices of this invention. The casing may

containing removable parts, such that the casing may be assembled in situ, for example, snaps may be incorporated within each half of the casing, such that the casing may be joined at a midline 6-40 via a snap to arrangement. As will be appreciated by the skilled artisan, any connection means may be used, such as hook/eye or tab/insert closure means, and others, as are known in the art. It is also understood that the casing may be assembled of more than 2 pieces, for example, the casing may be prepared as quadrants, which may be assembled in situ, as will be appreciated by the skilled artisan. In some embodiments, the casing may be comprised of a single piece, for example comprising a hinge structure, as well as a snap-to or other closure mechanism, such that the casing may be opened and closed in situ to accommodate implantation of the valves of the invention proximal to a desired vessel, at any desired location.

[00102] Figure 6B provides another embodiment of a casing of this invention, serving as an example for the considerations for constructing other appropriate casings to accommodate valve devices of this invention. In some embodiments, the casings may be so constructed to appropriately accommodate the spring-structure containing devices of this invention. Referring now to Figure 6B, the casing may comprise a disk-shaped structure or structures 6-20, which accommodate the spring structure 6-50, and may further comprise a cylindrical shaped structure or structures 6-30, which accommodate the proximal vessel, for example, an incorporated shunt, or artificial blood vessel 6-60, whose regulated constriction or occlusion is effected by the proximal placement of the devices of this invention. The casing may contain removable parts, such that the casing may be assembled in situ, for example, snaps may be incorporated within each half of the casing, such that the casing may be joined at a midline via a snap to arrangement, as described above.

[00103] In some embodiments, the systems of this invention may comprise a casing containing an artificial vessel located proximally to a valve device as described, enclosed within a casing, as described herein, which is fully assembled, and may be used in connection with surgical creation of an appropriate structure, for example, a fistula, as will be appreciated by the skilled artisan.

[00104] Figures 6C and 6D depict side views of the device 6-70 in which the positioning of the spring structure 6-90 with respect to the vessel 6-80 is evident, where the spring structure is in its extended form and vessel constriction is evident. Figure 7A-D depicts top, bottom and side views of this embodiment of the device.

[00105] The casing and shunt as described hereinabove, may be constructed of any biocompatible material, and include any of the polymers as listed hereinabove. In some embodiments, the thickness of the casing may range from about 50 micrometers to about 1 mm. In some embodiments, the thickness of the casing may range from about 100 micrometers to about 0.4 mm.

[00106] In some embodiments, the spring structure further comprises a base and a pressure plate,

wherein the pressure plate has a substantially rectangular profile with define length and wherein during extension the base is distal to the pressure plate. In some embodiments, the pressure plate and base are integral parts of the spring structure, which is comprised of a single solid structure, wherein the base and pressure plate represent basal and apical surfaces of the spring structure, and not separate structures attached to the spring. In another embodiment, the base and pressure plate represent separate parts attached to the apical and basal surfaces of the spring structure. In some embodiments, the base and pressure plate are comprised of the same materials as the spring structure, and in some embodiments, the base and/or pressure plate are comprised of different materials as the spring structure.

[00107] In some embodiments, at least the pressure plate is comprised of a magnetic, paramagnetic or superparamagnetic material. In some embodiments, according to this aspect, the base and spring structure are not comprised of a magnetic, paramagnetic or superparamagnetic material, as described hereinabove.

[00108] In some embodiments, the systems of this invention may be as depicted in Figure 8A. According to this aspect, in the active state, under the influence of an applied electro magnetic field, the controllable substantially rectangular collapsible piston 8-10 can be electrically, magnetically or electromagnetically actuated, resulting in the raising of the same, which then facilitates passage of fluids through the proximally located vessel 8-20 and thereby through the fistula 8-30. In contrast, when in the passive state, the controllable substantially rectangular collapsible piston 8-10 is not drawn upward, and thereby presses on the proximally located vessel, resulting in total or partial occlusion of the proximal vessel.

[00109] Figure 8B depicts another embodiment. According to this aspect, the controllable substantially rectangular collapsible piston is arranged as part of a lever 8-40, which can be electrically, magnetically or electromagnetically actuated, resulting in the raising of the same, which then facilitates passage of fluids through the proximally located vessel.

[00110] In some embodiments, the material of which the valve is comprised is a composite of a single part made of a ferromagnetic alloy. In some embodiments, the material is a composite of at least two materials. In some embodiments, the valve is comprised of at least one magnetic, paramagnetic or superparamagnetic material.

[00111] In some embodiments, the valve is comprised of two or more materials. In some embodiments, the valve is comprised of an outer biocompatible material, which encases an underlying magnetic, paramagnetic or superparamagnetic material. In some embodiments, according to this aspect, the outer biocompatible material does not interfere with the effects of an applied magnetic field on an underlying magnetic, paramagnetic or superparamagnetic material.

[00112] In some embodiments, the composite material may comprise any biocompatible material and further comprise a magnetic, paramagnetic or superparamagnetic material. In some embodiments, such biocompatible material may comprise a biocompatible elastomer , having magnetic particles dispersed therein. For example, and in some embodiments, the polymer may comprise polydimethylsiloxance (PDMS) having micro- or nano-particles dispersed therein, which particles contain Fe_3O_4. In one embodiment, the elastomer may be a copolymer. In another embodiment, the polymers may be homo- or, in another embodiment hetero-polymers. In another embodiment, the polymers may be synthetic, or, in another embodiment, natural polymers. In another embodiment, the polymers may be water-soluble. In another embodiment, the polymers may be free radical random copolymers, or, in another embodiment, graft copolymers. In one embodiment, the polymers may comprise polysaccharides, oligosaccharides, proteins, peptides or nucleic acids.

[00113] It is to be understood that any polymers, which may be incorporated within the described valve devices of this invention, such as, any natural or synthetic polymer, are to be considered as part of this invention.

[00114] In another embodiment, the polymer comprises a surfactant, a polyethylene glycol, a lignosulfonate, a polyacrylarnide or a biopolymer. In another embodiment, the biopolymer may comprise polypeptides, cellulose and its derivatives such as hydroxyethyl cellulose and carboxymethyl cellulose, alginate, chitosan, lipid, dextan, starch, gellan gum or other polysaccharides, or a combination thereof. In another embodiment, the polymer comprises polyethylene oxide or in another embodiment, the polymer comprises polyacrylic acid. In another embodiment, the polymeric matrix may comprise polyacrylic acid and SDS.

[00115] In one embodiment, magnetite particles may be incorporated within the polymers as herein described to form the composite materials used in accordance with the preparation of the valve devices of this invention. In another embodiment, the composite comprises ferromagnetic nanoparticles and an organic polymeric matrix. In another embodiment, according to this aspect of the invention, the nanoparticles are monodispersed within the polymeric matrix.

[00116] In some embodiments, the nanoparticles may comprise Fe, Co, Ni, Gd, Dy, MnAs, MnBi, MnSb, CrO_2, $MnOFe_2O_3$, $FeOFe_2O_3$, $NiOFe_2O_3$, $CuOFe_2O_3$, $MgOFe_2O_3$, EuO, $Y_3Fe_5O_{12}$.

[00117] In some embodiments, the piston or spring may comprise a composite of a polymer and magnetic, paramagnetic or superparamagnetic material, where each material is present as a separate layer.

[00118] In one embodiment, the choice of polymer utilized may be a function of the particles employed. In one embodiment, the polymer may comprise polyacrylic acid, polystyrene sulfonic

acid, polyvinyl sulfonic acid, polyethylene oxide polypropylene oxide, polyvinyl alcohol, or a combination thereof.

[00119] In some embodiments, the invention makes use of electroactive polymers.

[00120] Electroactive Polymers, or EAPs, are polymers that exhibit a change in size or shape when stimulated by an electric field. The most common applications of this type of material are in actuators and sensors. A typical characteristic property of an EAP is that they will undergo a large amount of deformation while sustaining large forces. EAP materials can be easily manufactured into various shapes due to the ease in processing many polymeric materials, making them very versatile materials. One potential application for EAPs is that they can potentially be integrated into microelectromechanical systems (MEMS) to produce smart actuators. As the most prospective practical research direction, EAPs have been utilized in artificial muscles. Their ability to emulate the operation of biological muscles with high fracture toughness, large actuation strain and inherent vibration damping draw the attention of scientists in this field.

[00121] In some embodiments, the device may be comprised of an electro-active polymer (EAP), which responds to external electrical stimulation by displaying a significant shape or size displacement.

[00122] In some embodiments, the EAP may be chosen from either of the two major categories that EAPs, i.e. either from electronic or ionic EAPs.

[00123] In some embodiments, EAPs are particularly suited for use, when the principle mode of operation of the device relies on the application of electric or electromagnetic energy, since under electrical excitation, EAPs contract and thus form a basis for flow control actuators.

[00124] In some embodiments, the devices of this invention are in the form of a shunt having an overal flat shape and constructed of a kinetic structure made of EAP material positioned on top of, for example, the arteriovenous fistula. Figures 9A and 9B provide a schematic of an embodied device operating in accordance with this aspect of the invention. According to this aspect, and in one embodiment, the kinetic structure 9-30 will respond to an external electrical stimulation 9-10 delivered by transmitting energy from the external side of the arm skin 9-20 to the internal side using transformer basic technology while on side of the coil is externally and the other side is internally under skin. A rectifier will in the internal side will create the required DC voltage. Figure 9A depicts the passive conformation, whereby the Flow regulators of this invention partially or entirely occlude the proximally located vessel. Figure 9B depicts the active mode, whereby upon appropriate application of the source for magnetic or electromagnetic actuation, the kinetic structure 9-30 is raised and thereby greater fluid flow is facilitated. Figures 9C and 9D demonstrate another embodiment of this invention, whereby instead of the power supply being located near the skin, as

shown in Figures 9A and 9B, in this aspect, the power supply is located proximally to the device, and therefore is implanted within the skin. According to this aspect, and in one embodiment, the kinetic structure 9-30 will respond to an internal electrical stimulation 9-10 delivered by transmitting energy from the internal side of the arm skin 9-20.

[00125] Figure 9E depicts an embodiment of this aspect, wherein a flat coil 9-90 may function as the internal and/or external power supply, which provides certain advantages, for example, a smaller profile, which is particularly useful in devices implanted under the skin.

[00126] A proposed energy transmission is based on high frequency of over ten kilo hertz power supply where the output is connected to one side of a split transformer coil that induce voltage to the other side the transformer coil located as part of the under-skin or internally power supply. The high frequency voltage is rectified by simple diode in order to create DC voltage for the activation of the EAP. The power correlates to the external power supply wattage while the voltage correlates to the ratio of the number of wire turns of the external coil to the number of wire turns of the internal coil. Working with high frequency allows a wide air gap that can reach up to three centimeters between the external coil to the internal coil.

[00127] In some embodiments, the systems of this invention may further comprise a solenoid whose long axis is positioned substantially perpendicularly to that of the pressure plate wherein generation of a magnetic field by the solenoid results in the pressure plate being drawn proximal to the base and minimal electromagnetic radiation is lost as a result of the diminished gap between the pressure plate and the base

[00128] In some embodiments, the solenoid may be a component of the systems of this invention, which comprise a spring structure or collapsible piston as herein described, which spring structure does not comprise a base or pressure plate, wherein the long axis of the solenoid is positioned substantially perpendicularly to that of the long axis of the spring structure or collapsible piston surface located most distally thereto, wherein generation of a magnetic field by the solenoid results in the distal surface of the spring structure or collapsible piston being drawn proximally and minimal electromagnetic radiation is lost as a result of the diminished gap between the proximal and distal surfaces of the spring and/or piston structures.

[00129] The ability to transmit energy (voltage and current) to the shunt flow control actuator enable the use of solenoids or other configuration of actuator to create the desired force required to reduce flow and pressure in the invented device.

[00130] The term solenoid is well known in the art. In some embodiments, reference to a solenoid herein is to a coil wound into a tightly packed helix, and in some embodiments, refers to a long, thin loop of wire, wrapped around a metallic core, which produces a magnetic field when an electric current is passed there-through.

[00131] In some embodiments, the solenoids create controlled magnetic fields and are applied herein as electromagnets. In some embodiments, reference to a solenoid herein includes its ability to act as a magnet designed to produce a uniform magnetic field in a volume of space.

[00132] In some embodiments, the use of a solenoid containing system as herein described, allows for creation of a magnetic field which raises the piston. In its passive state, such piston is kept in position by for example, a spring, which under non-active conditions results in at least partial occlusion of the proximally located vessel. .

[00133] Figures 10A and 10B provide a schematic of an embodied device operating in accordance with this aspect of the invention. According to this aspect, and in one embodiment, the kinetic structure 10-30 will respond to an external electrical stimulation 10-10 delivered by transmitting energy from the external side of the arm skin 10-20 to the internal side using basic transformer technology while one side of the coil is located externally and the other side is located internally under the skin. A rectifier will in the internal side will create the required DC voltage. Figure 10A depicts the passive conformation, whereby the Flow regulators of this invention partially or entirely occlude the proximally located vessel. Figure 10B depicts the active mode, whereby upon appropriate application of the source for magnetic or electromagnetic actuation, the kinetic structure 10-30 is raised and thereby greater fluid flow is facilitated**.** Figures 10C and 10D demonstrate another embodiment of this invention, whereby instead of the power supply being located near the skin, as shown in Figures 10A and 10B, in this aspect, the power supply is located proximally to the device, and therefore is implanted within the skin. According to this aspect, and in one embodiment, the kinetic structure 10-30 will respond to an internal electrical stimulation 10-10 delivered by transmitting energy from the internal side of the arm skin 10-20. The solenoid 10-50 location is depicted in each figure.

[00134] It will be appreciated that such embodiments operate similarly, and the skilled artisan will know, for example, to include additional elements, such as wiring, for proper activation of the device and appropriate creation of the magnetic field necessary to raise the piston in the device, as herein described.

[00135] In some embodiments, the device is fitted with a flat coil placed anteriorly with respect to positioning the device when implanted in the skin, to enable the use of a low height implanted power supply under the skin (Figure 11 and Figure 9E). **.**This element can be considered to be an equivalent of the volumetric coil, as seen in Figures 9 and 10 and as depicted in Figure 12**.**

[00136] The ability to transmit energy (voltage and current) to the implanted power supply is useful for many other application and devices like activation of solenoids, pumps, actuators, charging

of battery operated implanted device and others as will be appreciated by the skilled artisan.

[00137] The systems of this invention are distinguished, in some embodiments, over prior such graft systems in that the valve devices provide for a collapsible piston or spring structure, which piston/spring structure when in an extended form provides for a defined flow within the vessel, which flow is substantially laminar or pulsatile. In some embodiments, the result of such laminar or pulsatile flow is a flow through which exhibits minimal shear stress, minimal turbulence, minimal stagnation points or a combination thereof.

[00138] In some embodiments, such effects can readily be ascertained, for example via the use of a Doppler device or phonantiography, or other methods well known to the skilled artisan.

[00139] In one embodiment, the controllable displacement regulator systems of this invention may comprise a first and second valve, for example, for an application wherein the first valve is suitable for deployment proximally to an artery and a second valve is suitable for deployment proximally to a vein to form anastomoses thereto.

[00140] In accordance with the present invention, the system includes at least one valve device positioned at the arterial end of the arteriovenous graft. In one embodiment, for instance, the valve device comprises a controllable substantially rectangular collapsible piston or spring structure, which piston/spring structure when in an extended form provides for a defined blood flow within said blood vessel. The piston/spring structure is positioned so as to restrict blood flow through the arteriovenous graft when extended.

[00141] In one particular embodiment, the magnetically activated piston/spring structure may be activated when exposed to a changing magnetic field, such as a pulsing magnetic field. In this embodiment, the valve device may include a coil member configured to convert a changing magnetic field into an electric current. The coil member is in communication with a solenoid. The solenoid is configured to move the piston and open or close the valve device when electric current is received from the coil member.

[00142] In general, according to some aspects of the invention, the valve device may be positioned at the arterial end of the arteriovenous graft as close as possible to the intersection of the graft with an artery. For example, the valve device may be positioned so as to restrict blood flow through the arteriovenous graft at a location that is less than about 10 mm from the intersection of the arteriovenous graft and an artery.

[00143] In one embodiment, the valve device may comprise a magnetically activated piston. In this embodiment, when a magnetic field is placed in close proximity to the valve device, the piston is moved for either opening or closing the valve device. For example, in one embodiment, placing a magnetic field in close proximity to the valve device opens the device which normally remains

closed.

[00144] In one embodiment, according to this aspect, the controllable displacement regulator systems may further include a second valve device positioned at the venous end of the arteriovenous graft. The second valve device may be any suitable valve device as described above. The second valve device, for instance, may be identical to the first valve device or, alternatively, may be different.

[00145] In some embodiments, the controllable displacement regulator system may be used as an arteriovenous graft for hemodialysis applications.

[00146] During hemodialysis, a magnetic field is applied to the valve devices of this invention, such that the blood vessel partially, nearly completely or completely occluded is now in the open position meaning opening of full cross section of vessel, and blood can be flow from the arterial vessel to the vein vessel freely, means, blood from the said vessel close to the arterial vein is exerted into the dialysis machine where it is artificially purified and then injected back into the said vessel close to its connection to the vein vessel, therefore flushed by the said vessel inner flow and pressure into the vein vascular system in a synchronized manner, via the heart bit pulsatile flow comes from the arterial line and flushed into the vein line, as will be appreciated by the skilled artisan**.**

[00147] Referring now to Figure 13, activation of the valve devices of this invention **13-10** to be in the open position result in blood exchange via the fistula **13-20** which is shunted to a hemodialysis machine **13-30**. Detoxified blood is returned to the fistula **13-20**, where it can then be circulated through the proximally located artery **13-40** and vein **13-50**, and the valve devices of this invention can then be constricted partially or fully until a next detoxification is desired.**.** When hemodialysis is not being conducted, however, the valve devices of the present invention may be activated in order to minimize arterial steal and prevent thrombosis of the graft.

[00148] For example, in one embodiment of the present invention, when the arteriovenous graft system only includes a single valve device at the arterial end, after hemodialysis has ended, the valve device is closed in a way of partial occlusion which causes about seventy percent reduction in blood flow and pressure through the shunt, or in some embodiments, the valve device is essentially closed, thus preventing significant or undesired blood flow through the graft.

[00149] In another embodiment, after hemodialysis, the valve device is partially closed to a first position thereby constricting the arteriovenous graft and reducing blood flow and pressure through the graft.

[00150] According to this aspect and in some embodiments, the patient is monitored over a period of time, such as days or weeks, and the valve device may be selectively opened or closed from the first position until arterial steal is minimized. In this embodiment, the valve device is closed an

amount sufficient to reduce blood flow and blood pressure through the graft without slowing the blood flow to a point where blood clots may form.

[00151] As described above, in another embodiment of the present invention, the arteriovenous graft system includes a first valve device at the arterial end and a second valve device at the venous end. In this embodiment, after hemodialysis has ended, the first valve device at the arterial end is partially closed thereby preventing high blood flow and high blood pressure through the graft.

[00152] According to this aspect, and in some embodiments, when the arteriovenous graft system of the present invention contains a single valve device positioned at the arterial end, in one embodiment, the valve device may be positioned so as to constrict blood flow through the graft when hemodialysis is not occurring. In this embodiment, arterial steal is not being completely prevented but is being minimized. In particular, the single valve device constricts the graft so that blood flow through the graft continues without clotting but is at a reduced flow and pressure rate.

[00153] In this embodiment, the patient's condition may need to be monitored over a period of time, such as days or weeks, and the valve device may be adjusted in order to minimize arterial blood steal without causing a complete blood stoppage in the vessel into which the device has been implanted. For instance, over several days or weeks, the arteriovenous graft of the patient may be monitored and the valve device may be adjusted so as to gradually increase or decrease the narrowing of the arteriovenous graft. The ultimate position of the valve will vary depending upon the patient and the location of the arteriovenous graft.

[00154] In order to activate the valve device, an electromagnetic source, or magnetic source, for example a magnetic key is placed close to the skin of a patient into which a valve device of this invention has been implanted. According to this aspect and in one embodiment, the magnetic source may be an electromagnet that creates a pulsating magnetic field. In some embodiments, the pulsating magnetic field may be converted into an electric current, which in turn may be configured either to open or to close the valve device.

[00155] In one embodiment, for instance, the valve device may normally be found in a closed position partially occluding the arteriovenous graft reducing blood flow and pressure. When the magnetic source, however, is placed adjacent to the patient's skin, the valve device then fully opens allowing blood to flow through the graft. In other embodiments, however, it should be understood that the valve device may be configured to close when placed adjacent to the magnetic source.

[00156] In some embodiments, the systems of this invention are not restricted to hemodialysis applications.

[00157] In some embodiments, the systems of this invention may comprise valves which are regulatable by two mechanisms, i.e. in response to an applied electric field or electro-magnetic field,

and in addition, in response to the application of a threshold pressure value. For example, and in some embodiments, when the systems of this invention are used in applications to prevent or mitigate urinary incontinence, such valves may have a primary mechanism whereby flow through the vessel may be accomplished upon application of an appropriate electric field or electro-magnetic field, or in some embodiments, in response to internal pressure applied by the treated subject, for example due to the force applied during urination.

[00158] Urinary incontinence (UI) may manifest in the release of small or large amounts of urine in a subject suffering therefrom.

[00159] In some embodiments, the invention is particularly suited to the treatment of urinary incontinence. According to this aspect, and in some embodiments, a micro-system is implanted within the urethra, which assumes a "duck plug" arrangement. According to this aspect, the duck plug is a valve device, which when in a passive state prevents urinary passage, for example, with the aid of an active diaphragm, and whereby, when an external electro-magnetic field is applied, the diaphragm becomes distorted, allowing for valve opening and urinary passage. In some embodiments, the device according to this aspect is comprised of a flexible, biocompatible material.

[00160] In some embodiments, according to this aspect, the valve is magnetically actuated by a magnetic field generated from, for example, a controller located outside the patient body. In some embodiments, the controller allows for patient bladder control on-demand.

[00161] In some embodiments, according to this aspect, the device may implanted through non-surgical insertion into the urethra. According to this aspect, and in one embodiment, the device may comprise a tubular body having a valve member located at the proximal end of the tubular body. According to this aspect, the valve may be constructed to comprise a "Duck Beak" configuration, which is held together by the tubular body, and having a volumetric configuration, which prevents the patient from undesired urine discharge when in the closed configuration (Figure 14A). According to this aspect, and in one embodiment, when a magnetic field is applied to the "Duck Beak" type valve, the device facilitates an overall change in valve structure, for example, augmentation of the tubular shape via 14-20, resulting in the opening of "Duck Beak" thereby facilitating urine discharge in the direction of the arrow at 14-30 (Figure 14 B).

[00162] In some embodiments, the systems of this invention may be used in the treatment or alleviation of pulmonary congestion and edema. According to this aspect, and in one embodiment, when cardiac function becomes inadequate and the left ventricle can no longer handle pulmonary venous return, the blood volume entering the pulmonary circulation thereby surpasses the blood volume which the left ventricle can pump into the aorta, leading to increased cardiac preload, transudation of fluid into the alveolar space with the beginning of acute cardiogenic pulmonary

edema (life-threatening condition). Early aggressive preload reduction by activation “on demand” of a valve device of this invention placed in the inferior vena cave in patients with high risk for recurrent acute pulmonary congestion and edema can result in an immediate decrease of venous return and effective resolving of acute cardiogenic pulmonary edema.

[00163] In another embodiment, the systems of this invention find application in the treatment of erectile dysfunction. According to this aspect and in one embodiment, blood leaves the erectile tissue only through a drainage system of veins around the outside wall of the corpus cavernosum while the tunica albuginea helps trap the blood in the corpora cavernosa, thereby sustaining erection (preventing blood from leaving), resulting in penis rigidity. Use of the systems of this invention, for example, implantation of the valve devices of this invention within the deep dorsal vein, the main cavernous vein and/or the internal pudendal vein would improve sustaining erection by diminishing or preventing venous return. In some embodiments, an automatic deactivation mechanism for the device may be used, which for example, may be provided for about 20-minute interval following device activation. In this aspect, and in one embodiment, device activation entails constriction of the proximal blood vessels, as opposed to for example, some embodiments, described hereinabove with regard to hemodialysis application, where device activation entailed relief of vessel constriction/occlusion.

[00164] In some embodiments, for advanced stages of the erectile dysfunction combined use of the systems of this invention and the administration of available pharmaceutical treatments, such as, for example, PDE5 inhibitors (Viagra, Cialis, Levitra) may be useful.

[00165] In some embodiments, the systems of this invention may be useful in the treatment of hypertensive renal injury. Intra-renal injury caused by long-standing hypertension is the major factor responsible for renal dysfunction in the majority of patients who have hypertensive chronic kidney disease. High blood pressure is a key pathogenic factor that contributes to deterioration of kidney function. In some embodiments, the systems of this invention may be useful in the control of intra-kidneys blood pressure, for example, via implantation of the valve devices of this invention in one or both renal arteries in patients with severe uncontrolled hypertension. The regulation of blood flow and thereby blood pressure with the devices of this invention facilitates reduction of renal hypertension, according to this aspect of the invention.

[00166] In some embodiments, the systems of this invention may be useful in the treatment of hypertensive cerebral injury (encephalopathy). Hypertensive encephalopathy refers to the presence of signs of cerebral edema caused by breakthrough hyperperfusion from severe and sudden rises in blood pressure. In severe hypertension autoregulation fails. The ensuing rise in pressure in the arterioles and capillaries leads to damage to the vascular wall. Within the brain, failure of

autoregulation leads to the development of cerebral edema and the clinical picture of hypertensive encephalopathy.

[00167] In some aspects of this invention, controlled graded intra-cerebral blood pressure reduction may be achieved via the use of the systems of this invention. In some embodiments, the valve device may be implanted in one or both common carotid arteries, in the innominate and subclavian arteries, or internal carotid arteries in patients with severe uncontrolled hypertension, whereby immediate decrease of elevated blood pressure by valve device activation may be effected, and thereby resolving acute hypertensive encephalopathy.

[00168] In some embodiments, the systems of this invention may be useful in feeding tube applications. It is a known phenomenon that feeding tubes often become occluded, necessitate clearance after and before each use, and often require replacement, in addition to serving as a source of infection, due to the open nature of the systems in use to date. The systems of this invention would provide a means for effective closure of such feeding tubes, enhancing their lifespan in use in a patient and potentially reducing their serving as a source for infection.

[00169] It is to be understood that the implantation of the valve devices as herein described may be conducted via any of the means known in the art, and may include percutaneous, minimal invasive surgery or laparoscopy for insertion, or other surgical means.

[00170] The devices of this invention in accordance with the uses herein described, may be implanted in a permanent or semi-permanent manner, or may be removed within a short time frame (hours to weeks) post implantation.

EXAMPLES

Application Of An Implantable Controllable Displacement Regulator System In An Animal Model

[00171] A total of 4 mature mixed breed, farm pigs, weighing between 30-40 kg, will be utilized. Embodied shunts such as depicted in the various Figures of this inention, or as described herein are implanted as appropriate. For example, pigs are anesthetized with a combination of xylazine, telazol and atropine and intubated. Isoflurane may be used for maintenance anesthesia. Seven cm, 4 mm ID, loop PTFE grafts (30 micron internodal distance) are placed between the femoral artery and femoral vein using standard surgical techniques. End-to-side anastomoses are made with a continuous 6/0 polypropylene suture. Special care is taken to ensure that there are no kinks in the graft and that it is well placed in a created pocket. The fascia and skin are closed in layers using 3/0 Dexon and silk. Buprenex is used for post-operative analgesia as needed. All pigs are administered Aspirin EC 325 mg from day -1 to the time of sacrifice, together with a single dose of intra-operative heparin (150 U/kg). Graft patency is confirmed immediately by auscultation and Doppler.

[00172] Starting 6 days before the operation, the pigs receive acetylsalicylic acid 80 mg/d. Clopidogrel 225 mg is given 1 day before operation and continued at a dose of 75 mg/d until termination of the study. Optionally an intravenous bolus of 10 mg abciximab is added to the anticoagulant regimen. Once bilateral ePTFE-AV grafts are implanted, an ID-BFR device will be positioned over **one** of the 2 grafts at a randomly determined side and the contra-lateral AV graft will be served as a control.

[00173] Directly after AV grafting implementation and following ID-SBFR placement the different regimes (flow & pressure) of the shunt flow regulation through the fistula cross sectional reduction versus full open shunt flow volume will be measured several times by activating the ID-SBFR device using magnetic stimulation at cross section reduction levels of:

13.1 - 50%

13.2 - 70%

[00174] The different regimes (0 – full flow volume, 50, 70% cross section reduction) graft flow will be quantified, proximal arterial (before anastomosis) and distal arterial (post-anastomosis) flows using Doppler-Duplex ultrasonography. (Optionally: Flow measurements will be performed using a perivascular flow probe). Graft flow will be calculated as flow through the artery proximal to the arterial anastomosis minus the flow through the distal artery).

[00175] The performance and safety of the device will be evaluated in the study group immediately after graft creation by auscultation and Doppler **[**. In addition, the effect of SSCT implementation at different regimes during 1 hour on the shunt and the distal artery flow characteristics, in comparison to the fully open regular contra-lateral shunt serving as a paired control will be assessed, as well.

[00176] It is to be understood that repeated use of reference characters in the present specification and drawings is intended to represent the same or analogous features of the invention.

[00177] It will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as set forth in the appended claims. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the claims.

[00178] In the claims articles such as "a,", "an" and "the" mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" or "and/or" between members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes

embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also includes embodiments in which more than one or all of the group members are present in, employed in or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention provides, in various embodiments, all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim dependent on the same base claim unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. Where elements are presented as lists, e.g. in Markush group format or the like, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not in every case been specifically set forth *in haec verba* herein. Certain claims are presented in dependent form for the sake of convenience, but Applicant reserves the right to rewrite any dependent claim in independent format to include the elements or limitations of the independent claim and any other claim(s) on which such claim depends, and such rewritten claim is to be considered equivalent in all respects to the dependent claim in whatever form it is in (either amended or unamended) prior to being rewritten in independent format

CLAIMS

What is claimed is:

1. An implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion or partial occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined flow and pressure within said vessel, which piston is magnetically or electromagnetically actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material.

2. The regulator system of claim 1, wherein said regulator system specifically controls liquid transit through a body vessel.

3. The regulator system of claim 2, wherein said regulator system functions as a controllable arteriovenous graft system.

4. The regulator system of claim 2, wherein said regulator system functions such that fluid flow through said body vessel is substantially laminar or pulsatile.

5. The regulator system of claim 2, wherein when said piston is in said extended form, flow through said vessel exhibits minimal shear stress, minimal turbulence, minimal stagnation points or a combination thereof.

6. The regulator system of claim 1, wherein said piston is of a length that correlates with a desired flow rate, pressure rate or combination thereof in said vessel.

7. The regulator system of claim 1, wherein said piston is a composite of a single part made of ferromagnetic alloy.

8. The regulator system of claim 1, wherein said piston is a composite of at least two materials.

9. The regulator system of claim 1, wherein said magnetic, paramagnetic or superparamagnetic material is present as a hollow layer and additional layers of said piston collapse within said hollow layer when said system is subjected to a magnetic field.

10. The regulator system of claim 9, wherein when said system is no longer subjected to a magnetic field, said piston is present in an extended form.

11. The regulator system of claim 9, wherein when said system is no longer subjected to a magnetic field, luminal transit in said vessel is mitigated or abrogated.

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12. The regulator system of claim 1, further comprising a sensor or indicator, which sensor or indicator denotes when the piston is in an extended versus a collapsed form, said sensor or indicator denotes positioning and orientation of said valve, or a combination thereof.

13. An implantable controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion or partial occlusion, or a combination thereof, said regulator system comprising at least a first valve device suitable for deployment proximal to a body vessel, which may displace or occlude said vessel, wherein the valve comprises a controllable, extendible spring structure which may exist in an extended and compact form, which spring when in an extended form provides for a defined flow and pressure within said vessel, which flow is substantially laminar or pulsatile and which spring is magnetically or electromagnetically actuated.

14. The regulator system of claim 13, wherein said spring structure further comprises a base and a pressure plate, wherein said pressure plate has a substantially rectangular profile and wherein during extension said base is distal to said pressure plate.

15. The regulator system of claim 14, wherein at least said pressure plate is comprised of a magnetic, paramagnetic or superparamagnetic material.

16. The regulator system of claim 15, further comprising a solenoid whose long axis is positioned substantially perpendicularly to that of said pressure plate wherein generation of a magnetic field by said solenoid results in said pressure plate being drawn proximal to said base and minimal electromagnetic radiation is lost as a result of the diminished gap between said pressure plate and said base.

17. The regulator system of claim 16, wherein when said system is no longer subjected to a magnetic field, said spring structure is present in an extended form.

18. The regulator system of claim 13, further comprising a sensor or indicator, which sensor or indicator denotes when said spring is in an extended versus a collapsed form, said sensor or indicator denotes positioning and orientation of said valve, or a combination thereof.

19. A method of regulating luminal transit of a substance within a body vessel, said method comprising:

a. positioning a controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion or partial occlusion, or a combination thereof proximal to a desired body vessel, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined

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flow and pressure within said vessel, which piston is magnetically or electromagnetically actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material; and

b. exposing a body region proximal to said vessel to a magnetic or electromagnetic field;

whereby following exposure to said magnetic or electromagnetic field, said piston assumes said compact form, resulting in abrogation or mitigation of luminal occlusion of said vessel and facilitation of luminal transit in said vessel, thereby regulating luminal transit of a substance within a body vessel.

20. A method of regulating luminal transit of a substance within a body vessel, said method comprising:

a. positioning a controllable displacement regulator system enabling vessel wall displacement, vessel luminal occlusion, or a combination thereof proximal to a desired body vessel, said regulator system comprising at least a first valve device suitable for deployment proximal to a vessel, which displaces or occludes said vessel, wherein the valve comprises a controllable substantially rectangular collapsible piston, which piston may exist in an extended and compact form, which piston when in an extended form provides for a defined flow and pressure within said vessel, which piston is magnetically or electromagnetically actuated and which piston is comprised of at least one magnetic, paramagnetic or superparamagnetic material; and

b. exposing a body region proximal to said vessel to a magnetic or electromagnetic field;

whereby following exposure to said magnetic or electromagnetic field, said piston assumes said extended form, resulting in abrogation or mitigation of luminal occlusion of said vessel and facilitation of luminal transit in said vessel, thereby regulating luminal transit of a substance within a body vessel.

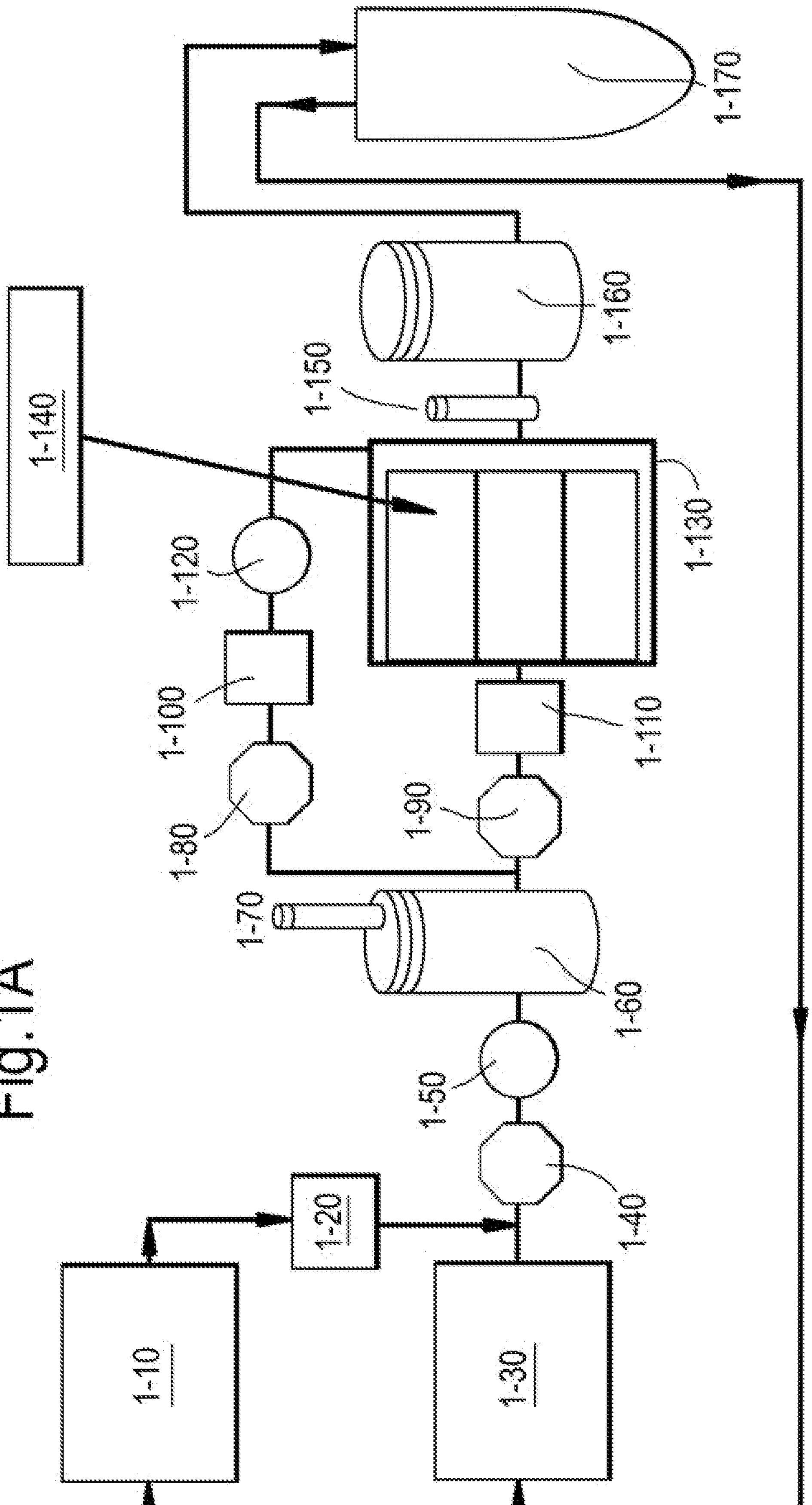
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Fig.1A

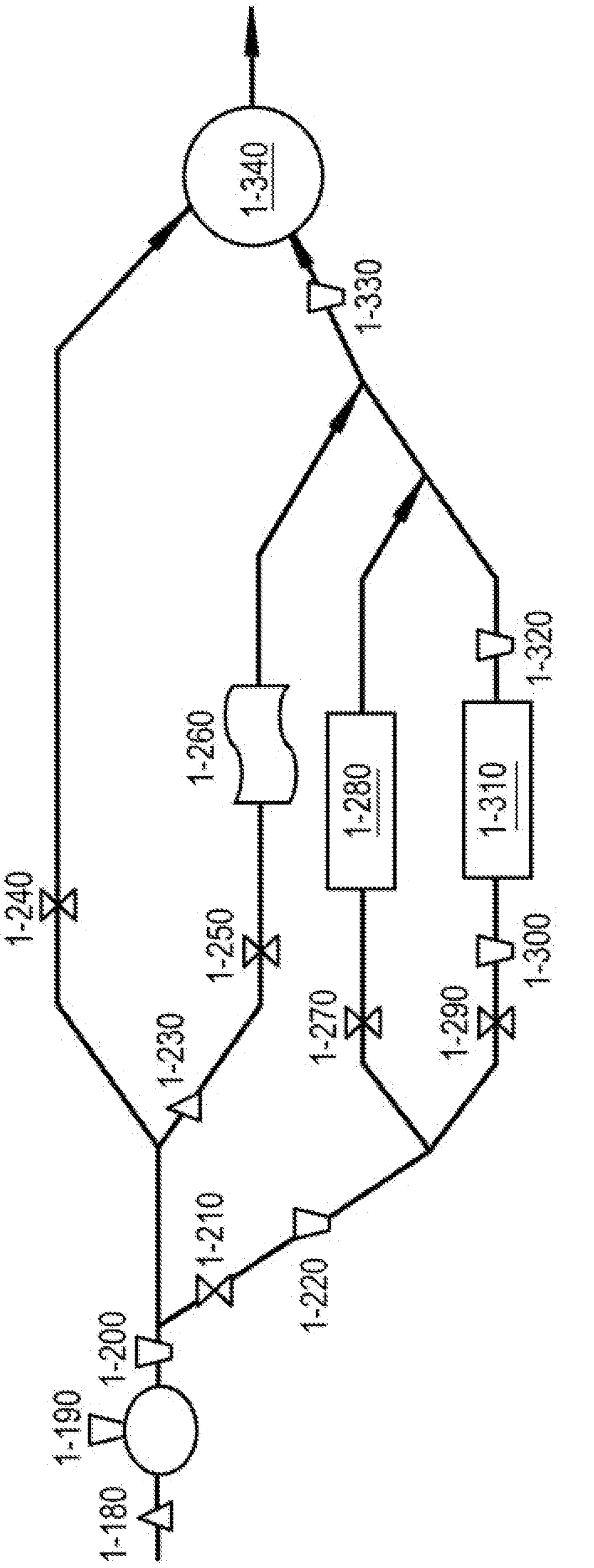
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Fig.1B

Fig.2

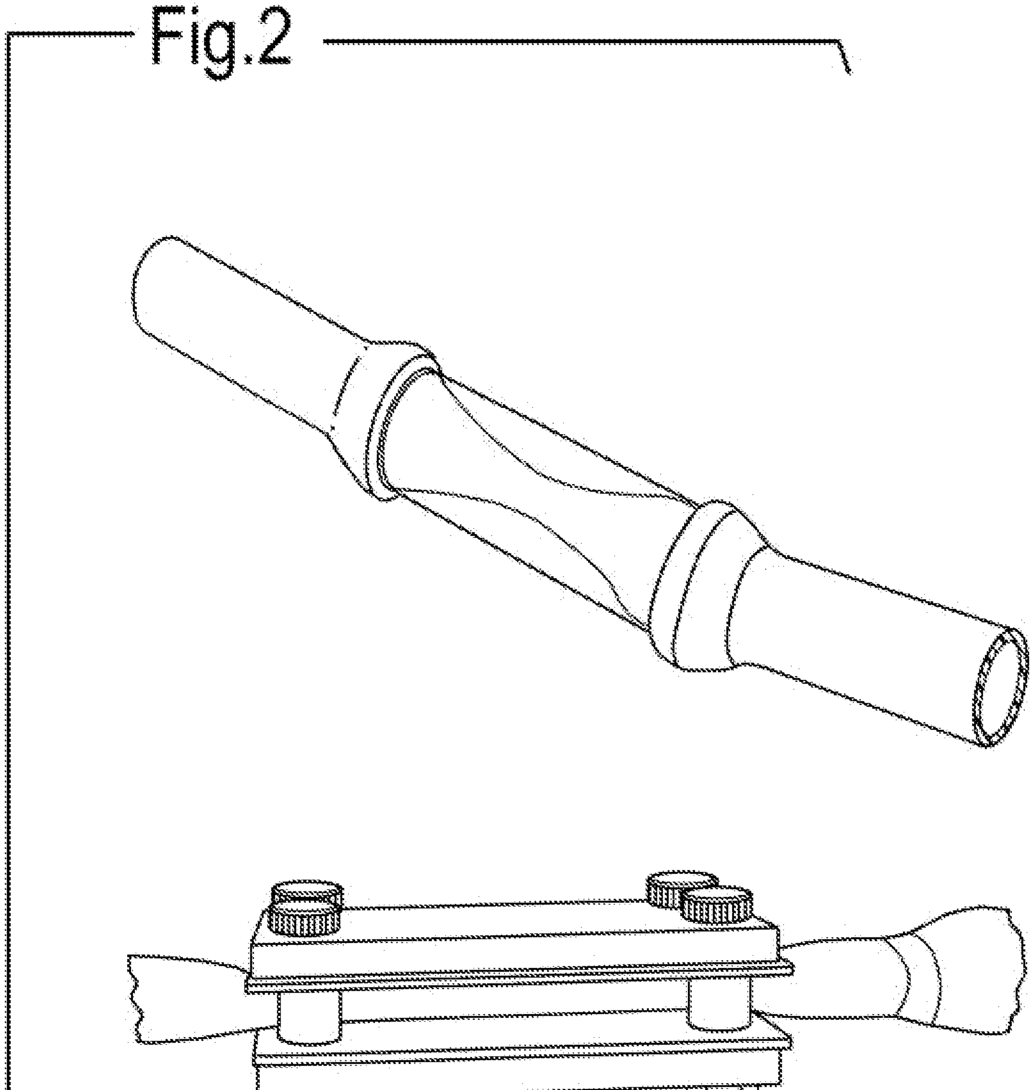


Fig.3A

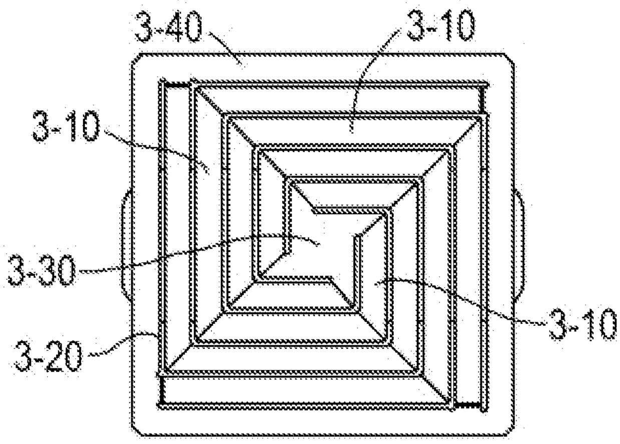


Fig.3B

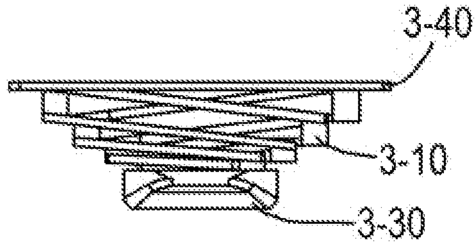


Fig.3D

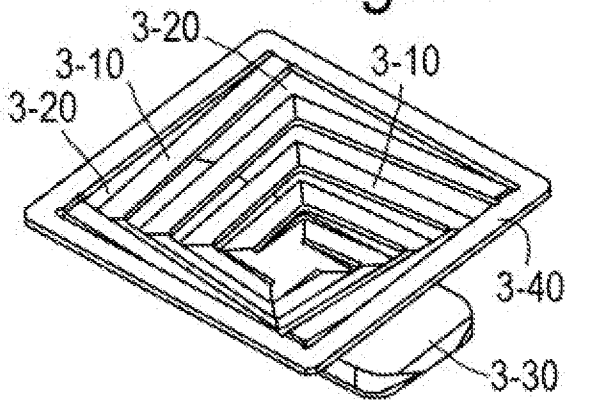


Fig.3C

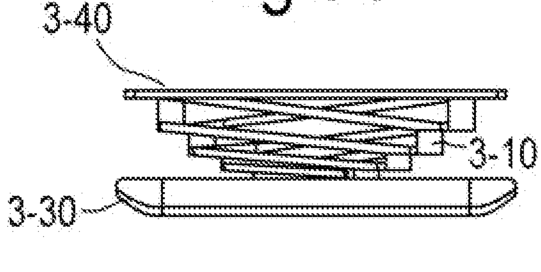


Fig.3E

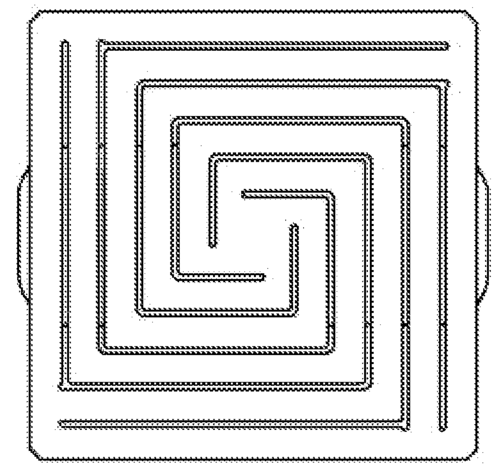


Fig.3F

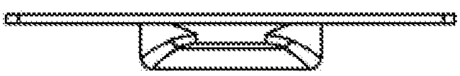


Fig.3H

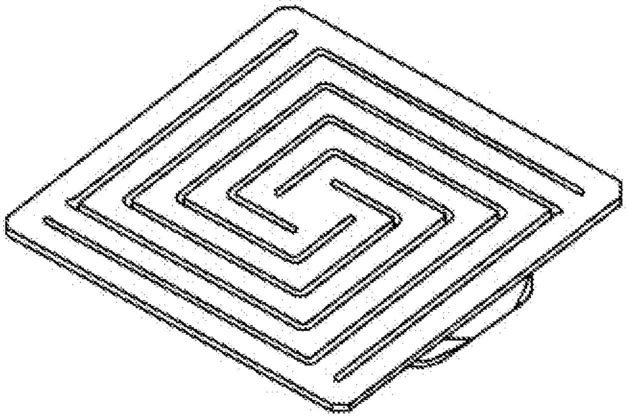


Fig.3G

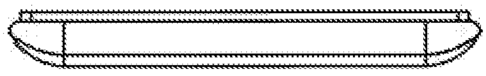


Fig.3I (1)

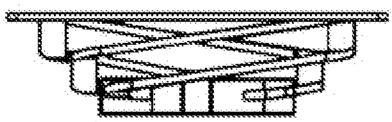


Fig.3J(1)

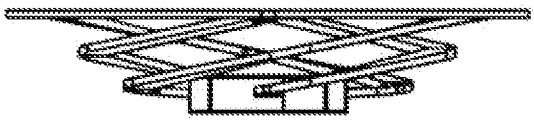


Fig.3I(2)

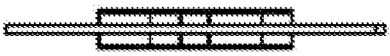


Fig.3J(2)

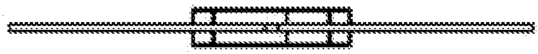


Fig.3K

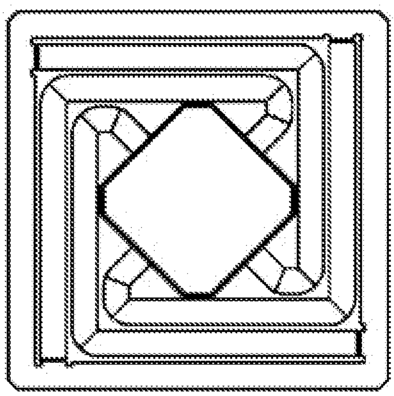


Fig.3L(1)

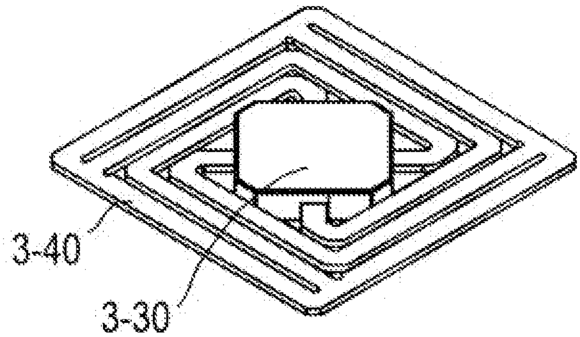


Fig.3L(2)

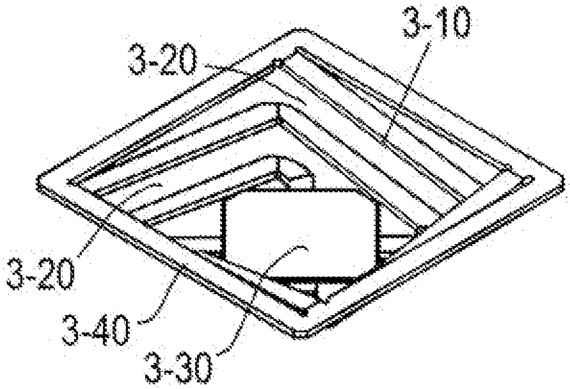


Fig.4A

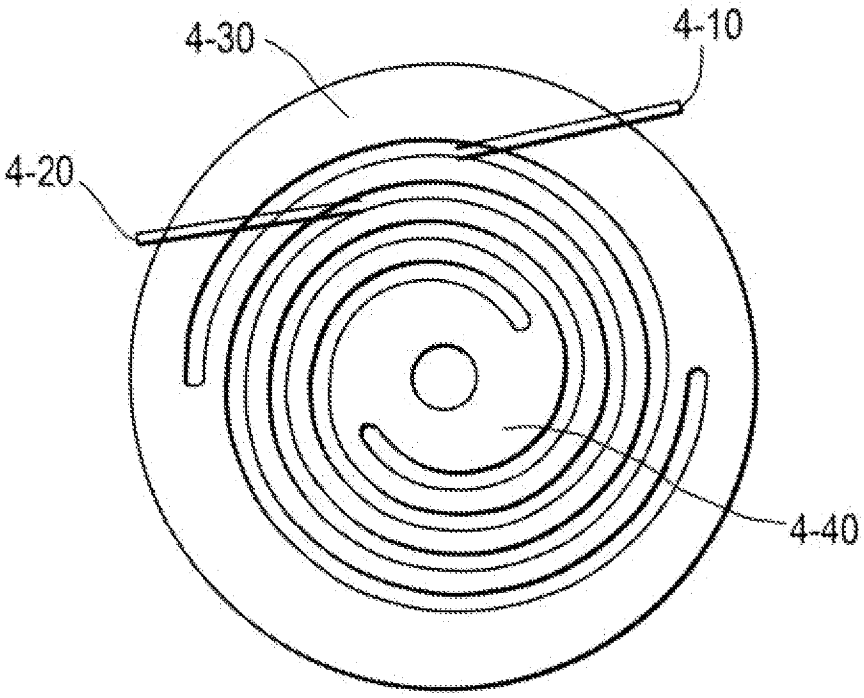


Fig.4B

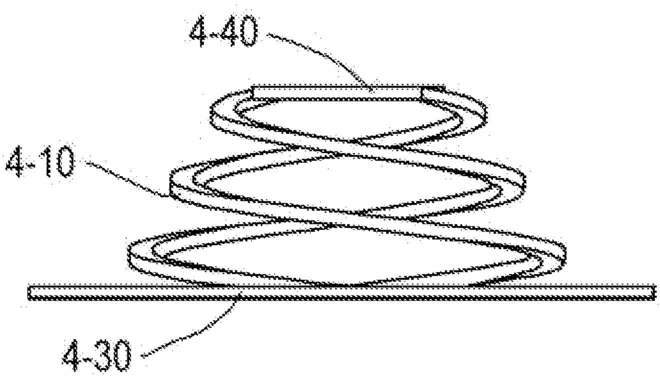


Fig.4C

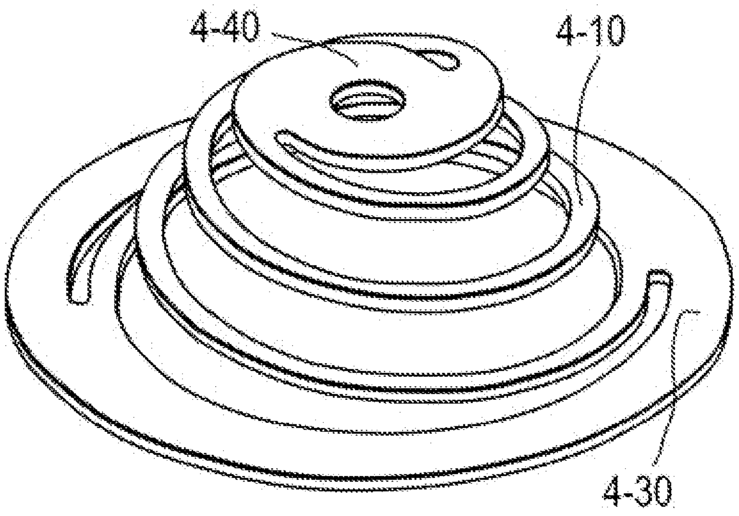


Fig.4D

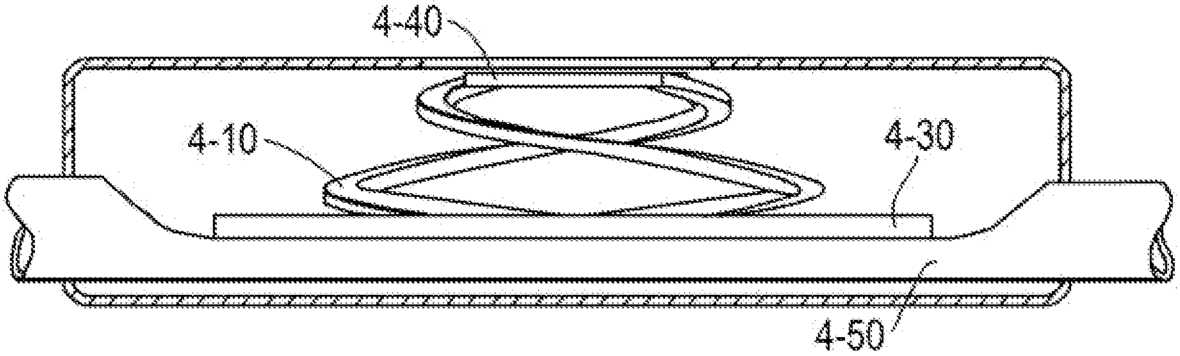


Fig.5A

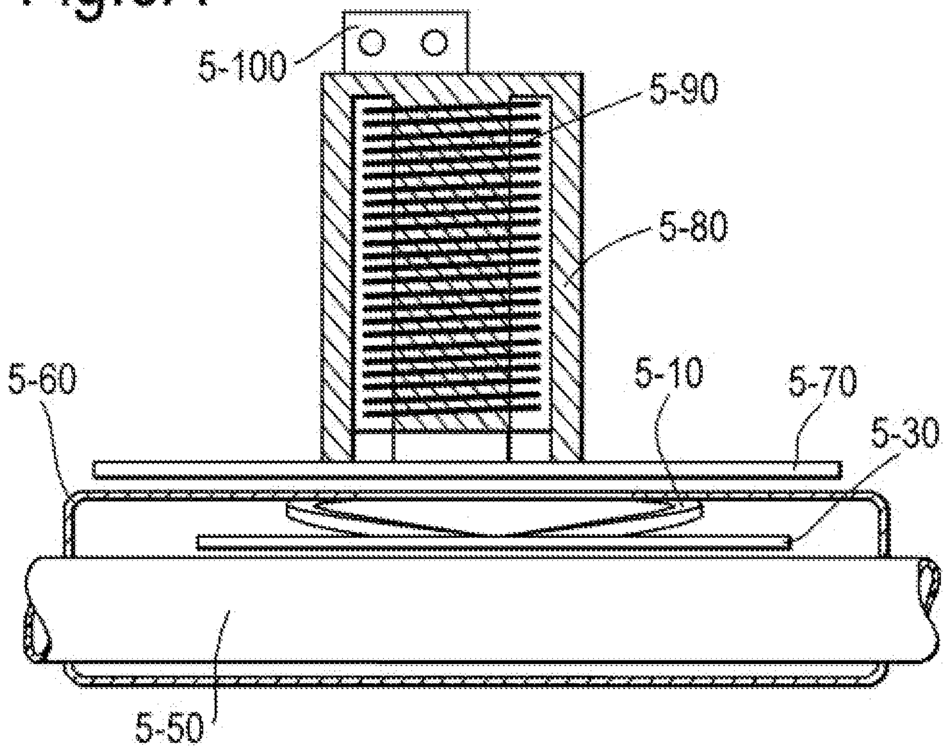


Fig.5B

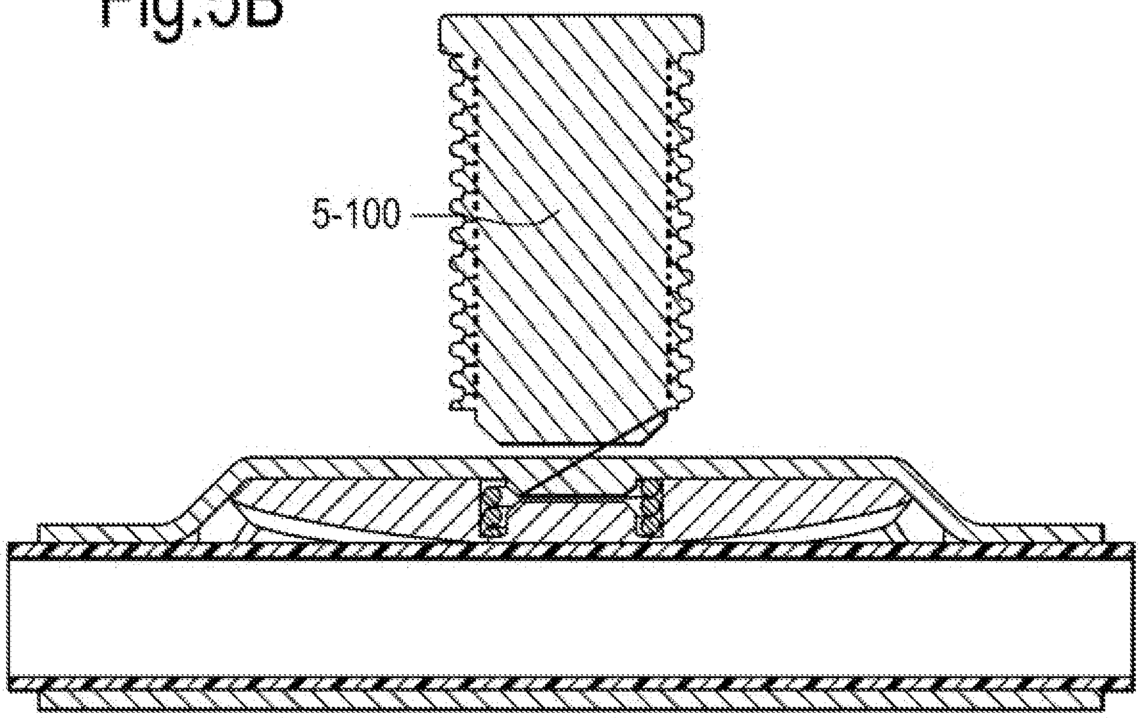


Fig.6A

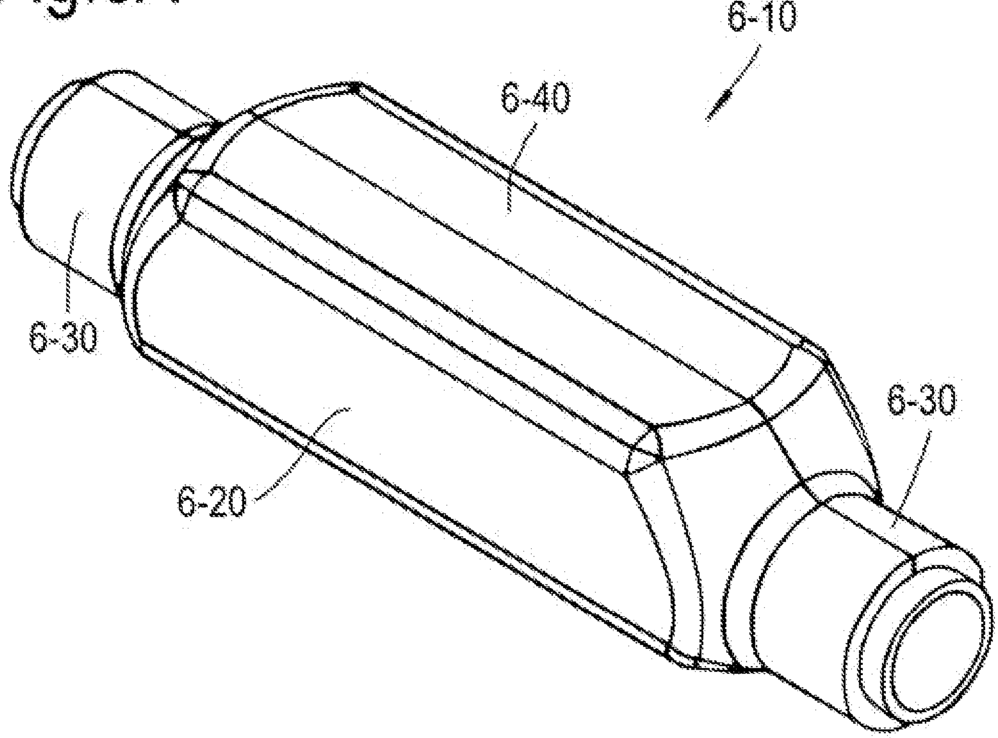


Fig.6B

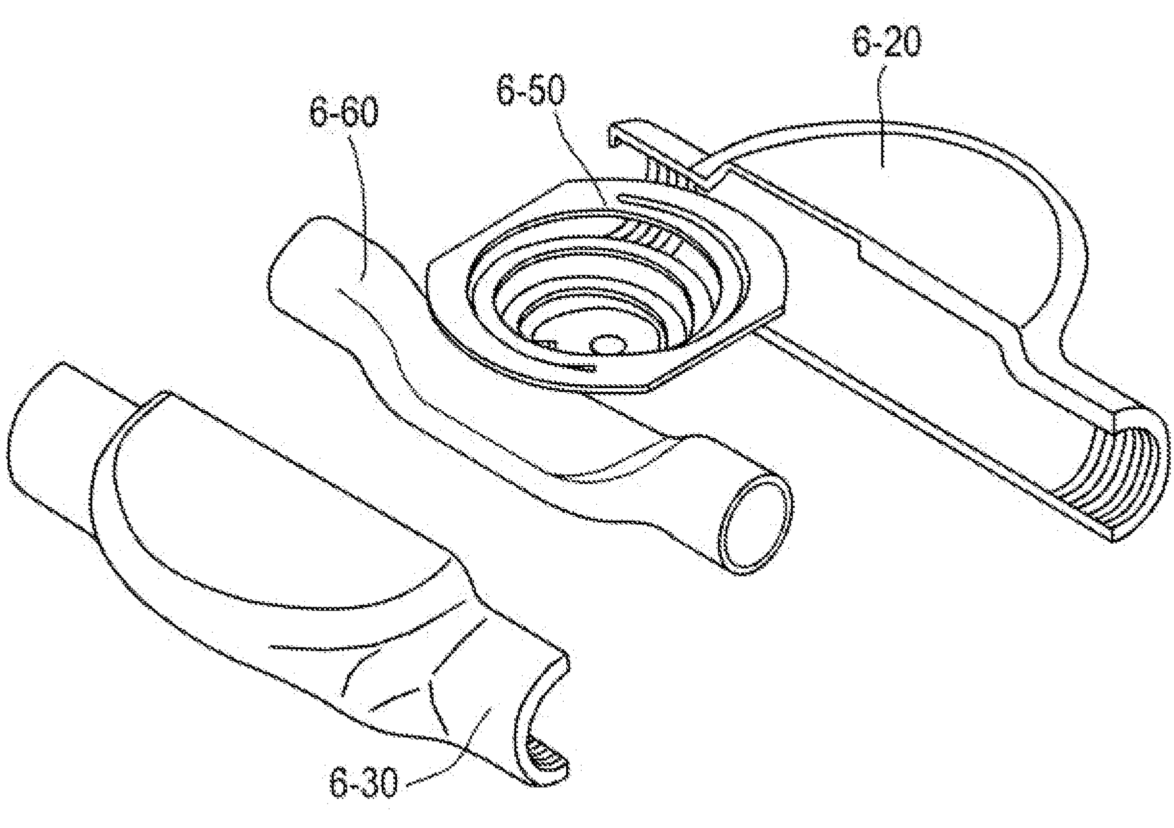


Fig.6C

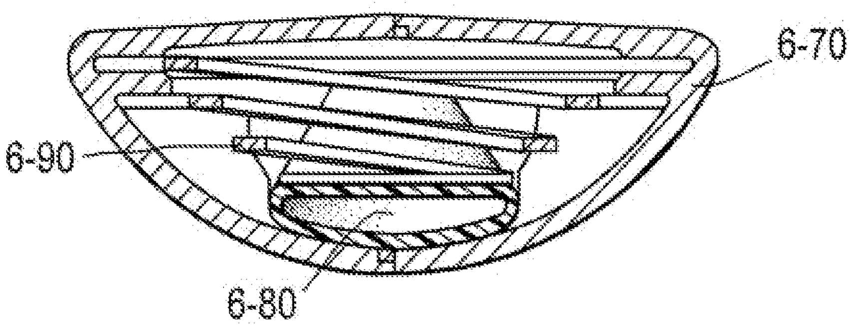
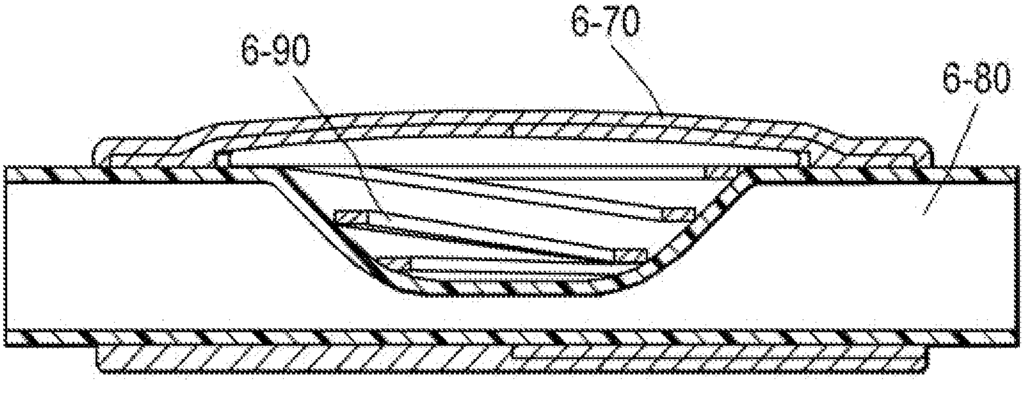


Fig.6D



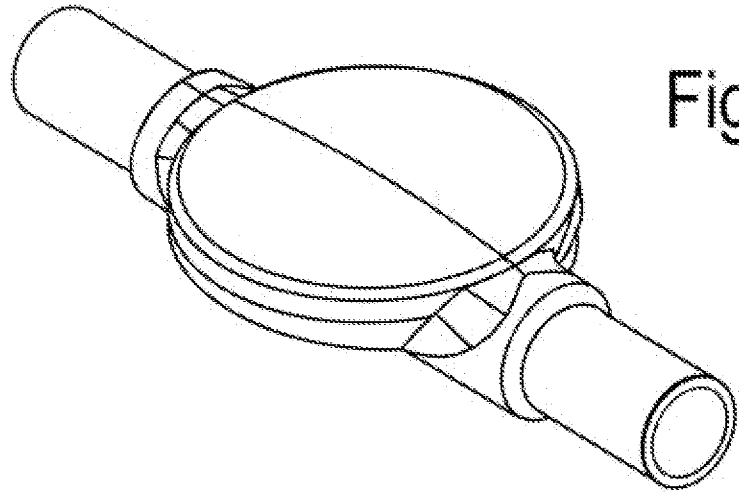


Fig.7A

Fig.7B

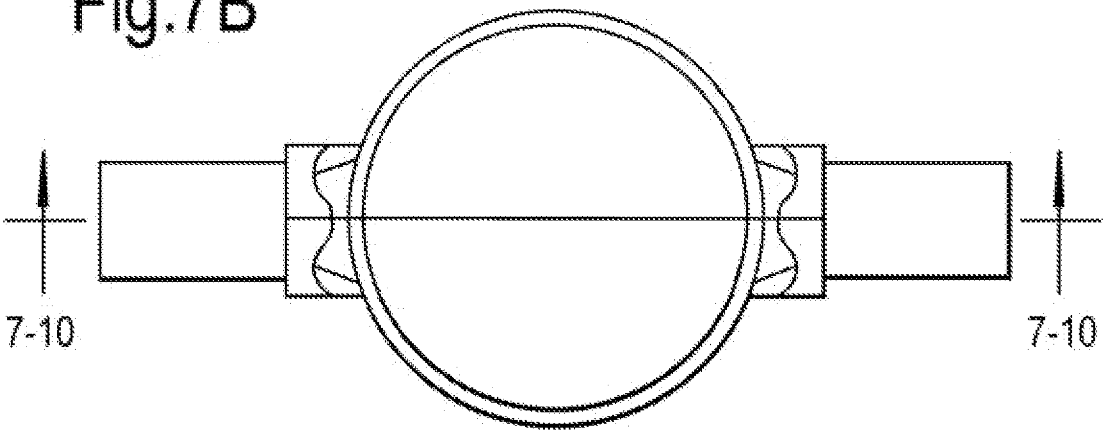


Fig.7C

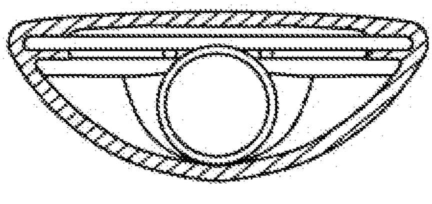
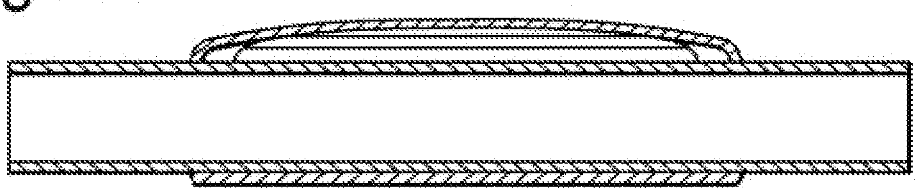


Fig.7D



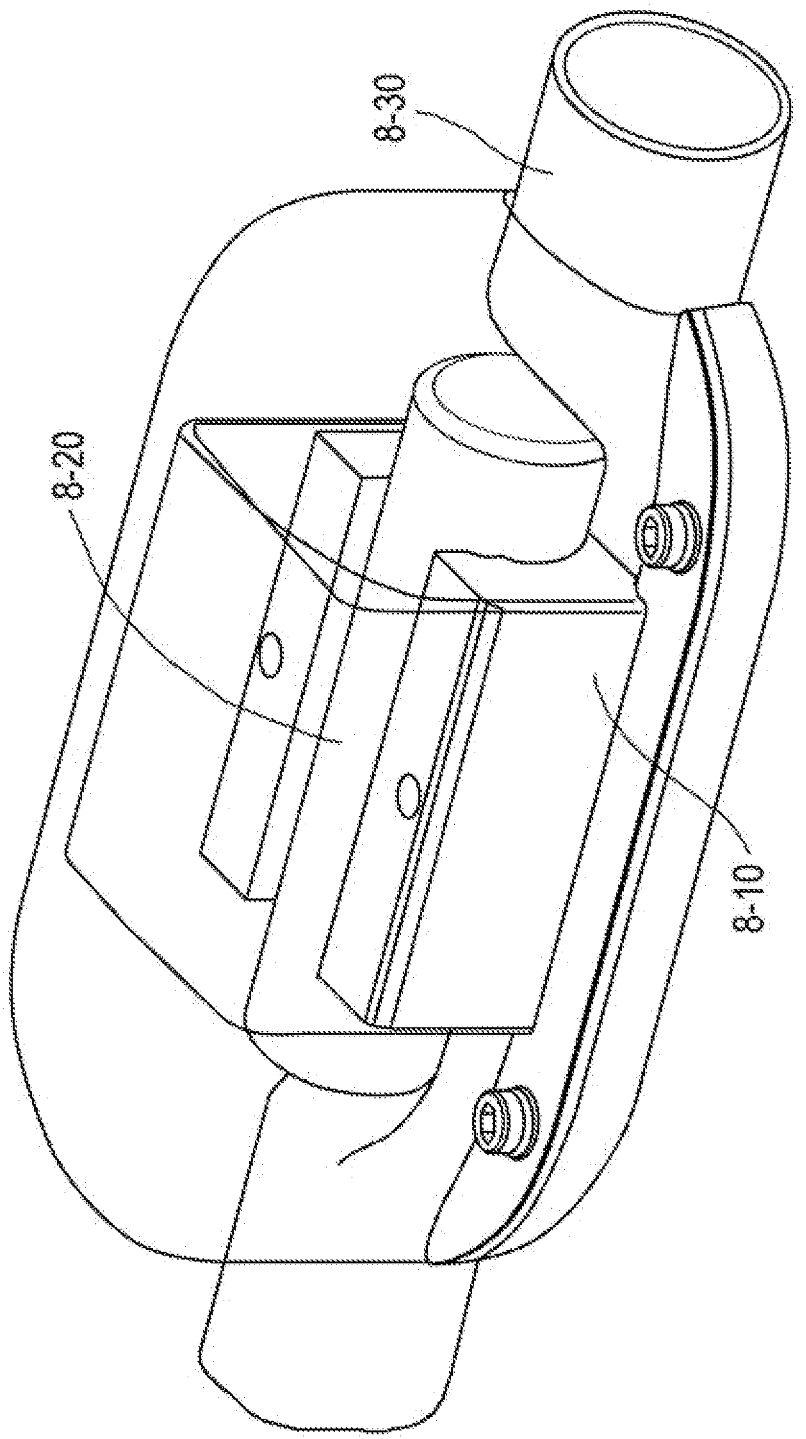


Fig.8A

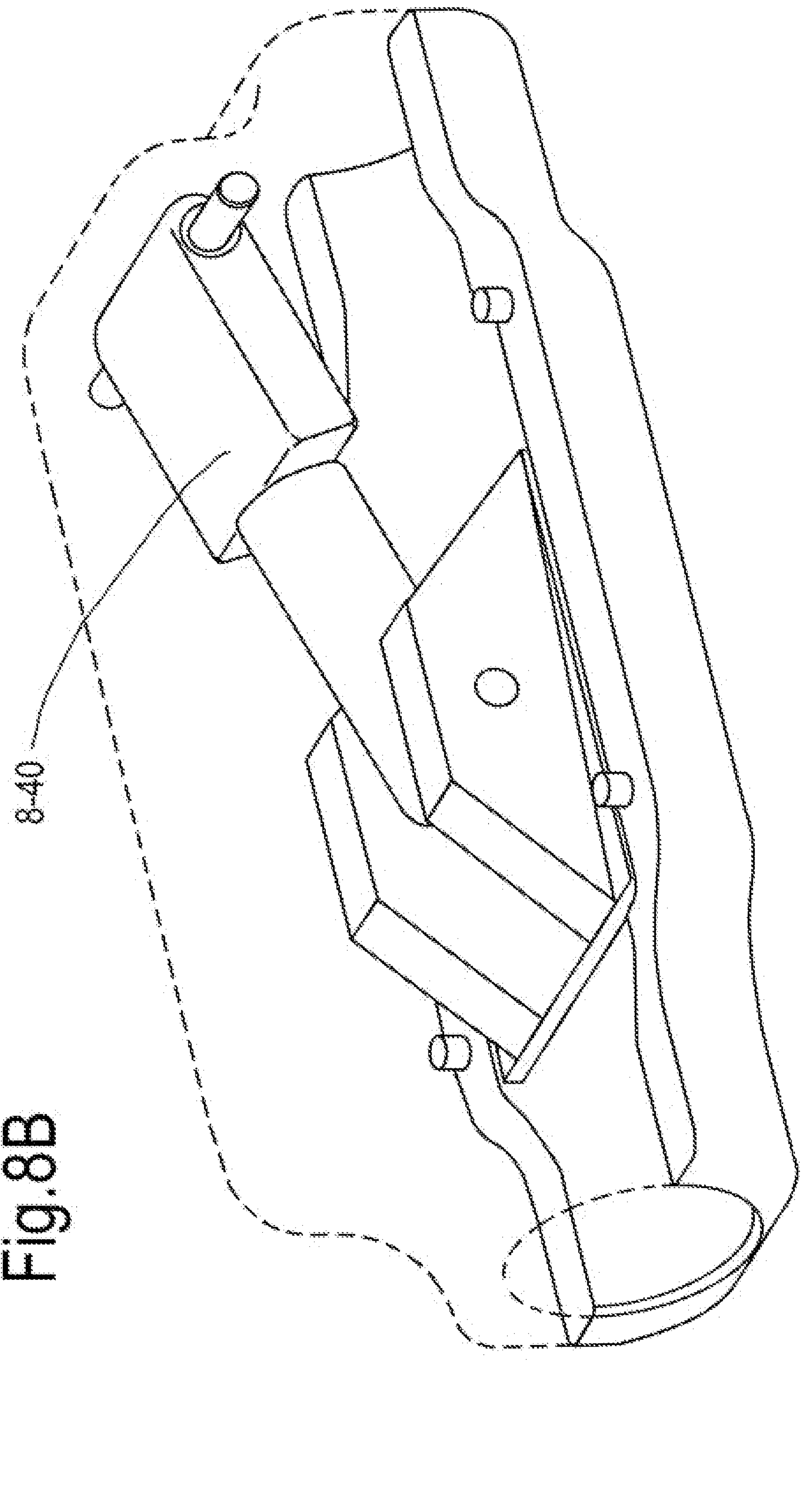


Fig.8B

Fig.9A

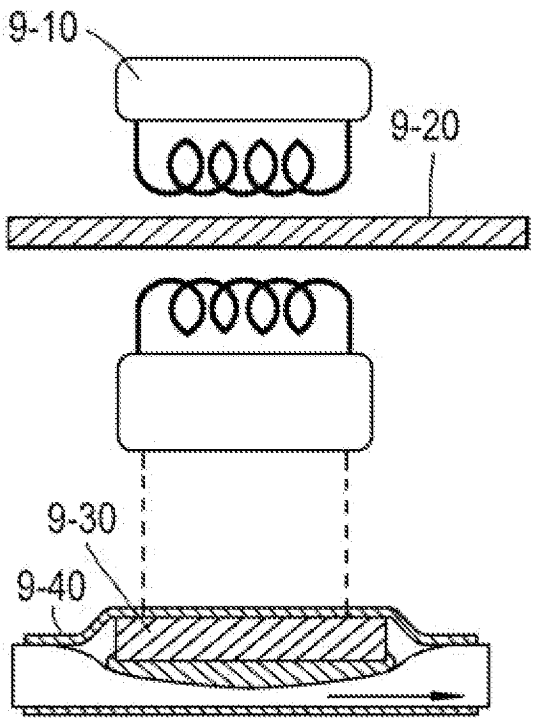


Fig.9B

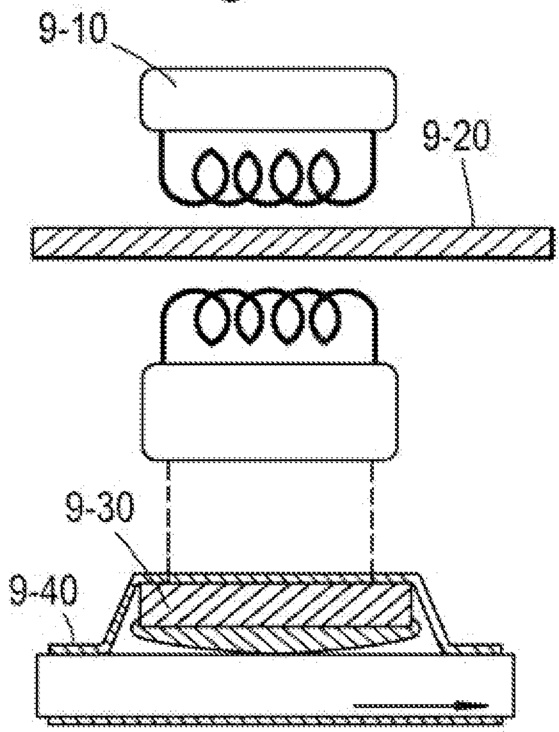


Fig.9C

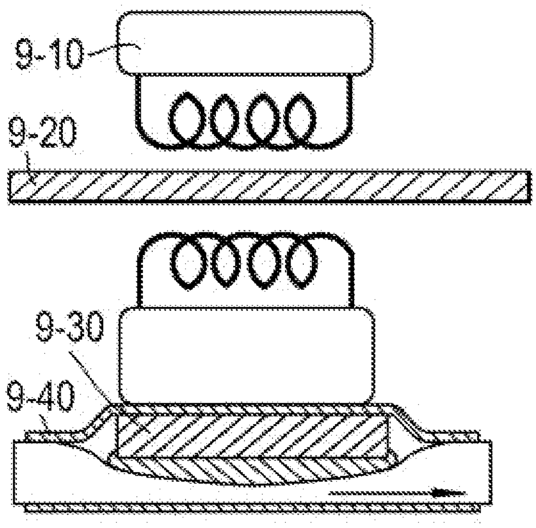


Fig.9D

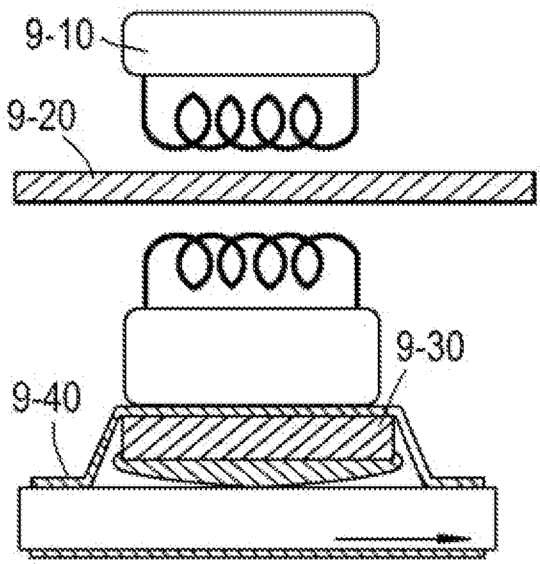


Fig.9E

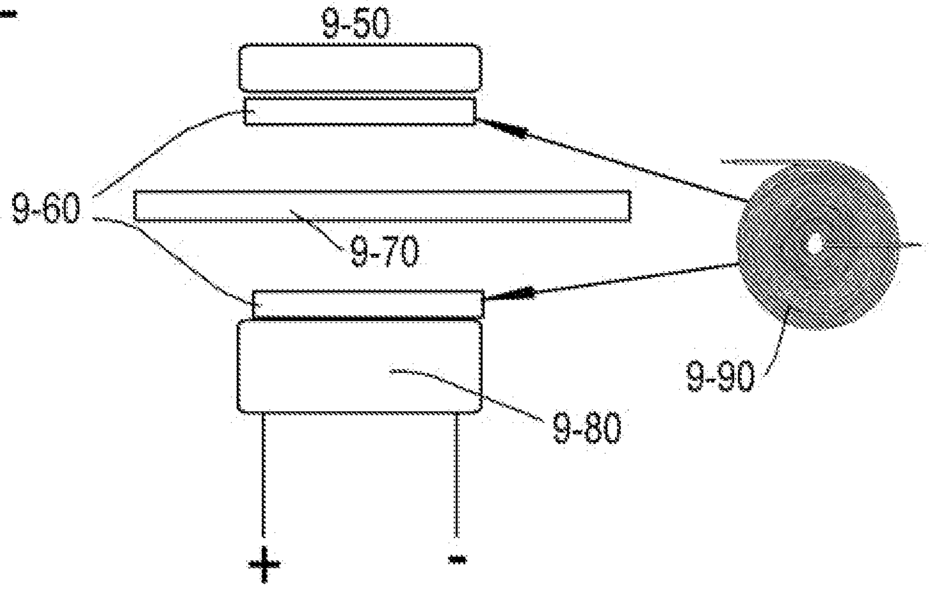


Fig.10A

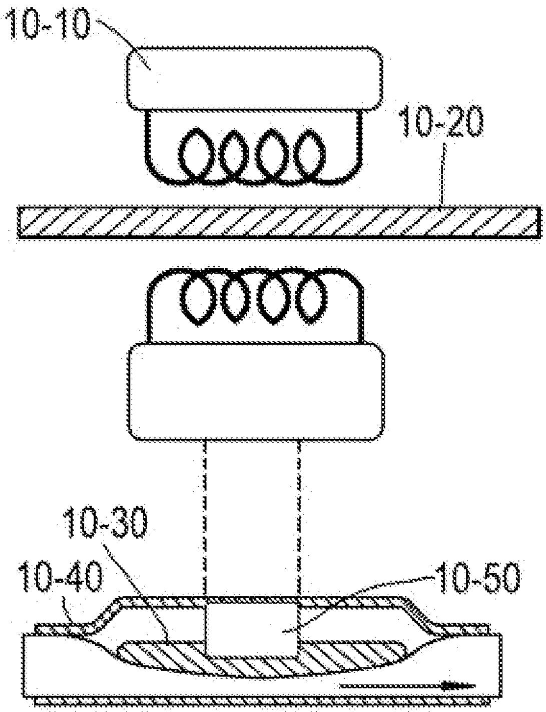


Fig.10B

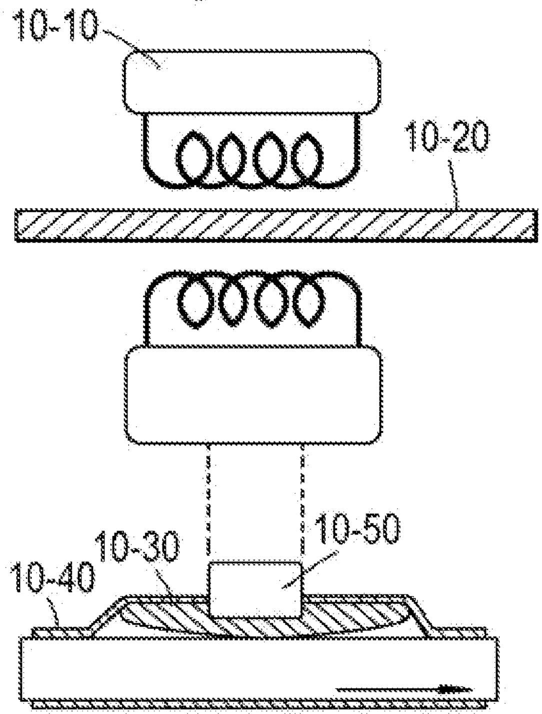


Fig.10C

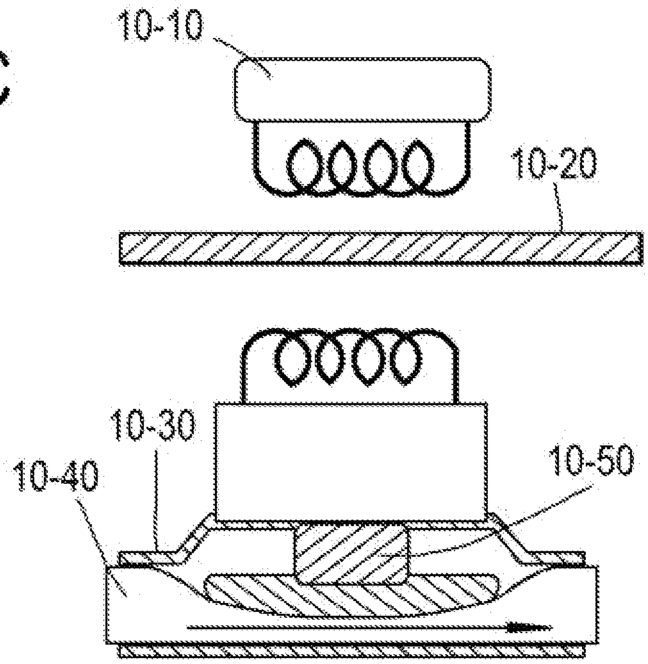


Fig.10D

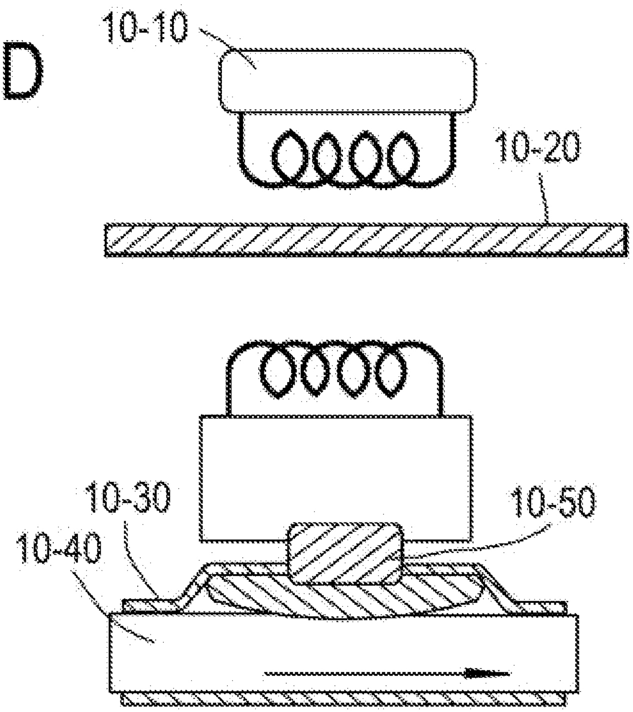


Fig.11

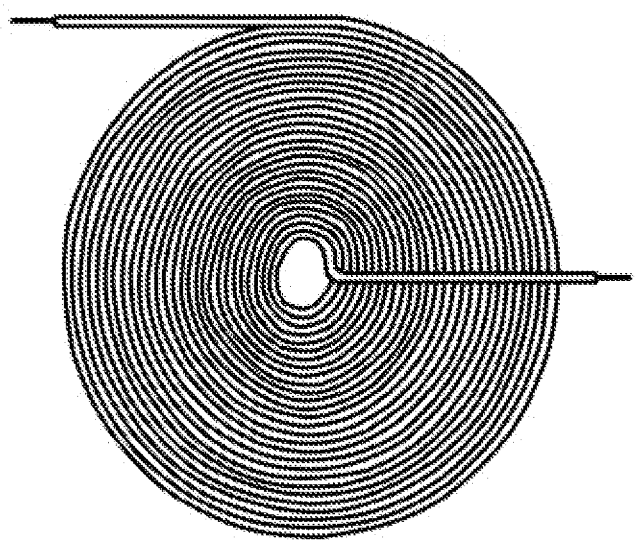


Fig.12

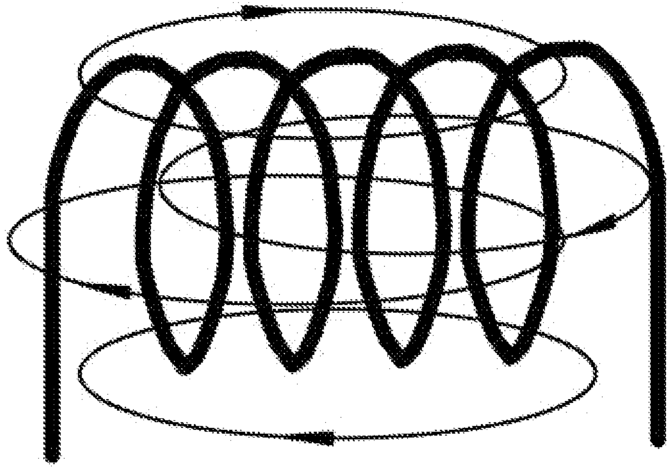


Fig.13

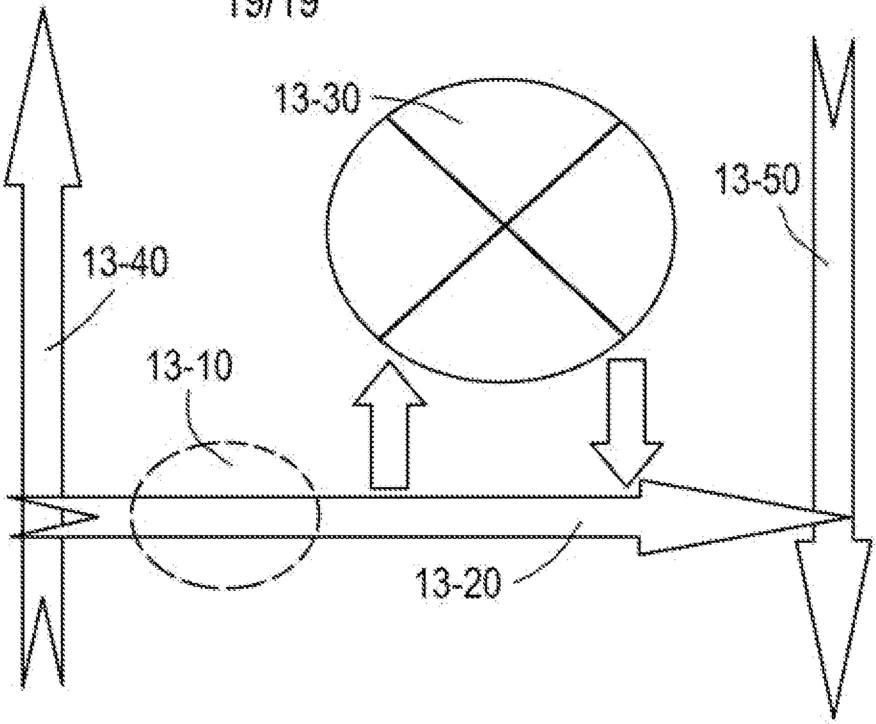


Fig.14A

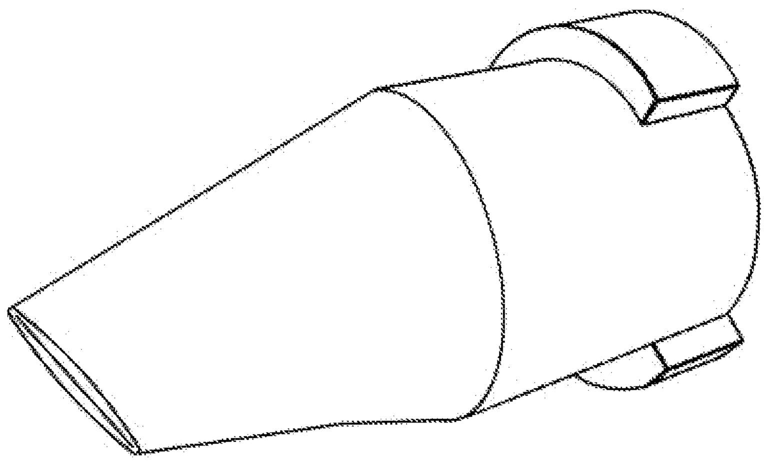
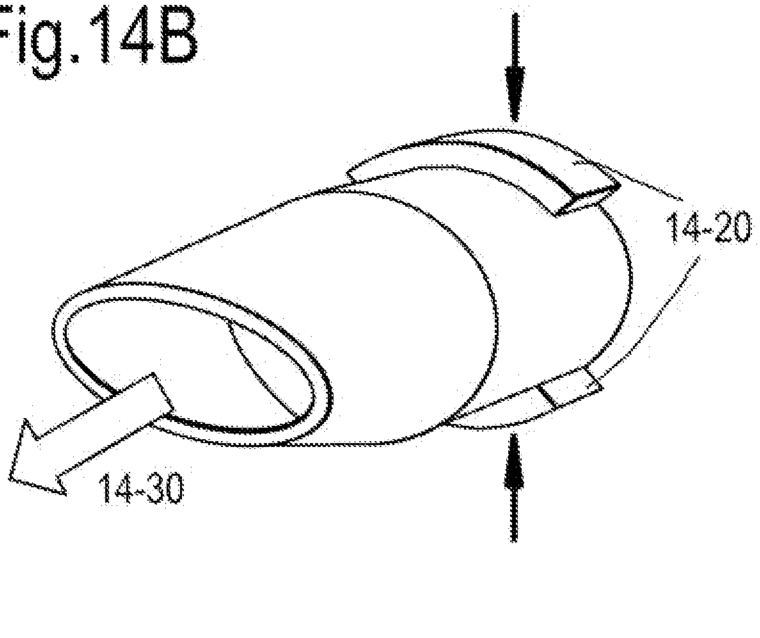


Fig.14B



INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2012/050022

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M1/36 A61B17/12 A61F2/06
ADD.

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)
A61M A61B A61F

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 072 282 A1 (ENDOART S A [CH]) 31 January 2001 (2001-01-31) abstract; figure 6 paragraphs [0007] - [0008], [0043] - [0044] -----	1-12
X	US 2009/030498 A1 (CULL DAVID L [US]) 29 January 2009 (2009-01-29) abstract; figure 3 paragraphs [0090] - [0093] -----	13-18
A	US 2003/014003 A1 (GERTNER MICHAEL [US]) 16 January 2003 (2003-01-16) abstract; figures 3,4 paragraphs [0131] - [0140] -----	1,13

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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	Date of mailing of the international search report
10 May 2012	18/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kaden, Malte

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19, 20
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2012/050022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1072282 A1	31-01-2001	AT 276790 T	15-10-2004
		AU 6275700 A	05-02-2001
		CA 2379788 A1	25-01-2001
		CN 1374877 A	16-10-2002
		DE 60014101 D1	28-10-2004
		DE 60014101 T2	06-10-2005
		EP 1072282 A1	31-01-2001
		EP 1200152 A1	02-05-2002
		ES 2226885 T3	01-04-2005
		JP 2003504166 A	04-02-2003
		MX PA02000624 A	21-07-2003
		US 7128750 B1	31-10-2006
		US 2007055296 A1	08-03-2007
		US 2011130701 A1	02-06-2011
		US 2011130702 A1	02-06-2011
		US 2011144670 A1	16-06-2011
		US 2011270288 A1	03-11-2011
		WO 0105463 A1	25-01-2001
US 2009030498 A1	29-01-2009	US 2009030498 A1	29-01-2009
		WO 2010028002 A1	11-03-2010
US 2003014003 A1	16-01-2003	US 2003014003 A1	16-01-2003
		US 2006224100 A1	05-10-2006
		US 2007249987 A1	25-10-2007
		US 2010262215 A1	14-10-2010