



(51) International Patent Classification:

A61M 1/38 (2006.01) A61M 1/18 (2006.01)
A61M 1/34 (2006.01)

(21) International Application Number:

PCT/US2012/031658

(22) International Filing Date:

30 March 2012 (30.03.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/470,998 1 April 2011 (01.04.2011) US

(71) Applicant (for all designated States except US): **AETH-LON MEDICAL, INC.** [US/US]; 8910 University Center Lane, Suite 660, San Diego, CA 92122 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **KENLEY, Rodney** [US/US]; 1402 Pearson Road, Libertyville, IL 60048 (US).

(74) Agent: **HART, Daniel**; **KNOBBE MARTENS OLSON & BEAR LLP**, 2040 Main Street, Fourteenth Floor, Irvine, CA 92614 (US).

(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).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

[Continued on next page]

(54) Title: METHODS AND DEVICES COMPRISING EXTRACORPOREAL BLOOD FLOW

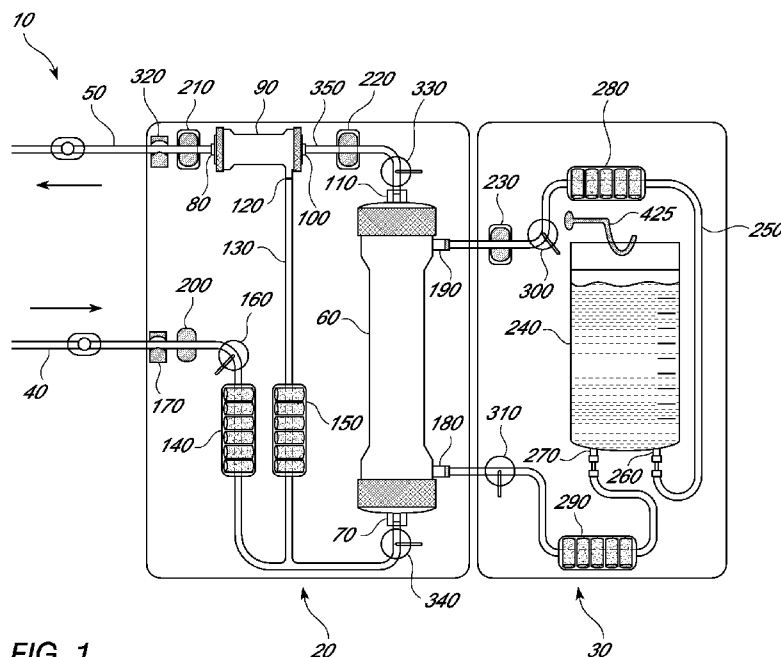


FIG. 1

(57) Abstract: Embodiments of the present invention relate to devices, systems and methods comprising extracorporeal blood flow. In some embodiments, a need for the use of anticoagulants is reduced or eliminated.



Published:

- *without international search report and to be republished
upon receipt of that report (Rule 48.2(g))*

METHODS AND DEVICES COMPRISING EXTRACORPOREAL BLOOD FLOW

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/470,998, entitled “METHODS AND DEVICES COMPRISING EXTRACORPOREAL BLOOD FLOW”, filed on April 1, 2011, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] Embodiments of the present invention relate to methods, systems and devices comprising extracorporeal blood flow. In some embodiments, a need for the use of anticoagulants is reduced.

BACKGROUND OF THE INVENTION

[0003] In extracorporeal blood purification procedures such as hemodialysis and plasmapheresis, the blood flow rate is approximately 200 ml/min -500 ml/min. Typically, patients undergoing extracorporeal therapies receive anticoagulants to prevent blood from clotting in the extracorporeal circuit which would result in suboptimal therapy and, ultimately, premature termination of the treatment. Anticoagulants are typically injected into the patient's blood access site a few minutes before the treatment starts and thereafter, continuously into the afferent blood tubing set. There are also occasions where it is given as intermittent boluses. In disorders such as end-stage renal disease (ESRD), a patient's hematopoiesis is impaired and they are typically treated with human recombinant erythropoietin in order to bring their hematocrit into range of 33-36 %. This compares to the normal range of 40-50% and the lower hematocrit of these patients actually makes it easier to dialyze their blood and to keep it anticoagulated during a multi-hour treatment.

[0004] Occasionally, a patient presents with a contraindication for anticoagulation. One example would be a patient that needs dialysis immediately after surgery. Another example would be a warfighter with a bleeding wound who has been recently evacuated from a battlefield. In an emergent case such as this, there may be no time or equipment to insert a central venous dual lumen catheter and veno-venous blood access may be all that is available for performing an extracorporeal blood purification therapy. Veno-venous access typically limits the blood flow rate to 20-70 ml/min. It is also likely that the hematocrit in this case would be in the normal range. Also in such cases, it would not be unusual for extracorporeal treatment therapy to be applied continuously for 24 or more hours.

[0005] Perfusing a blood treatment device, such as a hollow fiber dialyzer or plasma filter, in an extracorporeal circuit at blood flow rates below 70 ml/min without any systemic anticoagulant for treatment periods that may extend beyond 24 hours is extremely challenging and rarely successful. This is further exacerbated in patients with a hematocrit level of 40-50 % and whose clotting is not impaired by any other disease state. Two strategies for non-systemic anticoagulation have been historically employed: (1) Bolus injection of 200-300 ml of saline into the arterial bloodline every 15-20 minutes; (2) Regional anticoagulation, in which an anticoagulant, either heparin or citrate is continuously infused into the arterial line while its respective antagonist is simultaneously injected into the venous line, protamine sulfate for heparin or ionized calcium for citrate.

[0006] Repeated bolus injections of saline work with partial success for a limited period of time. The primary downside to this technique is that the dilution results in a concomitant reduction in the activity of the blood treatment device. This technique is also limited if the patient has impaired renal function unless there is also an extracorporeal mechanism for removing the added intravenous fluid such as ultrafiltration. Regional anticoagulation with citrate is also limited in time due to accumulated calcium toxicity. Regional heparinization, like regional citrate, requires two infusion pumps thereby adding complexity and must be used with the older unfractionated heparin since protamine does not completely reverse the effects of low molecular weight heparin.

[0007] Accordingly, there is a need for devices, methods and systems which could reduce and/or effectively eliminate the need for anticoagulation in an extracorporeal blood flow device and circuit.

SUMMARY OF THE INVENTION

[0008] Some embodiments of the methods, systems and device provided herein include a method for continuously diluting a fluid circuit comprising (a) providing an input stream of blood *ex vivo* to a fluid circuit; (b) diluting the input stream of blood with a diluent; (c) processing said stream of diluted blood to obtain a stream of treated blood; (d) obtaining an acellular fraction and a cellular fraction from said stream of treated blood; (e) removing an output stream of blood comprising said cellular fraction from the fluid circuit; and (f) repeating steps (a)-(e), wherein the diluent comprises at least a portion of the acellular fraction from said stream of treated blood.

[0009] In some embodiments, the initial diluent comprises saline.

[0010] In some embodiments, the processing comprises performing hemofiltration or hemodialysis.

[0011] In some embodiments, the obtaining an acellular fraction and a cellular fraction from said stream of treated blood comprises passing said treated blood through at least one hollow fiber, wherein the cellular fraction of the treated blood remains in the lumen of said hollow fiber and at least a portion of the acellular fraction of said treated blood passes through at least one pore in the wall of said hollow fiber.

[0012] In some embodiments, a hematocrit level of said output stream of blood is within 10% of a hematocrit level of the input stream.

[0013] In some embodiments, a hematocrit level of the output stream of blood is within 5% of a hematocrit level of the output stream of blood.

[0014] In some embodiments, the input stream of blood is obtained from a mammal.

[0015] In some embodiments, the input stream of blood is obtained from a human.

[0016] In some embodiments, the input stream of blood is in fluid communication with blood *in vivo*.

[0017] In some embodiments, the output stream is in fluid communication with blood *in vivo*.

[0018] Some embodiments of the methods, systems and device provided herein include a continuous dilution blood treatment apparatus comprising an arterial inlet line coupled to a first inlet port of a blood treatment device, an arterial pump configured to convey blood through said arterial inlet line from a source of blood to said blood treatment device, wherein the blood treatment device is configured to provide a cellular fraction of blood and an acellular fraction of blood during operation of the apparatus; a hemofilter inlet line coupled to a first outlet port of said blood treatment device, configured to convey treated blood from said blood treatment device to an inlet port of a hemofilter, wherein the hemofilter is configured to provide a cellular fraction of blood and an acellular fraction of blood during operation of the apparatus; a venous outlet line coupled to a first outlet port of the hemofilter configured to be in fluid communication with said cellular fraction of blood; and a pre-dilution line coupled to a second outlet port of the hemofilter, configured to be in fluid communication with said acellular fraction of blood and configured to convey fluid from said hemofilter to said arterial inlet line.

[0019] In some embodiments, the pre-dilution line is coupled to the arterial inlet line at a location on the arterial inlet line between the arterial pump and the source of blood.

[0020] In some embodiments, the pre-dilution line is coupled to the arterial inlet line at a location on the arterial inlet line between the arterial pump and the blood treatment device.

[0021] In some embodiments, the pre-dilution line comprises a controllable orifice configured to control the rate of flow of fluid from the hemofilter to the arterial inlet line.

[0022] In some embodiments, the pre-dilution pump is configured to convey fluid from the hemofilter to the arterial inlet line.

[0023] In some embodiments, a reservoir inlet line is coupled to a second outlet port of said blood treatment device and an inlet port of a fluid reservoir.

[0024] In some embodiments, the reservoir inlet line is in fluid communication with the acellular fraction of the blood.

[0025] In some embodiments, a first reservoir pump is configured to convey the flow of fluid through said reservoir inlet line.

[0026] In some embodiments, a reservoir outlet line is coupled to a second inlet port of said blood treatment device and an outlet port of a fluid reservoir.

[0027] In some embodiments, the reservoir outlet line is in fluid communication with the cellular fraction of the blood.

[0028] In some embodiments, a second reservoir pump is configured to convey the flow of fluid through said reservoir outlet line.

[0029] In some embodiments, the hemofilter line comprises a valve to control the flow of fluid through the hemofilter line.

[0030] In some embodiments, the arterial inlet line comprises a valve to control the flow of fluid through the arterial inlet line.

[0031] In some embodiments, the hemofilter inlet line comprises a hematocrit inlet hematocrit sensor.

[0032] In some embodiments, the arterial inlet line comprises an inlet hematocrit sensor.

[0033] In some embodiments, the venous outlet line comprises an outlet hematocrit sensor.

[0034] Some embodiments also include a processing unit communicatively coupled to at least one sensor, configured to analyze data from said at least one sensor, and to modulate the flow of fluid through said pre-dilution line.

[0035] In some embodiments, the processing unit maintains a hematocrit level measured by inlet hematocrit sensor and outlet hematocrit level sensor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] FIG. 1 depicts an embodiment comprising an extracorporeal fluid circuit.

[0037] FIG. 2 depicts an embodiment comprising an extracorporeal fluid circuit.

[0038] FIG. 3 depicts an embodiment comprising an extracorporeal fluid circuit control system.

DETAILED DESCRIPTION

[0039] Embodiments of the present invention relate to methods, systems and devices comprising extracorporeal blood flow. In some embodiments, a need for the use of anticoagulants is reduced.

[0040] Applicant has discovered that the need for the use of anticoagulants can be reduced in the treatment of blood. In some embodiments of the methods, systems and devices provided herein, blood enters an extracorporeal fluid circuit in which the volume of the blood is increased by dilution prior to treatment in a blood treatment device. Post-treatment, the treated blood is fractionated into a portion comprising an acellular fraction of the treated blood, and a portion comprising a cellular fraction of the treated blood. In some embodiments, the acellular portion of the treated blood is used to dilute blood entering the fluid circuit. Certain embodiments of the methods, devices and systems provided herein may be utilized in fluid communication with a subject, for example, in fluid communication with the blood system of a subject. More embodiments can be utilized with fluids, such as blood *ex vivo*, for example, to treat blood *ex vivo* in a blood bank system.

[0041] There are a number of strategies useful to reduce the need for anticoagulants with an extracorporeal fluid circuit. Some such strategies include ensuring a more linear blood flow within the extracorporeal fluid circuit. Whatever can be done to reduce the pulsations of the blood (e.g., to linearize the blood flow) as it passes through the extracorporeal circuit, the less likely the cellular components (e.g. platelets) will be to contact the surfaces of the extracorporeal structures through which they are passing thereby activating them and enhancing the prospects of clot formation. Unfortunately, the most linear and constant flow blood pumps such as axial flow pumps used in ventricular assist devices are very limited in their ability to overcome high resistance to flow and back pressure. Occlusive pumps such as peristaltic pumps or pneumatic diaphragm pumps may be used and should be implemented in such a way that multiple pumps or pump heads are employed out of phase so that the peaks and valleys of flow rate are minimized and linearity is maximized.

[0042] An additional strategy to reduce the need for anticoagulants with an extracorporeal fluid circuit is to reduce the presence of any air/blood surfaces within the extracorporeal fluid circuit. Air/blood surfaces are sometimes found in the pressure monitoring chambers normally included in blood tubing sets as a means of monitoring the pressure existing in the pre-pump, post-pump, and venous return segments of the extracorporeal circuit. The pressure is measured in the air space created over the blood in these chambers. Some blood lines (e.g., Streamline[®] Medisystems) can be used to reduce the need for the air space by

replacing the chamber with a pressure monitoring pod that incorporates a flexible membrane which transduces the pressure directly from the blood to the pressure sensor in the instrument. It will be useful to design the blood lines for the device similarly in order to minimize clotting.

Fluid circuits comprising continuous pre-dilution loops

[0043] Additional strategies to useful to reduce the need for anticoagulants with an extracorporeal fluid circuit include fluid circuits comprising continuous pre-dilution loops.

[0044] Diluting the blood reduces the propensity of the blood to clot while it is in the extracorporeal circuit, advantageously extending the time that a treatment may be applied before clotting terminates the treatment. Fluid circuits comprising a continuous pre-dilution loop significantly improve upon other devices and methods of anticoagulant-free extracorporeal circulation, such as prior methods in which a bolus of saline is periodically infused into the arterial line of an extracorporeal device. Some embodiments of the methods, systems and devices provided herein include fluid circuits comprising a continuous pre-dilution loop. In some such embodiments, blood entering a fluid circuit is continuously diluted before entering a blood treatment device, after passing through the blood treatment device the volume of the diluted blood may be reduced and excess fluid reclaimed before the blood exits the fluid circuit. The reclaimed fluid may be used to further dilute blood entering the fluid circuit. In preferred embodiments, during operation of a fluid circuit comprising a continuous pre-dilution loop, the level of the hematocrit of the blood exiting the device to a subject is the same, about the same, or substantially similar to the level of the hematocrit of the blood entering the device from a subject. In other embodiments, it may be desirable to increase or decrease the level of hematocrit of the blood exiting the device to a subject. For example, in subjects that are dehydrated it may be desirable for blood exiting a fluid circuit to the subject to have a reduced hematocrit level compared to the hematocrit level of blood entering a fluid circuit from the subject.

[0045] Fluid circuits comprising a continuous pre-dilution loop create a recirculation loop and cause a specific flow of ultrafiltrate from a hemofilter to continuously dilute the blood prior to its entering a blood treatment device by a known amount. In some embodiments, the blood is diluted by at least about 5%, at least about 10% at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 95%.

[0046] In some embodiments, a hemofilter is inserted into the venous blood line of an extracorporeal device, and the ultrafiltrate compartment of the hemofilter is connected by a

length of tubing to a “t” site in the arterial line of an extracorporeal device. The rate of flow of the ultrafiltrate, and consequently the percentage dilution of the blood, may be controlled in one embodiment by a pump inserted in this ultrafiltrate tubing segment.

[0047] FIG. 1 schematically shows an example embodiment of an extracorporeal fluid circuit (10) comprising a continuous pre-dilution loop (20) coupled to a fluid reservoir loop (30). The continuous pre-dilution loop comprises an arterial line (40) for receiving fluid and a venous line (50) for discharging fluid. The arterial line (50) is coupled to a first inlet port (70) of a blood treatment device (60). The blood treatment device can comprise any device for treating blood. Examples of blood treatment devices include blood filter devices, blood dialysis devices, plasmafilters, and the like (*See e.g.* U.S. Patent No. 4,787,974, and 7,226,429, incorporated by reference herein in its entirety). In some embodiments, the blood treatment device can be any device which results in at least a portion of fluid, such as blood or diluted blood, being separated into an acellular fraction and at least a portion of the fluid, such as blood or diluted blood, comprising a cellular fraction. In some embodiments the blood treatment device comprises at least one hollow fiber. Fluid, such as blood or diluted blood, passes through the lumen of the hollow fiber, and an acellular fraction of the fluid, such as blood or diluted blood, passes through pores in the hollow fiber. Valves (330, 340) can be used to isolate the blood treatment device. Blood is conveyed along the arterial line towards the blood treatment device by arterial pump (140). Examples of pumps that may be used with embodiments provided herein include occlusive pumps such as peristaltic pumps or pneumatic diaphragm pumps. In some embodiments, such pumps may be configured such that multiple pumps or pump heads are employed out of phase so that the peaks and valleys of flow rate are minimized and linearity of blood flow is maximized. A first outlet port (110) of the blood treatment device (60) is coupled to the inlet port (100) of the hemofilter (90) by the hemofilter inlet line (350). The hemofilter can be any device which results in at least a portion of the treated blood being separated into an acellular fraction and at least a portion of the treated blood comprising a cellular fraction. In some embodiments, the hemofilter comprises a membrane. In some embodiments, the hemofilter comprises a flat plate design well known in the art. In some embodiments the hemofilter comprises at least one hollow fiber. Treated blood passes through the lumen of the hollow fiber, and an acellular fraction of the treated blood passes through pores in the hollow fiber. (*See e.g.*, U.S. Patent No. 7,758,533, 7,780,619 incorporated by reference herein in its entirety). A first outlet port (80) in fluid communication with the cellular output portion of the hemofilter and a second outlet port (100) of the hemofilter (90) in fluid communication with the acellular output portion of the hemofilter are coupled to the venous line

(50) and a pre-dilution line (130), respectively. The pre-dilution line (130) is coupled to the arterial inlet line (40), either downstream or upstream of the arterial pump (140), relative to the flow of blood through the arterial inlet line. A pre-dilution pump (150) conveys fluid along the pre-dilution line from the hemofilter to the arterial inlet line. An arterial hematocrit sensor (200), a venous hematocrit sensor (210) measure the hematocrit levels of the fluids entering and exiting the fluid circuit device, respectively. A pre-dilution hematocrit sensor (220) measures the hematocrit levels of fluid being conveyed between the blood treatment device (60) and hemofilter (90). Optional clamps (170, 320) can be used to isolate the fluid circuit.

[0048] The fluid reservoir loop (30) comprises a fluid reservoir (240), optionally containing fluid such as sterile saline, Ringer's Lactate, 5% Dextrose in Water or similar sterile intravenous substitution fluids, preferably suitable for diluting the blood passing through the treatment device. A person of ordinary skill in the art is able to select a suitable fluid for the fluid reservoir. A reservoir inlet line (250) couples a second outlet port (190) of the blood treatment device to a reservoir inlet port (260). In some embodiments, the second outlet port (190) of the blood treatment device is in fluid communication with the acellular output portion of the blood treatment device.

[0049] Fluid is conveyed from the blood treatment device by a first reservoir pump (280). Hemoglobin levels in the fluid are measured by sensor (230). An optional reservoir outlet line (250) couples a second inlet port (180) of the blood treatment device to a reservoir outlet port (270). In some embodiments, the second inlet port (180) of the blood treatment device is in fluid communication with the acellular portion of the blood treatment device. In some embodiments, the second inlet port (180) of the blood treatment device is in fluid communication with the cellular portion of the blood treatment device.

[0050] Fluid is conveyed to the blood treatment device by a second reservoir pump (290). In some embodiments, the reservoir inlet line (250) and first reservoir pump (280) can also be used to return fluid from the reservoir to the device. Valves (300, 310) can be used to isolate the fluid reservoir loop (30) from the continuous dilution loop (20). In some embodiments, valves (160, 300, 310, 330, 340) pressure sensors can replace the valves. In some embodiments, such pressure sensors are communicatively coupled to a processing unit (e.g., FIG. 3, 520).

[0051] In some embodiments, blood is conveyed along the length of arterial line (40) by pump (140) towards the blood treatment device, the hematocrit of the blood is measured by hematocrit sensor (200). The blood is diluted by diluent fluid entering the arterial line (40) from the pre-dilution line (130). The diluted blood enters the blood treatment device (60) and is

processed. Examples of processes include dialysis, filtration, and binding of blood components to affinity matrices. The treated blood exits the blood treatment device to hemofilter inlet line (350) and the hematocrit of the diluted fluid is measured by hematocrit sensor (220). The diluted blood enters the hemofilter (90). At least a portion of the acellular fraction of the diluted blood is drawn through the hemofilter towards the pre-dilution pump (150) along the pre-dilution line (130). At least a portion can include at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, and at least about 90%, and at least about 100%. The remaining portion of the treated blood exits the hemofilter outlet port (80) and enters venous line (50). In some embodiments, the remaining portion of the treated blood is returned to a subject from which the inlet blood is obtained. The hematocrit level of the exiting fluid is measured by hematocrit sensor (210). In some embodiments, the portion of the non-cellular component of the diluted blood drawn through the hemofilter towards the pre-dilution pump is adjusted such that the hematocrit levels measured by hematocrit sensors (210, 200) are similar, substantially similar, or the same.

[0052] In some embodiments, the inlet stream of a fluid circuit is in fluid communication with blood *in vivo*. For example, a fluid circuit can be coupled to the blood system of a subject, such that blood flows from the subject into the fluid circuit. In some embodiments, arterial inlet line (40) is in fluid communication with the blood flowing from a subject into a fluid circuit. In some embodiments, the outlet stream of a fluid circuit is in fluid communication with blood *in vivo*. For example, a fluid circuit can be coupled to the blood system of a subject, such that blood flows from the fluid circuit into the subject. In some embodiments, venous outlet line (50) is in fluid communication with the blood flowing from a fluid circuit into a subject.

Adjusting hematocrit levels

[0053] Some embodiments of the methods, systems and devices provided herein include adjusting the hematocrit level of a fluid exiting a fluid circuit. In some embodiments the hematocrit level of the venous outlet line fluid is adjusted. In some embodiments, hematocrit sensors are located around both the arterial inlet line (200) and the venous outlet line (210). Hematocrit sensors are capable of quantifying the hematocrit of the incoming blood and returning fluid. Such sensors include optic sensors, for example, an optical device that transmits one or more wavelengths of light that is absorbed or scattered by blood components such as hemoglobin. In some such embodiments, increased hematocrit levels result in increased

absorbance of the light by the fluid. By using such sensors (210, 200) on the arterial inlet line (40) and venous outlet line (50), one can construct a closed feedback loop that adjusts the speed of the pre-dilution pump (150) to a rate required to cause the signal of the venous line sensor (210) to be the same, substantially similar or similar, to that of the arterial line sensor (200). Such embodiments ensure that the returning hematocrit equals the incoming hematocrit. In some embodiments, quantification of the actual hematocrit level is not necessary. In some such embodiments, indications that the hematocrit level in both the arterial inlet line and venous outlet line are similar, substantial similar, or the same, are sufficient. Similar sensors can be used as air/foam detectors to prevent any air from being injected into the patient.

[0054] Further control of the system can be accomplished by placing a hematocrit sensor between the point in the arterial inlet line (40) where the pre-dilution line (130) joins the arterial inlet line (40) line and the blood treatment device (60). By so doing, the degree of blood dilution perfusing the blood treatment device can be compared to the incoming and returning blood hematocrit levels and even quantified to a specific hematocrit. In some embodiments, the hematocrit level of a fluid entering the device, such as blood, and the hematocrit level of a fluid exiting the device, such as treated blood, are within no more than about 5%, no more than about 10%, no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, and no more than about 100%.

[0055] The degree of dilution can be altered, even while the feedback loop is controlling the incoming and returning blood to the same hematocrit level, by adding or subtracting fluid from the internal recirculation loop in the extracorporeal circuit, for example, by injecting or extracting fluid through the blood treatment device (60) using pumps 280 and/or 290.

[0056] The hematocrit level of the fluid entering the venous line (50) can be adjusted by a number of mechanisms. In some embodiments, the hematocrit level of the fluid entering the venous line can be adjusted by modulating the pre-dilution pump (150). In some embodiments, the hematocrit level of the fluid entering the venous line (50) can be adjusted by modulating the volume of fluid entering or exiting the blood treatment device (60) from the fluid reservoir (240) of the fluid reservoir loop (30). In some embodiments, the hematocrit level of the fluid entering the venous line can be adjusted by modulating the pre-dilution pump, and by modulating the volume of fluid entering or exiting the blood treatment device (60) from the fluid reservoir (240) of the fluid reservoir loop (30).

[0057] In some embodiments, the portion of the non-cellular component of the diluted blood that is drawn through the hemofilter towards the pre-dilution pump is adjusted. In some embodiments, the pre-dilution pump is adjusted by a controller module coupled to at least one of the hematocrit sensors (220, 200, 210). Increasing flow through the pre-dilution line (130) by increasing the action of the pre-dilution pump can reduce the portion of the non-cellular component of the diluted blood entering the venous line (50) and thus increase the hematocrit level of the fluid entering the venous line (50). Conversely, decreasing flow through the pre-dilution line (130) by decreasing the power (speed) of the pre-dilution pump can increase the portion of the non-cellular component of the diluted blood entering the venous line (50) and thus increase the hematocrit level of the fluid entering the venous line (50).

[0058] In some embodiments, fluid may be added or subtracted from the dilution circuit by using at least one fluid reservoir pump (280, 290) to either inject or extract fluid from fluid reservoir (240). In some embodiments, the volume of fluid entering or exiting the blood treatment device (60) from the fluid reservoir (240) of the fluid reservoir loop (30) can be modulated. In some embodiments, the flow of fluid between the fluid reservoir (240) and the second inlet port (180) and/or second outlet port (190) of the blood treatment device (60) can be controlled by adjusting the direction and/or rate of fluid flow using first reservoir pump (280) and/or second reservoir pump (290). In some such embodiments, first reservoir pump (280) and second reservoir pump (290) can each comprise a pump that modulates the rate and direction of fluid flow between the fluid reservoir (240) and blood treatment device (60). In some embodiments, diluted blood present in the blood treatment device can be diluted further, wherein fluid flows from fluid reservoir (240) into the blood treatment device under the control of pump (280) or pump (290) or both further diluting the diluted blood with the fluid, and thereby providing further diluted fluid that flows to the hemofilter. Conversely, fluid can be removed from the blood treatment device by opening valve (230). Fluid can be drawn through reservoir outlet line (250) by reservoir pump (280) or through port (180) by reservoir pump (290), or both..

[0059] FIG. 2 schematically shows another example embodiment of an extracorporeal fluid circuit (430) comprising a continuous pre-dilution loop (440) and a fluid reservoir loop (30). In this example, a pre-dilution line (400) is coupled from the hemofilter (90) to the arterial inlet line (40) upstream of the arterial pump (140). The pre-dilution line includes a controlled orifice (450) that regulates the flow of fluid from the hemofilter (90) to the arterial inlet line (40). During operation, the flow of fluid through the pre-dilution line can be regulated by opening and constricting the controlled orifice (450) by controllable modules

coupled to at least one of the hematocrit sensors (220, 200, 210). In some embodiments, the flow of fluid through the pre-dilution line can be regulated in combination with modulating the arterial pump (140) and the opening or constricting the controlled orifice (450). Alternatively, or in addition, fluid in the dilution loop could be controlled by adding or subtracting fluid from the fluid reservoir as described above.

Methods to prime fluid circuits

[0060] Some embodiments of the methods, systems and devices provided herein include priming fluid circuits to initiate use. Prior to initiating any extracorporeal therapy, the extracorporeal circuit must be substantially devoid of any contained air which, if allowed to enter the patient, could result in an air embolus. In most cases, this is accomplished by replacing the air originally contained in the circuit when it is first removed from its packaging with sterile saline or another sterile physiologic fluid; a process known as “priming”. As a blood purification therapy is initiated, blood is drawn into the arterial blood tubing set by a blood pump and as it proceeds around the extracorporeal circuit it mixes with the priming fluid. Often the priming fluid is allowed to drain out the venous blood tubing and into a collection vessel until the blood is seen coming down the venous line. At this point, the venous patient connection is made and the treatment is started. Automatic priming at the beginning of therapy and the rinse back of blood at the end of therapy entirely under the control of the instrument is also useful.

[0061] In some embodiments, priming a fluid circuit provided herein includes obtaining a fluid circuit filled with a fluid, such as saline. The arterial inlet line (40) of the fluid circuit is connected to a source of blood, such as a subject. Blood is drawn into the fluid circuit by the arterial pump (140). Blood flows through the fluid circuit and exits through the venous outlet line (50). In some embodiments, the flow-through is discarded until fluid exiting the venous outlet line of the fluid circuit is suitable to enter the subject and the venous outlet line is connected to a subject. For example, in some embodiments, the flow-through may be discarded until the hematocrit levels of fluid entering the device at the arterial inlet line are the same, substantially similar, or similar to the hematocrit levels of fluid exiting the device at the venous outlet line.

[0062] In some embodiments, a pump (or pumps; e.g. 280, 290) located on the opposite side of the blood purification membrane of a blood treatment device (60) from the blood can be used to draw priming fluid through the membrane and into a collection vessel (e.g., 240). By so doing, blood can be drawn up both the arterial inlet line (40) and venous outlet line (50) simultaneously where they would ultimately come together in the middle of the blood

treatment device (60). If one knows the fluid volume contained in the extracorporeal circuit and one also knows how much clear priming fluid is desirable to be left in the blood for use in this continuous dilution technique, one can hang the priming fluid collection container on a scale (425) (e.g. load cell) and measure how much fluid is removed from the circuit as blood is being drawn into it. At a predetermined point, the extraction of priming fluid from the extracorporeal circuit may be stopped, leaving the desired amount of priming fluid in the circuit mixed with blood, and the treatment may be initiated with the contained priming fluid being used for continuous recirculation and dilution within the extracorporeal circuit. In an example embodiment, a fluid circuit comprising a continuous pre-dilution loop and a fluid reservoir can be primed by obtaining a fluid-filled fluid circuit. In some embodiments, the volume of the priming fluid in the circuit is known. The arterial inlet line (40) and venous outlet line (50) are connected to a subject. Blood is drawn into the fluid circuit from the subject through both the arterial inlet line (40) and venous outlet line (50) by activating at least one reservoir pump (280 or 290). Blood is drawn into the device and is diluted by fluid within the device. Fluid within the device is drawn into the fluid reservoir (240). In some embodiments, the amount of fluid drawn into the reservoir is measured by any of a variety of known methods. In some embodiments, the mass of the reservoir is measured by attaching the fluid reservoir to a scale (425). Priming the device can be stopped once a desired volume of priming fluid is drawn into the fluid reservoir.

[0063] In some embodiments, the amount of priming fluid left in the circuit and the rate of ultrafiltration can be calculated to ensure that the hematocrit level of fluid returning to a subject is similar, substantially the same, the same as the is the same as the hematocrit level of blood entering the fluid circuit form the subject.

Back flushing fluid circuits

[0064] Some embodiments of the methods, systems and devices provided herein include back flushing. Back flushing includes a technique for maintaining the patency and performance of the blood treatment device by periodically back flushing the device by creating a higher pressure on the permeate side than on the feed water side of the device. Back flushing further reduces the probability of clotting in the extracorporeal circuit and specifically, the blood treatment device and hemofilter.

[0065] In some embodiments, back flushing a fluid circuit can be accomplished by flushing sterile fluid through the membrane of a blood treatment device (60) and simultaneously down the arterial inlet line (40), the hemofilter inlet line (350), the venous outlet line (50), and reversing the arterial pump (140). In some embodiments of such methods, ultrasonic air/foam

detectors on both arterial inlet line and venous outlet line are useful to prevent air entering the patient's vascular space where an embolism could result. Back flushing can be implemented, by connecting a fluid reservoir loop (30) to a continuous pre-dilution loop (20).

[0066] In some embodiments, membranes of a fluid circuit are periodically back flushed. In some such embodiments, reservoir pumps (280,290) push fluid from the fluid reservoir (240) through the second inlet port (180) and second outlet port (190) into blood treatment device (60). Fluid is pushed through the membranes of the blood treatment device and through the arterial inlet line (40) and hemofilter inlet line (350) and venous outlet line (50). In further embodiments, the membranes of the hemofilter (90) can be back flushed by driving the pre-dilution pump (150) in reverse. In other embodiments, in which the pre-dilution line (400) is connected upstream of an arterial pump (40), the membranes of a hemofilter (90) can be back flushed by running the arterial pump in reverse.

[0067] In some embodiments, the fluid used during back flushing is used to further dilute blood during the operation of the fluid circuit. The amount of fluid used during back flushing can be quantitated by measuring the amount of fluid drained from the fluid reservoir (240), for example by using the scale (425). Fluid used during back flushing may be sent to the patient and then removed by gradual ultrafiltration during the intra-back flush interval noting that the exact amount of fluid used in a back flush can be quantitated by the scale on which the priming solution container hangs and the same scale can be used to denote when the amount of back flush solution is once again removed from the patient by ultrafiltration.

Fluid circuit control systems

[0068] Some embodiments of the methods, systems and devices provided herein include fluid circuit control systems to carryout one or more of the operations of the dilution and fluid reservoir circuits described herein. FIG. 3 schematically shows an example embodiment of a fluid circuit control system. In the fluid circuit control system (490), arterial pump (200) conveys blood through arterial inlet line (40) to blood treatment device (60). The blood is diluted in the arterial inlet line before it reaches the blood treatment device by diluent flowing from the hemofilter (90) through the pre-dilution line (130) conveyed by pre-dilution pump (150). Treated blood exits the blood treatment device to the hemofilter through the hemofilter inlet line (350). A portion of the acellular fraction of the treated blood is removed in the hemofilter and is pulled through the pre-dilution line (130) by the pre-dilution pump (150). A portion of the treated blood exits the hemofilter through the venous outlet line (50). Hematocrit sensor (200) measures the hematocrit level of blood entering the fluid circuit, hematocrit sensor (210) measures the hematocrit level of a portion of the treated blood exiting the fluid circuit, and

hematocrit sensor (220) measures the hematocrit level of treated blood. Hematocrit sensors are communicatively coupled to a processing unit (520). Controller module (500) and controller module (510) are coupled to the pre-dilution pump (150) and arterial pump (140), respectively. The controller modules control the pump and thus rate of fluid flow. The processing unit is communicatively coupled to the controller modules (500, 510). The processing unit is configured to compare the hematocrit levels measured by the hematocrit sensors and configured to adjust the level of fluid flow through the system accordingly. For example, to increase the hematocrit level of treated blood flowing from the device, the processing unit can increase the flow of fluid through the pre-dilution line (130) by increasing the power of the pre-dilution pump (150). Conversely, to decrease the hematocrit level of treated blood flowing from the device, the processing unit can decrease the flow of fluid through the pre-dilution line (130) by increasing the power of the pre-dilution pump (150). In some embodiments, blood flow entering the system can be adjusted by modulating the power of the arterial pump (200). In some embodiments of a fluid circuit control system, a fluid circuit includes a fluid reservoir loop. In some such embodiments, the processing unit (520) is communicatively coupled to the controller modules (530, 540) and hemoglobin sensor (230). Controller module (530) and controller module (540) control reservoir pump (280) and reservoir pump (290), respectively.

[0069] In some embodiments, such as the fluid circuit depicted in FIG. 2, a processing unit can be communicatively coupled to a controllable orifice (450). In such embodiments, the processing unit can adjust flow rate through the pre-dilution line (130) by modulating the controllable orifice and power of the arterial pump (140).

[0070] In some embodiments, the processing unit can be communicatively coupled to any sensor, any controller module, and any valve of the fluid circuits provided herein. In some embodiments, the processing unit can be communicatively coupled to an element directly. In more embodiments, the processing unit can be communicatively coupled to an element over a network. In some embodiments, the processing unit comprises a processor, memory, a display, and/or an input device for a subscriber.

[0071] The above description discloses several methods and systems of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

[0072] All references cited herein including, but not limited to, published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0073] The term “comprising” as used herein is synonymous with “including,” “containing,” or “characterized by,” and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

WHAT IS CLAIMED IS:

1. A method for continuously diluting a fluid circuit comprising:
 - (a) providing an input stream of blood *ex vivo* to a fluid circuit;
 - (b) diluting the input stream of blood with a diluent;
 - (c) processing said stream of diluted blood to obtain a stream of treated blood;
 - (d) obtaining an acellular fraction and a cellular fraction from said stream of treated blood;
 - (e) removing an output stream of blood comprising said cellular fraction from the fluid circuit; and
 - (f) repeating steps (a)-(e), wherein the diluent comprises at least a portion of the acellular fraction from said stream of treated blood.
2. The method of claim 1, wherein the initial diluent comprises saline.
3. The method of any one of claims 1-2, wherein said processing comprises performing hemofiltration or hemodialysis.
4. The method of any one of claims 1-3, wherein said obtaining an acellular fraction and a cellular fraction from said stream of treated blood comprises passing said treated blood through at least one hollow fiber, wherein the cellular fraction of the treated blood remains in the lumen of said hollow fiber and at least a portion of the acellular fraction of said treated blood passes through at least one pore in the wall of said hollow fiber.
5. The method of any one of claims 1-4, wherein a hematocrit level of said output stream of blood is within 10% of a hematocrit level of the input stream.
6. The method of any one of claims 1-5, wherein a hematocrit level of the output stream of blood is within 5% of a hematocrit level of the output stream of blood.
7. The method of any one of claims 1-6, wherein the input stream of blood is obtained from a mammal.
8. The method of any one of claims 1-7, wherein the input stream of blood is obtained from a human.
9. The method of any one of claims 1-8, wherein the input stream of blood is in fluid communication with blood *in vivo*.
10. The method of any one of claims 1-9, wherein the output stream is in fluid communication with blood *in vivo*.
11. A continuous dilution blood treatment apparatus comprising:
 - an arterial inlet line coupled to a first inlet port of a blood treatment device,

an arterial pump configured to convey blood through said arterial inlet line from a source of blood to said blood treatment device, wherein the blood treatment device is configured to provide a cellular fraction of blood and an acellular fraction of blood during operation of the apparatus;

a hemofilter inlet line coupled to a first outlet port of said blood treatment device, configured to convey treated blood from said blood treatment device to an inlet port of a hemofilter, wherein the hemofilter is configured to provide a cellular fraction of blood and an acellular fraction of blood during operation of the apparatus;

a venous outlet line coupled to a first outlet port of the hemofilter configured to be in fluid communication with said cellular fraction of blood; and

a pre-dilution line coupled to a second outlet port of the hemofilter, configured to be in fluid communication with said acellular fraction of blood and configured to convey fluid from said hemofilter to said arterial inlet line.

12. The apparatus of claim 11, wherein the pre-dilution line is coupled to the arterial inlet line at a location on the arterial inlet line between the arterial pump and the source of blood.

13. The apparatus of claim 11, wherein the pre-dilution line is coupled to the arterial inlet line at a location on the arterial inlet line between the arterial pump and the blood treatment device.

14. The apparatus of any one of claims 11-13, wherein the pre-dilution line comprises a controllable orifice configured to control the rate of flow of fluid from the hemofilter to the arterial inlet line.

15. The apparatus of any one of claims 11-14, wherein a pre-dilution pump is configured to convey fluid from the hemofilter to the arterial inlet line.

16. The apparatus of any one of claims 11-15, wherein a reservoir inlet line is coupled to a second outlet port of said blood treatment device and an inlet port of a fluid reservoir.

17. The apparatus of claim 16, wherein the reservoir inlet line is in fluid communication with the acellular fraction of the blood.

18. The apparatus of any one of claims 16-17, wherein a first reservoir pump is configured to convey the flow of fluid through said reservoir inlet line.

19. The apparatus of any one claims 16-18, wherein a reservoir outlet line is coupled to a second inlet port of said blood treatment device and an outlet port of a fluid reservoir.

20. The apparatus of claim 19, wherein the reservoir outlet line is in fluid communication with the cellular fraction of the blood.
21. The apparatus of any one of claims 19-20, wherein a second reservoir pump is configured to convey the flow of fluid through said reservoir outlet line.
22. The apparatus of any one of claims 11-21, wherein the hemofilter line comprises a valve to control the flow of fluid through the hemofilter line.
23. The apparatus of any one of claims 11-22, wherein the arterial inlet line comprises a valve to control the flow of fluid through the arterial inlet line.
24. The apparatus of any one of claims 11-23, wherein the hemofilter inlet line comprises a hemocrit inlet hematocrit sensor.
25. The apparatus of any one of claims 11-24, wherein the arterial inlet line comprises an inlet hematocrit sensor.
26. The apparatus of any one of claims 11-25, wherein the venous outlet line comprises an outlet hematocrit sensor.
27. The apparatus of any one of claims 11-26, further comprising a processing unit communicatively coupled to at least one sensor, configured to analyze data from said at least one sensor, and to modulate the flow of fluid through said pre-dilution line.
28. The apparatus of claim 27, wherein the processing unit maintains a hematocrit level measured by inlet hematocrit sensor and outlet hematocrit level sensor.

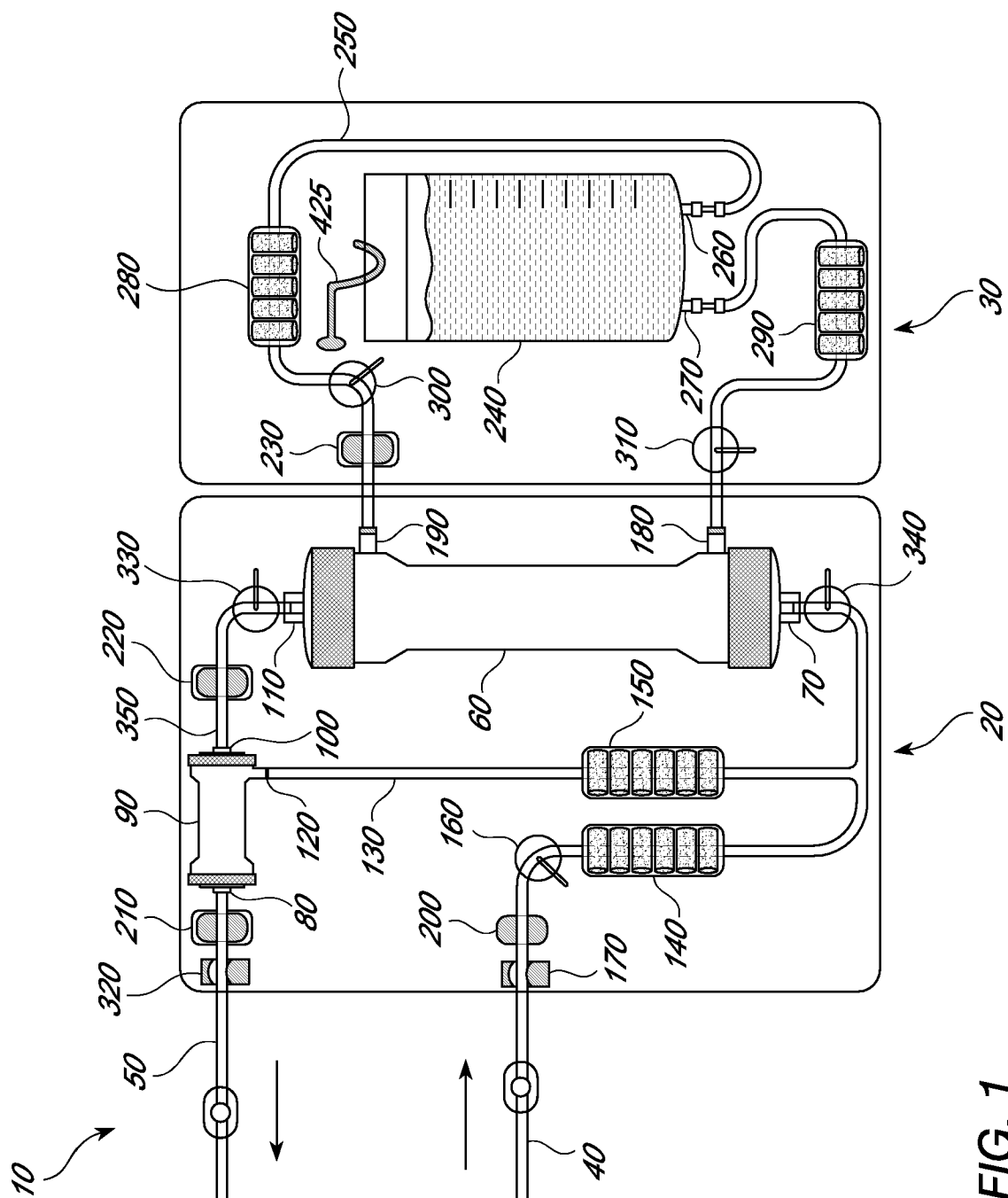


FIG. 1

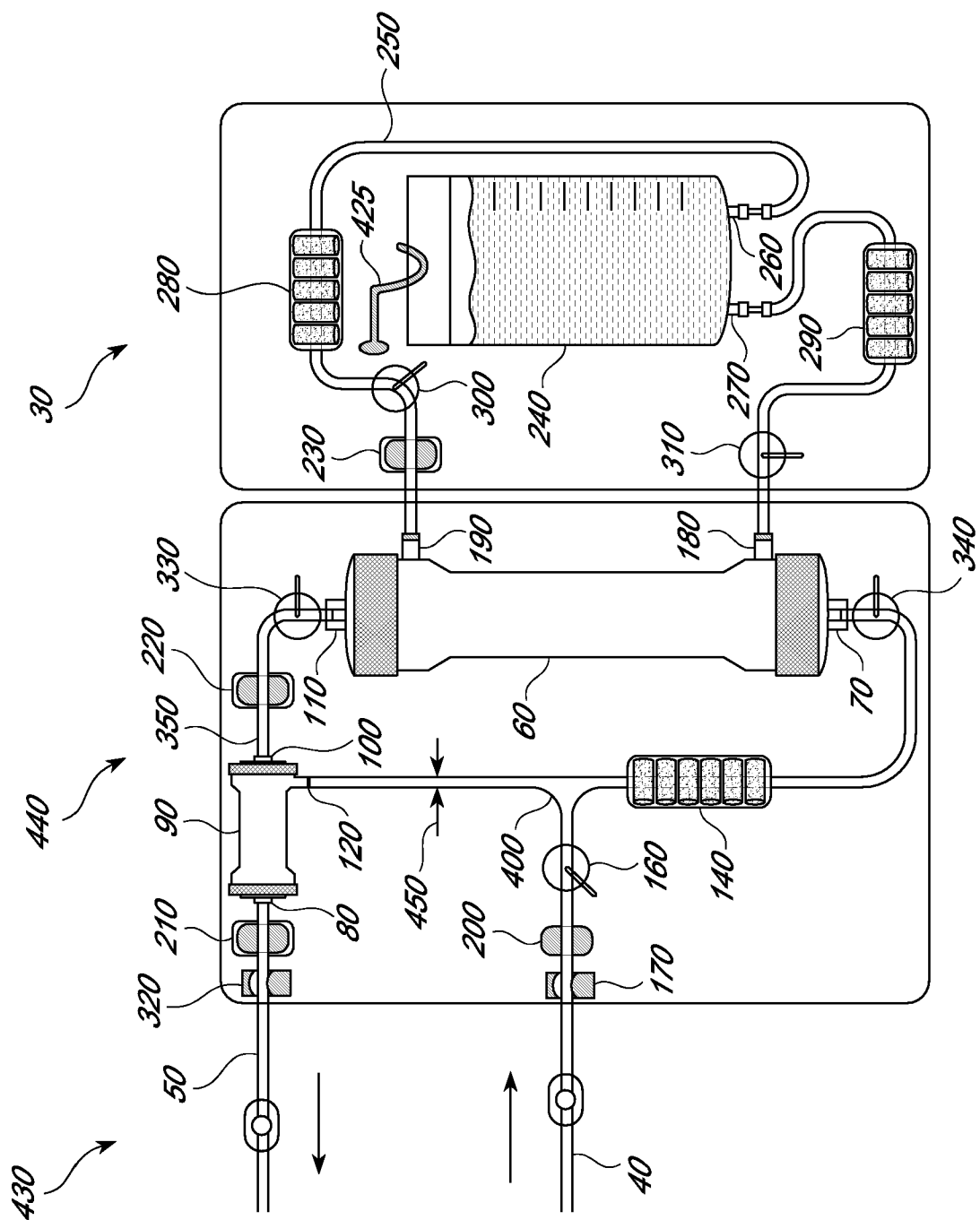


FIG. 2

