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(54) Title: PROGRAMMABLE SYSTEM FOR CONDITIONING OF CEREBROSPINAL FLUID

(57) Abstract: A programmable system (10) to control the extracorporeal circulation and conditioning of cerebrospinal fluid for the treatment of brain maladies. The system (10) includes an extracorporeal fluid circuit (30) with pressure sensors (41, 42, 43), compositional analysis units (45), pumps (65, 72) and medicament dispensers (80) as well as a controller (100) which synchronizes the automated sensing, analysis and conditioning functions with the operation of the pumping system (65, 72) so as to increase the precision of the measurements and optimize the effectiveness of the treatment.

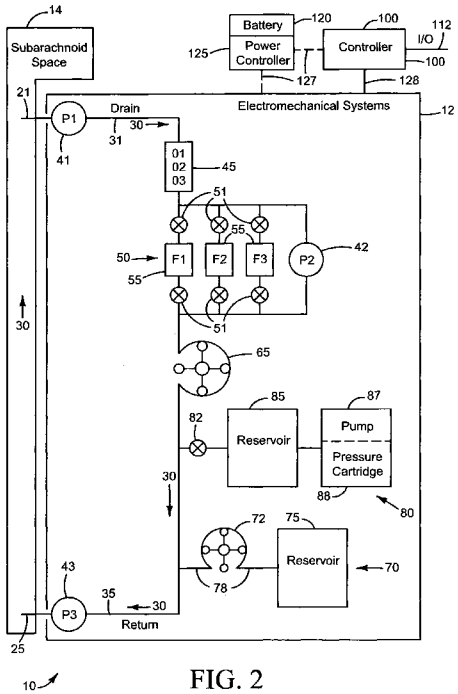

FIG. 2

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Programmable System for Conditioning of Cerebrospinal Fluid

by Olin Palmer, Shivanand P. Lad, Richard Allen, Alex Butterwick, Thomas Saul

Cross Reference to Related Applications

This application claims priority from a Unites States Provisional Application No. 61/171,577 filed on 22 April 2009 by Palmer et al. The entire contents of that application are incorporated by reference herein.

Technical Field

The present invention relates generally to medical devices and methods. More specifically, the present invention relates to devices and methods for extracorporeal circulation, analysis, filtering and conditioning of cerebrospinal fluid (CSF).

Background Art

Cerebrospinal fluid (CSF) is a clear, watery fluid that surrounds the brain and spinal cord. It is produced in the human central nervous system (CNS) at a rate of about 0.3 ml/min in healthy adults. The total volume found in the ventricles and subarachnoid space is about 150ml at any moment. Thus the total volume is naturally replaced approximately 3 times a day. In normally functioning anatomy, the fluid naturally follows a circuit from production in the lateral ventricles, circulation over the surface of the brain and spinal cord and eventual drainage through the arachnoid granulations at the venous sinuses and lymphatic vessels. It is understood that due to the exposure of the fluid to the brain that the composition of the fluid can have a direct impact on the health of the brain with beneficial components in the fluid promoting brain health and pathogenic components having a deleterious effect on the brain. In fact pathology of a variety of compounds found within the CSF is increasingly understood, and it is believed that the elimination or treatment of these pathogens will lead to the prevention or amelioration of diseases such as Alzheimers, Parkinsons, Amyotrophic Lateral Sclerosis, Multiple Sclerosis and Guillain Barre Syndrome as well as others.

The detection and removal, or at least reduction in concentration, of these compounds has been shown to have therapeutic effect. Likewise, the introduction of medicament into this fluid has also been shown to produce beneficial results. Given the relatively low rate of production of this low viscosity cerebrospinal fluid in the CNS and the presence of a natural production and re-adsorption process already ongoing there, the opportunity exists to create an extracorporeal circulation loop to treat the fluid in a space outside the sensitive environment of the CSF space. Accomplishing this direct conditioning of the CSF though, is made difficult by the very low volume of the space in

the body that the fluid occupies and the sensitivity of the nerves and organs that are exposed to pressure and composition changes. Even slight fluctuations in intracranial pressure caused by incorrect removal or reintroduction rates of the fluid can cause pain or injury to the patient ranging from headache at the mild end to death. The problem is compounded by the small diameter and long length of the extracorporeal circulation which causes "head loss" during flow, with pressures dynamically increasing in front of restrictions, and decreasing behind restrictions in the flow loop. Anticipating these artificial pressure artifacts and extrapolating the native pressures in the patient can be difficult. In addition, the pressure in the extracorporeal circulation loop can change for a variety of other reasons such as restrictions (clogs, kinks, crushed tubing, closed valves, filter loading, etc), or changes in the patient's condition. (CSF leak, CSF overproduction, brain swelling, patient motion, etc). In light of this, measuring some pressures, such as patient ICP, is best preformed while the pump is stopped, while other pressures, such as transmembrane pressure at the CSF conditioning filter, are best performed while the pump is running. Information relevant to attempts to create such a treatment system can be found in US Patent Nos. 4,686,085; 4,904,237; 5,980,480; 6,575,928; 6,875,192; 7,309,330; 7,025,742; 7,189,221 and US Published Application Nos. 2003/006530; 2005/0038371; 20080033400; 2005/0010159. However, each one of these references suffers from one or more of the following shortcomings: they rely on passive drainage of the CSF to the extracorporeal circulation loop which limits the drainage to the natural generation rate of the fluid in the CNS thereby limiting the amount of fluid that can be treated in a reasonable treatment session; they provide imprecise measurement of pressure in the circulation loop which exposes the patient to risk of excessive or insufficient CSF pressure in subarachnoid space with all the attendant risks already mentioned for that condition; they measure the pressure in the circulation loop at only one location so that they are not assured that the pressure at the point of drainage and reintroduction are equivalent thereby potentially creating undesirable intracranial pressure fluctuations in the subarachnoid space; the pressure monitoring alarm limits applied by the referenced systems do not take into account the shape of the pressure waveforms that exists in CSF pumping system so they must be set outside optimal limit levels to avoid false alarms caused by natural spikes and troughs in pressure waveforms thereby exposing the patient to unsafe pressure fluctuations or sub-optimal flow rates; the pressure sensing performed by the referenced devices is not synchronized with the pumping states of the circulation pumps so they cannot distinguish between the native pressure attributed to the CNS and that caused by the pumps; they do not provide a mechanism for creating turbulence in the CSF that is reintroduced in the subarachnoid space to so there is not sufficient mixing of the conditioned CSF in that space limiting the

effectiveness of the treatment;. they replace the patient's drained CSF with synthetic CSF rather than the patient's own reconditioned CSF which may present compatibility issues and may not actually remove the toxins from the CSF but simply dilute it with non toxin containing artificial CSF; the dispensing of medicament into the CSF is not tied to the results of the compositional analysis of the fluid and the identification of pathogens in the fluid so that dosages are not optimized according to the presence and concentration of pathogens.

Therefore what is needed is programmable cerebrospinal fluid conditioning system that does not rely on passive drainage, nor suffer from an imprecise pressure sensing and control system which does not sense pressure at drainage and reintroduction points, cannot distinguish between the native pressure of the CSF system and the pressure induced by the pumping system and cannot apply adaptive alarms to the pressure-wave forms thereby avoiding false alarm conditions. Furthermore the device must not suffer from the inability to synchronize the dispensing of medicament with the results of the compositional analysis.

Disclosure of Invention

The present disclosure advantageously addresses one or more of the aforementioned deficiencies in the field of CSF conditioning by providing a portable and programmable CSF conditioning system that provides precise pressure monitoring and pumping control of the CSF through an extracorporeal fluid circuit as well as compositional analysis of pathogenic components of the fluid and dosing of medicament into the CSF in response to that analysis. It also provides turbulent reintroduction of the conditioned fluid into the subarachnoid space so that the conditioned fluid is more thoroughly dispersed in the desired area.

The device is a closed loop extracorporeal fluid circuit for draining, pumping, controlling, analyzing and conditioning the flow of CSF for the purpose of treating brain injuries and disease. The system, designed to be worn by the patient in an in-patient or outpatient setting without connection to mobility impeding apparatus, actively pumps fluid from the subarachnoid space of a patient through the lumens of a specialized catheter which is positioned in this space. It then circulates the fluid through an attached circuit at desired pressures and rates so that the fluid can be analyzed by a variety of sensors, treated by filters and medicament dispensers and reintroduced through another lumen of the same or separate catheter. In some embodiments the point of attachment of the catheter is in the lumbar thoracic or cervical CSF space. In yet another embodiment, the drain and return points may be positioned in different CSF spaces, for example the drain

may by attached in the lumbar thoracic CSF space while the return is in the subarachnoid CSF space.

One embodiment of the device comprises a specialized, multi-lumen catheter for accessing the subarachnoid space for purposes of draining and re-introducing the CSF from that space through the different lumens of the catheter. The lumens of the catheter are connected to a fluid circuit which guides the flow of the CSF outside the body. Integrated into the circuit are other components such as pressure sensors for measuring the pressure at various locations along the circuit, devices for compositional analysis of the fluid, filter banks for removing targeted compounds from the CSF, medicament dispensers for dosing medicine into the fluid and pumps for controlling the flow of the CSF and for creating pressure waveforms in the flow. The sensors, filters, pumps and dispensers are also electrically connected to a controller for synchronizing the operation of the various units in a manner that optimizes the CSF conditioning process with the first order of optimization being that of collecting accurate pressure readings and the second being the minimization of undesirable pressure fluctuations in the system due to sub-optimal pumping control and the third being the synchronization of medicament dispensing with the results of the compositional analysis. The controller can toggle the pump between on and off duty cycle and can further synchronize the collection of pressure measurements with these pump states so that the system can record measurements in both the pump stopped, and pump running state conditions, each of which provide a specific and unique piece of data about the system. The pressure readings collected during the various pump states can then be analyzed by the microprocessor in order to determine true intracranial and transmembrane pressures.

In another embodiment the system may additionally measure the time constants of the transients in the pressure wave-forms following the pump starting or stopping (how long the system takes to reach steady state and the shape of the pressure build or decay curves). These time constants may provide diagnostic information for system configuration or performance. At the beginning of therapy, a time constant outside of normal parameters may indicate an incorrectly configured flow loop. Over the course of therapy, changes in the time constants may indicate impending need for maintenance of the conditioning element or some component of the fluid circuit.

In another embodiments it is anticipated that there will be a need for pressure alarms such as: static ICP too high, static ICP too low, running drain or return pressures outside of limits, transmembrane pressure at the conditioning element too high, or pulsatility too low (note that measurement of pulsatility from patient breathing or cardiac cycle is normal, and the absence of that pulsatility may be interpreted as a possibly occluded flow path or other problem). Normally the alarms relevant to static pressures

should only be triggered during static measurement, and the alarms relevant to dynamic pressures should only be triggered during pump running steady state conditions. If the system measures and records the characteristics of the pressure transients, these alarm set-points can be adaptable to vary with the system's duty cycle, not only in the "steady – on" condition, or "steady-off" condition, but also potentially during the transient conditions.

In yet another embodiment the measured pressures approaching an alarm condition may cause the system to adapt its operation, such as slowing down the flow if the transmembrane or patient return flow pressure is too high.

In another embodiment the system measurements may include detection of the presence and concentration of deleterious or beneficial elements in the CSF. For example if the therapeutic target is the prevention of vasospasm post hemorrhage by blood removal; the system may include one or more optical measurement flow cells which measure red blood cell concentration in the CSF, oxygen saturation level of the red blood cells, the concentration of free hemoglobin, etc. These data may be tracked and integrated with flow data to track total blood removed, changes in the condition of the blood, and potentially predict either the completion of therapy by removal of all blood, or the onset of vasospasm due to the breakdown of remaining blood in the CSF.

In other embodiments the integrated measurement of total blood filtered from the CSF, trends in historical pressure measurements, or residence time of the cells on the filter membrane allow for prediction of required service interval for the CSF conditioning element, either by element replacement, or purging.

In another embodiments the system may incorporate the capability to deliver therapeutic agents to the CSF if certain alarm conditions are approached or met, such as delivering vasodilators if the conditions believed to trigger vasospasm are observed.

In some embodiments, the system can include a capability for intentional use of increasing and decreasing pressure waveforms within an acceptable range and over a defined time span. Natural bulk and oscillatory flow of CSF between the spinal and cerebral areas is slow, so actively increasing the exchange and mixing of fluid between the intracranial and spinal region is anticipated to have the advantage of enhancing the effectiveness and efficiency of the CSF conditioning process, resulting in potentially improved patient outcomes. These pressure cycles promote flow between intracranial and intraspinal space due to the relative inelasticity of volume in the spinal space, and elasticity (compliance) of volume in the intracranial space. As a net volume of fluid is pumped in through the lumbar catheter, there is a bulk flow from the intraspinal space into the intracranial space as the brain and blood vessels contract due to the increased pressure. When this is reversed with a new fluid drainage, a bulk flow from intracranial

to intraspinal spaces occurs. In this oscillatory flow, the transport of blood in the CSF or other deleterious agents out of the intracranial space may be enhanced, carrying them into an area where the dual lumen catheter circulation and filtering can be more effective. This effect may be achieved by incorporating an extracorporeal reservoir of fluid (collected native CSF, or a bio-compatible CSF replacement, or other therapeutic fluid), where net increase or decrease of the fluid in the body can be pumped from or to this reservoir causing the pressure cycles.

In still another embodiment, the control algorithms which control the shape and timing of the pressure waveforms may vary so as to have a maximizing effect of the fluid movement within the patient, especially in regard to the exchange of fluid between the cerebral and spinal regions. For example, a gradually increasing and then comparatively more rapidly decreasing pressure may have a beneficial fluid exchange effect. Other waveforms may also provide a therapeutic benefit as determined by further experimentation. In addition, the timing of the pressure cycle can be so designed to take advantage of the natural pressure cycles and compliance of tissue within this space, for example by synchronizing with cardiac or respiratory cycles.

In an alternate embodiment, the CSF is not circulated but is instead drained internally or externally to the body while at the same time artificial CSF is introduced through a separate line. Pressure sensors are attached to the infusion line while pressure and optical sensors are attached to the drain line and the signals collected by those devices are transmitted to the controller for analysis. Since the patient's CSF is not being reintroduced the need for filtering is obviated. The infusion line may also be configured for the introduction of medicament, as in the preferred embodiment, although here it is introduced on a separate infusion line which also has a pressure wave unit attached to it as in the preferred embodiment. The advantage of this embodiment, as stated earlier, is that the filter bank is eliminated but because this configuration requires an artificial source of CSF the arrangement is not as self contained and would likely reduce the patients' mobility.

In some embodiments the measuring elements (pressure, compositional, etc) are collocated with the control and pumping unit while in others they may be remotely located from the control and pumping unit. For example attached to the extracorporeal fluid path, or embedded in the intraspinal catheter.

A novel and non obvious feature of the device and associated method is the synchronization of the pressure measurement function with the pumping control and pressure waveform generation functions so that more precise pressure measurements can be made.

Another novel and non obvious feature of the device is the application of sophisticated process control apparatus to the system which provides for the synchronization of the sensing, analysis and diagnostic functions with the pump duty cycle of the system in order to customize the treatment and therapeutic activities based on the feedback from transducers, compositional analysis sensors, and filters and the analysis of that feedback by the controller.

Another novel feature is the generation of pressure waveforms in the circulated fluid in order to create turbulence at the fluid reintroduction point so there is more complete mixing of the fluid in the subarachnoid space, or in the bulk flow between the intracranial and intraspinal spaces if the drain and return points are positioned in a manner to promote flow through those regions.

Another novel feature is the feedback of the results of the compositional analysis to the controller so that dosing of medicament is influenced by the composition of the fluid.

The device may afford the user one or more of the following advantages:

a. enhanced pressure monitoring in both the drain and reintroduction flows by applying an on/off duty cycle to the re-circulation and waveform pumps and then synchronizing the pressure sensing with that cycle so that measurements are recorded under both the static and dynamic conditions. This provides for enhanced precision of measurement of the patient's intracranial pressure (ICP), which is best measured under static conditions, and the transmembrane pressure of the filters, which is best measured under dynamic conditions. Precise measurements of these two pressures are provided as feedback to the controller which responds with modulations to the pumping waveform and filter maintenance schedule which would not be available without this feature.

b. integrated feedback of therapy effectiveness by examining trends in pathogen concentrations detected by sensors and using that information to analyze filter effectiveness in the device and pathogen production rates in the patient; this information could then be used to modify the treatment regimen in real time;

c. enhanced control of pressure waveforms to promote mixing of the medicament in the circulation circuit and in the CSF space. Because the bulk and oscillatory flow of CSF between the spinal and cerebral areas is slow, actively increasing the exchange and mixing of fluid between the intracranial and spinal regions is anticipated to have the advantage of enhancing the effectiveness of the CSF filtering and infusion process. Since the volume in the spinal space is quite inelastic while the volume of the intracranial space is somewhat more compliant, oscillations caused by induced pressure waveforms

from the device should improve the transport of deleterious agents out of the intracranial space and into areas where they can be accessed by the catheter ports;

d. the ability to synchronize the generation of pressure waveforms in order to take advantage of native pressure cycles and compliance of tissue that may exist with cardiac or respiratory cycles;

e. the ability to measure the time constants of the transients following pump start and stop and, based on the change to the shape of the transient curve over time, use this information as an indicator of the need for filter change out, maintenance functions or configuration adjustments;

f. adaptive pressure waveform generation and alarm control which reduces the pumping pressures as measured pressures approach alarm conditions while also allowing for alarm limits to the follow the shape of pressure waveforms so that tighter pumping control can be provided without the risk of false alarms;

g. historical usage and trend monitoring so that consumables that are approaching end of life can be exchanged before alarm conditions are exceeded and so that treatment algorithms can be optimized based on extrapolation of past trends in filtration efficiency and medicament delivery and distribution.

It is therefore the purpose of this invention to treat diseases of the brain and central nervous system by draining, conditioning and reintroducing CSF via a portable, extracorporeal fluid circuit which provides automated compositional analysis, filtering and dispensing of medicament under precise pressure control and pumping conditions.

The present invention will now be described more fully with reference to the accompanying drawings, which are intended to be read in conjunction with both this summary, the detailed description, and any preferred or particular embodiments specifically discussed or otherwise disclosed. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided by way of illustration only so that this disclosure will be thorough, and fully convey the full scope of the invention to those skilled in the art.

Brief Description of Drawings

FIG. 1 is a block diagram of the system and subsystems.

FIG. 2 is a schematic of the system showing relative positioning of the components of the system in the fluid circuit.

FIG. 3 is an illustration of the system connected to a patient.

FIG. 4A is a diagram of the pressure waveforms created by the pump duty cycle and the associated static alarm limits.

FIG. 4B is a diagram of the pressure waveforms created by the pump duty cycles and the associated adaptive alarm limits.

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Best Mode for Carrying out the Invention

To provide context for the invention, it may be useful to understand that Cerebrospinal fluid (CSF) is produced in the human central nervous system (CNS), primarily in the choroid plexus in the ventricles of the brain. The normally clear, watery fluid maintains a gradient between it and the interstitial fluid of the nervous system. Thus many neurotransmitters, peptides and other neuroactive substances can be found within the CSF. Although the functional role of many of these peptides is currently under research, there are two functions of CSF that are presently understood: 1) by surrounding and bouying the brain and spinal cord it provide a protective function upon impact to the skull or spinal column; 2) and it contributes to the maintenance of a constant composition of the neuronal environment.

In healthy adults, CSF is produced at a rate of about 0.3 ml/min and the total volume found in the ventricles and subarachnoid space is about 150ml at any moment. Thus the total volume is naturally replaced approximately 3 times a day. In normally functioning anatomy, the fluid naturally follows a circuit from production in the lateral ventricles, circulation over the surface of the brain and spinal cord and eventual drainage through the arachnoid granulation at the venous sinuses and lymphatic vessels.

The concentration of various neuroactive substances in the CSF is of great interest, because it represents a direct view of the extracellular fluid in the immediate vicinity of the neurons of the brain and spinal cord. In the same manner that beneficial components of this fluid likely serve to maintain the health and function of the brain, the presence of pathogens and other unwanted compounds in this fluid are thought to have a direct and deleterious effect on the CNS. The pathology of a variety of endogenous and exogenous pathogens found within the CSF is increasingly understood and it is believed that the elimination or treatment of these pathogens will lead to the prevention or amelioration of diseases such as Alzheimers, Parkinsons, Amyotrophic Lateral Sclerosis, Multiple Sclerosis and Guillain Barre Syndron as well as others. In addition to the compounds and the associated disorders already mentioned, physical injury to the brain can also introduce elements into the CSF which impede the healing of the injury.

Whether the source of unwanted compounds in the CSF is disease or injury, the detection and removal, or at least reduction in concentration, of these compounds has been shown to have therapeutic effect. Furthermore, the introduction of medicament into

this fluid has also been shown to produce beneficial results. This treatment can prevent or reduce the severity of many brain diseases and injuries that result from the exposure of the brain to these pathogens, proteins, and other unwanted compounds.

This description of anatomy and physiology is provided in order to facilitate an understanding of the invention. Persons of skill in the art will also appreciate that the scope and nature of the invention is not limited by the anatomy discussion provided.

Detailed Description

The device **10** is a closed loop extracorporeal fluid circuit **30** for draining, pumping, controlling, analyzing and conditioning the cerebrospinal fluid (CSF) for the purpose of treating brain injuries and disease and is designed to be worn by the patient **16** in an in-patient or outpatient setting without connection to mobility impeding apparatus. The device **10** comprises a multi-lumen catheter **20** for accessing the CSF in the subarachoid space **14**, fluid drain **21** and fluid return lines **22**, a plurality of pressure sensors **41, 42, 42**, compositional analysis sensors **45**, a filter bank **50**, a circulation pump **65**, a medicament dispenser **80**, a pressure wave generating system with reservoir **70**, and a controller **100**.

Starting at the point where the CSF exits the patient's body **16** through the lumen **21** of a temporarily inserted, specialty catheter **20**, the catheter connects to a fluid drain line **31**. The drain line **31** comprises standard medical attachment hardware, medical grade fluid tubing and a pressure transducer **41**. The tubing is made of material which can be laterally flexed to accommodate positioning requirements but which limits volumetric expansion or contraction under pumping conditions. Suitable materials used in simple monolithic or composite structures include typical cardiovascular and neurovascular catheter materials such as silicone, polyvinychloride, urethane and other common medical grade polymers. Since precise pressure monitoring is crucial to the optimal function of the system, the pressure transducer **41** is positioned in the line **31** as close to the union with the catheter **20** as practical in order to avoid distortion of the signal by line loss or undesired perturbations in the system. The transducer **41** has an inlet and outlet port for connection to the fluid circuit and will be connected through the power **127** and data grid **128** to the controller **100**. The transducer **41** may be commanded by the controller **100** to measure and transmit signals in a continuous mode or may be commanded to measure according to some schedule. The outlet port of the transducer is connected to additional tubing needed to move the fluid further along the circuit **30**.

The device **10** further comprises compositional analysis sensors **45** which are designed to detect the presence and concentration of various constituent elements of the CSF including, but not limited to, the concentration of red blood cells, the oxygenated state of the blood, the concentration of free hemoglobin from lysed cells, and bilirubin. The sensors **45** may comprise LED emitters capable of emitting discrete wavelengths of light at desired wavelengths and detectors which sense either the emitted light after it has passed through or been reflected by particles in the fluid, or light induced by flouresence from substances in the fluid . The presence of certain elements in the fluid cause intensity shifts at specified wavelengths with the relative intensities create by each constituent fluid component of interest being reversed for the emitted wavelengths. This two point sensing algorithm aids in the precision of measurement. Sensing accomplished by the collector is transmitted to the controller **100** where it is converted to digital form for analysis, data storage and treatment scheme response. The compositional analysis sensors **45** can be arrayed sequentially or in parallel and may be situated as a stand-alone unit somewhere along the fluid circuit **30** or as an integrated unit of the console **60**. The only positional requirement being that it must be located along the fluid circuit **30** so that the sensors **45** can view the fluid as it passes, and preferentially while the fluid is in motion to avoid settling of cells or particulate in stagnant fluid. Once the CSF has flowed passed the sensors **45** it will continue to flow through the extracorporeal circuit **30**.

A filter bank **50** is positioned in the circuit **30** in order to removed target pathogens from the CSF which may contribute to diseases of the brain. The filter bank **50** comprises a plurality of cartridges **55** containing disposable membranes, a purge mechanism and a filter transmembrane pressure transducer **42**. The cartridges **55** are hollow housings capable of removal or reinsertion. They are arrayed in parallel or series within the filter bank **50** to facilitate switching between filters and sequestering the filtrate out of the flow loop after some period of time. The filter membranes are disposable hollow fiber membranes, or convoluted sheets with high surface area to volume ratios. The membranes are selected by pore size and capacity depending on the type of compound to be removed from the fluid. Each parallel filter cartridge **55** is isolated from an upstream and downstream manifold by electrically actuated isolation valves **51** so that cartridges **55** in one path can be isolated and replaced while allowing the fluid flow to continue through parallel paths. The filter cartridges **55** may be configured with the same filter membranes, in which case they are operated in parallel, or different filters in which case the filters not desired for current use are isolated by upstream and downstream valves **51**. The filter bank **50** further comprises a purge unit which is connected to each filter cartridge in order to back-flow or tangentially flow a fluid through

the filter in the event the filter is clogged or needs to be cleaned. The filter bank **50** further comprises a pressure transducer **42** in parallel with the filter cartridges **55** to measure transmembrane pressure and transmit that information via attached data grid **128** to the controller **100** where the information is stored and analyzed for the purpose of triggering maintenance prompts and alarms.

The device **10** further comprises a motorized circulation pump **65** connected to the fluid circuit **30** downstream from the filter bank **50** for the purpose of pumping the CSF from the subarachnoid space **14** through the extracorporeal circuit **30**. The pump **65** comprises a housing, inlet's and outlets for connection to the circuit **30** and a mechanical pumping mechanism. The pumping mechanism can be any type of commonly used mechanical pump such as a peristaltic roller, piston, bellows, pneumatic, screw mechanism or any other suitable means for creating vacuum or pressure in the range of +/- 200 mmHg. The housing surrounding the moving pumping mechanism is in place in order to shield collocated components from entanglement in the moving components of the pumping mechanism. The pump **65** is connected to a power supply via the power grid **127** and is connected to controller via the data grid **128** so that it may received signals for the purpose of controlling the pump's state. It is desirable that the pump **65** be located downstream from the filter bank **50** so that any blood cells in the CSF are removed prior to pumping, to avoid hemolysis. Otherwise, vasospasm from blood degradation by-products may be accelerated.

The system further comprises a medicament dispenser **80** attached to the fluid circuit **30**. The dispenser **80** comprises an electrically actuated isolation valve **82** connected to the fluid circuit **30**, a reservoir **85** for holding medicament, and a pressure source **87, 88** for infusing the medicament into the fluid circuit **30**. The isolation valve **82** is an electrically powered valve and is connected to the power supply and the central processor and controller by power **127** and data grid **128**. The valve **82** opens in response to signals sent from the controller **100** which controls the dispensing of medicament into the fluid stream while the pressure created by the pump **87** or pressure cartridge **88** inject the medicament into the CSF circuit. Alternately, it may be a passive pressure valve that only opens upon injection of the therapeutic agent under pressure. The medicament reservoir **75** comprises a chamber to hold fluid medicament with a port opening to the isolation valve **82** and a second port which exposes the chamber to the pressure source **87, 88**. The pressure source **87, 88** can be any pumping mechanism or a replaceable pressure cartridge and exerts pressure on the fluid in the medicament reservoir thereby infusing it into the fluid circuit when the isolation valve **82** is opened. The medicament dispenser **80** may be positioned anywhere downstream of the filter bank **50** but preferably downstream of the re-circulation pump **65**.

A pressure waveform generating unit **70** may also attached to the fluid circuit and comprises a section of tubing **78**, a motor driven pump **72** and a fluid reservoir **75**. The purpose of the unit **70** is to create pressure waveforms in the circulating CSF in order promote mixing of the CSF between the intracranial and intraspinal spaces, thereby improving the distribution of the conditioned CSF in those spaces. The tubing **78** connects to the fluid circuit **30** and runs through the mixing pump **72** and into a reservoir **75**. The pump **72** may be electrically powered and can be any of the kinds previously described for the circulation pump **65**. It can be connected to the power supply **125** and controller **100** via the power **127** and data grid **128** respectively. The reservoir **75** is in line with the pump **72** and may be positioned upstream or downstream of the pump in the wave generating unit **70**. When activated, the pump **72** draws in CSF from the fluid circuit **30** to the reservoir **75** and then expels it back into the circuit in response to commands sent by the controller **100**. The pressure-wave generating unit **70** may be located anywhere in the circuit **30** downstream of the circulation pump **65**.

The device **10** further comprises a return line **35** to transport the conditioned fluid from the pressure waveform generator **70** to the return lumen **25** of the catheter **20**. The return line **35** may contain a pressure transducer **43** to sense the actual pressure created by the combination of native pressure in the CSF from the patient, as well as the pressure created by the circulation pump **65** and the pressure waveform generator **70**. The transducer may be situated in the fluid circuit **30** as close as possible to the point where the CSF is re-introduced into the body, preferably just upstream of the union between the fluid return line **35** and the lumen **25** of the catheter **20** used to re-introduce the fluid into the patient's body **16**. The transducer is connected by the data grid **128** to the controller **100** and transmits signals to that unit which describe the actual waveform present in the circuit.

The device further comprises a controller **100** which controls the functionality of the device by: receiving user inputs from the user interface **115**, receiving analog and digital signals from the electromechanical systems **12**, analyzing the received signals, storing and retrieving data from the memory, applying algorithms to the data and signals, and sending analog and digital commands to various components in order to accomplish the functions of the device. The controller consists of a central processing unit (CPU) **103**, an analog to digital converter **104**, a programmable memory **105** and algorithm unit **108**, and a command output unit **106**. The programmable memory **105** comprises an EPROM or other programmable memory for programming with various software algorithms and code. It communicates with the CPU **103** of the controller **100** and applies the software algorithms **108** to direct the controller **100** functions.

The controller **100** is connected to the external input/output **112** which contains the user interface **115** and manufacturer's interface **118**. The user interface **115** displays information including but not limited to, instantaneous data from pressure transducers **41, 42, 43** and compositional analysis sensors **45**, processed data such as flow rates and pressure waveforms, historical data such as filter life and volume of medicament dispensed. The user interface **115** also accepts inputs from the user including but not limited to, on/off commands, selection of pumping algorithms and waveforms, selection of medicament dispensing routines, and alarm conditions. The manufacturer's interface **118** comprises an electrical interface compatible with standardized electrical cabling such as USB, Firewire, and RS232 ports to facilitate the loading of software and algorithms.

The device **10** also comprises a power controller **125** and power supply **120**. The power supply **120** may be any AC or DC source but preferably a DC rechargeable supply. It provides power to the controller **100** and the electromechanical systems **12**.

The device **10** also comprises an alarm unit **90** that can be triggered when limits set in the pumping and pressure sensing algorithms are exceeded. The alarms comprise audible alarm tones and visible message displays on the user interface **115**. In addition alarms can be configured to trigger power relays in order to halt operations of the unit.

In a preferred embodiment the power supply **120**, and controller **100** as well as the compositional analysis sensors **45**, filter bank **50**, circulation pump **65**, medicament dispenser **80** and pressure waveform generator **70** are all consolidated in a single, integrated console **60** that is wearable by the patient on a belt or other load-bearing device. In that case the only components not integrated into the console would be the fluid drain **21** and fluid return lines **25** as well as the pressure transducers **41, 42** positioned near the terminus of each of those sections of line. The advantage of this embodiment is the mobility it provides to the patient, a reduction of risk associated with tangling of tubing and pulling out of catheters, as well as obviating the need to drain CSF into another body cavity or to provide artificial CSF for mixing with the medicament for infusion.

In an alternate embodiment, the CSF is not re-circulated but is instead drained internally or externally to the body while at the same time artificial CSF is introduced through a separate infusion line. Pressure transducers **43** are attached to the infusion line while another pressure transducer **41** and compositional analysis sensors **45** are attached to the drain line **31** and the signals collected by those devices are transmitted to the controller **100** for analysis. Since the patient's CSF is not being reintroduced the

need for filtering is obviated. In this configuration the medicament is introduce on the infusion line which also has a pressure waveform generator **70** attached to it. The advantage of this embodiment, as stated earlier, is that the filter bank **50** is eliminated but because this configuration requires an artificial source of CSF the arrangement is not as self contained and would likely reduce the patients' mobility.

While exemplary embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will occur to those skilled in the art without departing from the disclosure. It should further be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the invention.

Industrial Applicability

Whatever embodiment is chosen, the device **10** is used by attaching the CSF drain **21** and return **25** lines and their associated transducers **41, 43** to a specialty catheter **20** which has been inserted into the patient's spine and subarachnoid space in order to access the CSF. The user inputs the parameters of a desired treatment regimen including but not limited to treatment time, pumping volume, dispensing volume and pathogen concentration by means of the user interface. The CSF is then pumped through the fluid circuit **30** under precise pressure monitoring and control. The compositional analysis sensors **45** identify types and concentrations of pathogens or unwanted compounds in the blood and provide this information to the controller **100** which monitors the trends in concentration levels and responds by applying custom medicament treatment routines that are indicated by the analysis of the patient's CSF. In stream filters **50** remove target pathogens from the CSF with the resulting decreasing concentration of the pathogens being confirmed by the optical sensors. The medicaments dispensed by the dispenser **80** may provide therapy to the brain and can be dispensed under precisely monitored conditions whereby instantaneous and historical data may be synthesized by the controller **100** so that the therapy regime is continuously updated based on feedback from the compositional analysis sensors **45** which indicate the changing concentrations of pathogens as a result of the filtering and treatment of the CSF. The pressure waveform generator **70** further tailors the therapy by not only ensuring the medicament is mixed with the in-line CSF but also by promoting turbulence or bulk flow inside the subarachnoid space to ensure enhanced distribution of the medicament and treated fluid. The controller **100** analyzes the inputs from the pressure **41, 42, 43** and compositional analysis sensors **45** as well as historical data stored in the memory **105** and modifies operating algorithms and treatment regimens by changing

pump duty cycles, sampling schemes and medicament dosages to customize the treatment. In addition the controller **100** can apply adaptive alarms and usage alarms to ensure safety and maintenance limits are adhered to.

While exemplary methods of use of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such methods are provided by way of example only and that other methods of employment are also contemplated by this disclosure.

Claims

We claim:

1. A device (10) for the extracorporeal monitoring and conditioning of cerebrospinal fluid (CSF), comprising:

a. a catheter (20) for accessing the CSF drain and return points in the body;

b. an extracorporeal fluid circuit (30) attached to the catheter (20) to direct the flow of the CSF;

c. a plurality of electromechanical systems (12) attached to the extracorporeal fluid circuit (30) for regulating the flow and conditioning the CSF;

d. a controller (10) for monitoring and controlling the conditioning of the CSF comprising:

i. a programmable memory (105); and,

ii. a plurality of algorithms (108) capable of synchronizing the operations of the electromechanical systems (12) of the device (10) to optimize the monitoring and conditioning process.

2. The device of claim 1, further comprising a pressure and flow monitoring and control system positioned in the circuit (30) and the controller (100) for regulating pressure and flow, and for generating warnings and alarms, said system comprising:

a. a plurality of pressure transducers (41,42,43) in the fluid circuit (30) for measuring pressure, said transducers being electrically connected to the controller (100);

b. a plurality of pumps (65, 72) connected to the fluid circuit (30) and electrically connected to the controller (100), said pumps capable of operating in an on and off duty cycle; and

c. an algorithm (108) in the controller (100) for commanding the pumps (65, 72) to produce the desired flow and pressure waveforms in the CSF.

3. The device of claim 2, further comprising an algorithm in the controller (100) for analyzing the feedback from the pressure sensors (41, 42, 3) and adjusting the pumps (65, 72) to produce the desired flow and pressure waveforms.

4. The device of claim 3, further comprising: an algorithm (108) in the controller (100) for synchronizing readings from the pressure transducers (41, 42, 42) with the pump states specified by the controller (100) in order to collect static and dynamic pressures in the fluid circuit.

5. The device of claim 4, further comprising: an algorithm (108) in the controller (100) which applies alarm conditions (97) to the steady state pressure conditions resulting from the pump duty cycles and to the transient pressure waveforms (92) that exist between the steady states.

6. The device of claim 5, further comprising:

a. an algorithm (108) in the controller (100) for analyzing the transient time constant of the pressure waveform induced by the on/off duty cycle of the pump (65, 72); and,

b. an indicating means (115) connected to the controller (100) for displaying the results of the analysis to indicate maintenance and system configuration conditions.

7. The device of claim 6, further comprising:

a. an algorithm (108) in the controller (100) for monitoring the total fluid flow based on pump activity; and,

b. an indicating means (115) connected to the controller for indicating the need for maintenance based on the total fluid flow.

8. The device as in claim 1 further comprising a pressure waveform generating unit (70), comprising:

a. a connection (78) to the fluid circuit (30);

b. a pump (72) in line with the connection (78) and electrically connected to the controller (100);

c. a reservoir (75) connected to the pump (72); and,

d. an algorithm (108) in the controller (100) which cycles the pump (72) in a manner to produce prescribed pressure waveforms in the fluid circuit (30) so as to promote mixing of the treated fluid at the points of re-introduction to the CSF space (14).

9. The device (10) as in claim 8 further comprising a means for dispensing medicament (80) based on compositional analysis results, comprising:

a. a means for performing compositional analysis (45) exposed to the fluid circuit (30) and connected to the controller (100);

b. a medicament dispenser (80) exposed to the fluid circuit (30) and connected to the controller (100);

c. an algorithm (108) in the controller (100) for analyzing the signal from the compositional analysis means (45) and for commanding the medicament

dispenser (80) to dispense dosages in response to the compositional analysis results; and,

d. an indicator (115) connected to the controller (100) for displaying the results of the compositional analysis and the dosage history.

10. The device (10) as in claim 9, further comprising a filter bank (50) for removing pathogens from the CSF.

11. A method of conditioning CSF in an extracorporeal circuit to treat maladies of the brain, said method comprising:

a. providing an extracorporeal CSF processing device (10);

b. attaching the device to the CSF drain and reintroduction points of a patient (16);

c. extracting the CSF from the central nervous system into the fluid circuit (30) of the device (10);

d. circulating the CSF through the circuit (30) by passive or active means;

e. monitoring the pressure of the CSF at multiple points (41, 42, 43) in the circuit (30);

f. generating pressure waveforms in the CSF of the circuit (30) to promote improved mixing of the CSF upon reintroduction to the subarachnoid space (14);

g. controlling the pumps (65, 72) of the device (10) to ensure the flow and pressure waveforms conform to that specified by the controller (100);

h. applying adaptive alarm limits (97) to the pressure waveforms to detect blockages and out of limit pumping conditions;

i. performing compositional analysis of the CSF and providing the results of said analysis to the controller (100);

j. removing targeted agents from the fluid;

k. introducing medicament to the CSF based on input from the controller (100) said input derived by analyzing the results of the compositional analysis;

l. re-introducing the treated CSF back into the subarachnoid space (14) at the point where the device (10) attaches to the patient (16); and,

m. modifying treatment and maintenance regimens based on system data.

12. A method as in claim 11 wherein the monitoring step further comprises:

a. measuring the transient time of pressure wave forms in the CSF when the pumps (65, 72) are toggled between on and off duty cycles;

b. comparing the recorded transient times with look-up values in the memory (105); and,

c. indicating that maintenance or configuration conditions exist.

13. A method as in claim 12, wherein the monitoring step further comprises:

a. cycling the circulation (65)and pressure waveform pumps (72) between the on and off state;

b. measuring the pressure in the circuit (30) while the pump is on and while it is off;

c. providing the pressure readings to the controller (100) for comparison to look-up values for intracranial and transmembrane pressure; and,

d. triggering alarms (90) when actual values exceed alarm limits.

13. A method as in claim 12, wherein the generating step further comprises:

a. collecting CSF in an extracorporeal reservoir (70); and,

b. reintroducing the CSF from the reservoir (70) into the circuit (30) under a pressure waveform created by a pump (72).

14. A method as in claim 13, wherein the applying step further comprises:

a. establishing an alarm condition that is offset from the monitored pressure by a given amount;

b. modifying the alarm condition (92) so that the offset from the monitored pressure remains constant even as the monitored pressure changes due to the cycling of the pump between states; and,

c. triggering an alarm warning when the pressure reading exceeds an alarm condition (92).

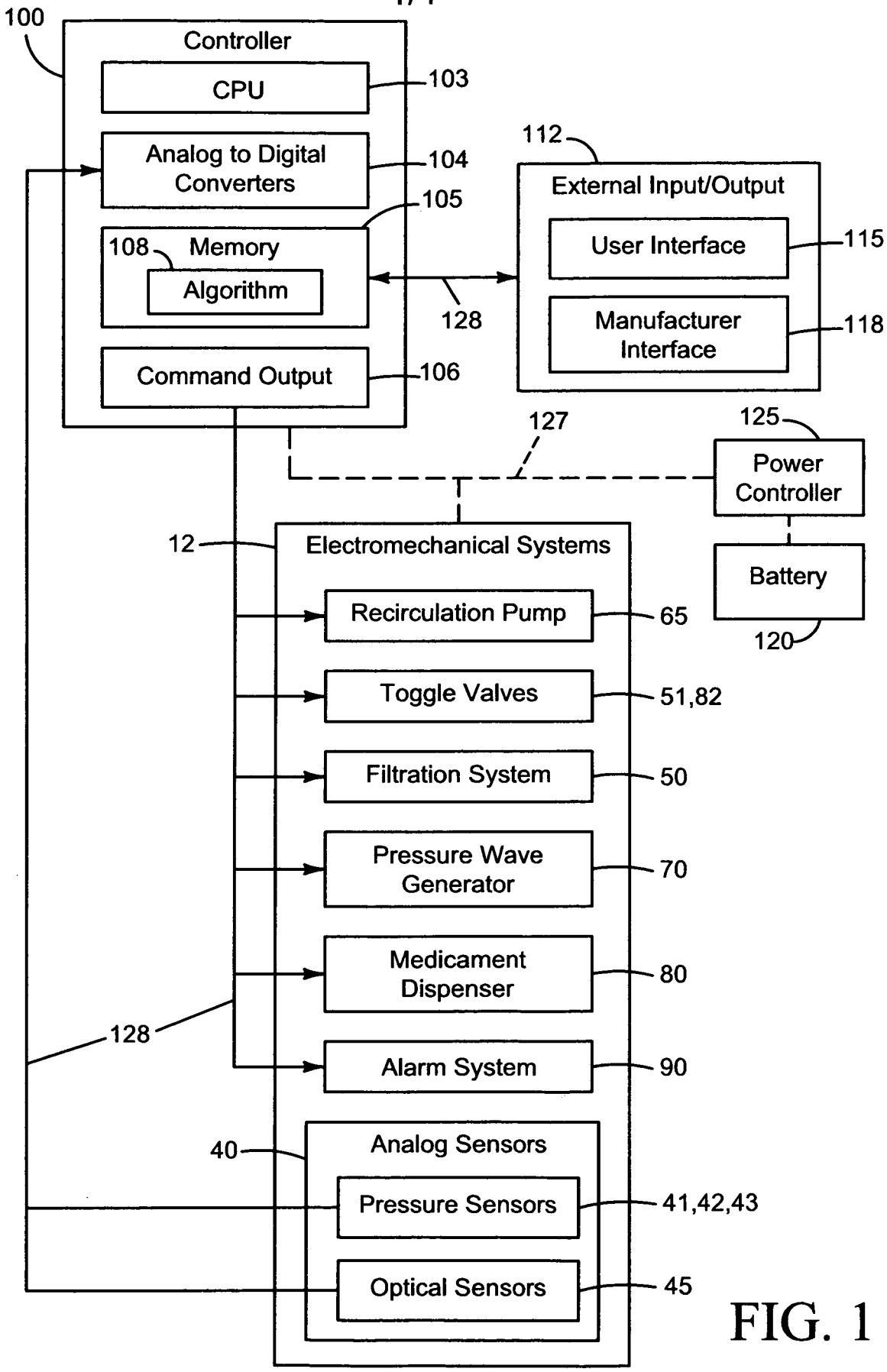
15. A method as in claim 14, wherein the modifying step further comprises:

a. measuring the decrease over time in pathogen concentration detected by the compositional analysis sensors;

b. projecting when pathogen concentration will reach target levels given current changes in concentration;

c. indicating remaining time before termination of treatment regimen; and,

d. terminating treatment when target pathogen concentration is attained.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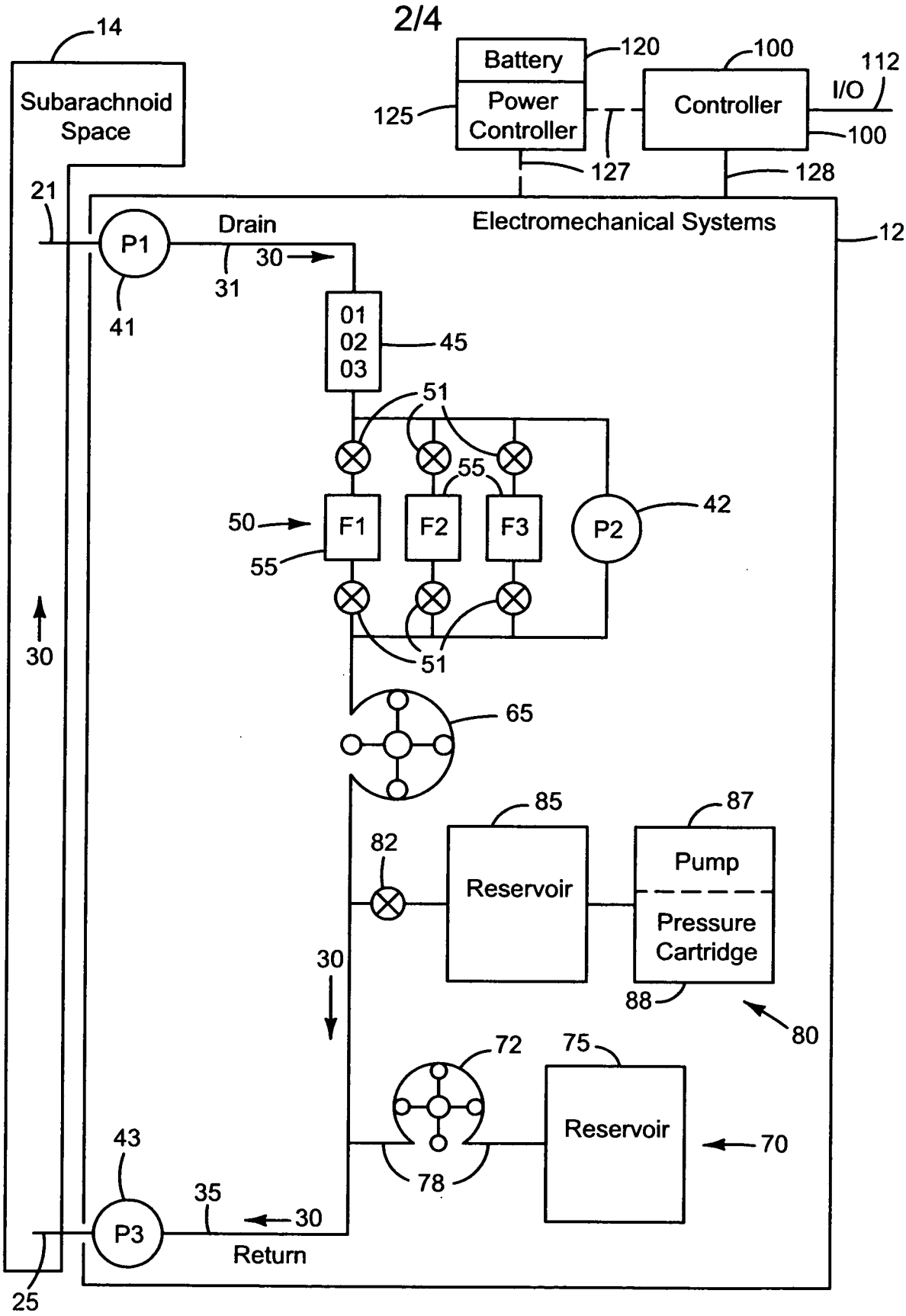
Controller
CPU
103
Analog to Digital Converters
104
105
108
Memory
Algorithm
128
Command Output
106
112
External Input/Output
User Interface
115
Manufacturer Interface
118
127
125
Power Controller
Battery
120
12
Electromechanical Systems
Recirculation Pump
65
Toggle Valves
51,82
Filtration System
50
Pressure Wave Generator
70
Medicament Dispenser
80
128
Alarm System
90
40
Analog Sensors
Pressure Sensors
41,42,43
Optical Sensors
45

FIG. 1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Subarachnoid Space
Battery
120
100
112
I/O
125
Power Controller
Controller
100
127
128
21
Drain
Electromechanical Systems
12
P1
30
31
41
01
02
03
45
51
55
50
F1
F2
F3
P2
42
55
30
51
65
85
87
82
Reservoir
Pump
Pressure Cartridge
30
88
80
72
75
Reservoir
70
43
35
30
78
P3
Return
25
10

FIG. 2

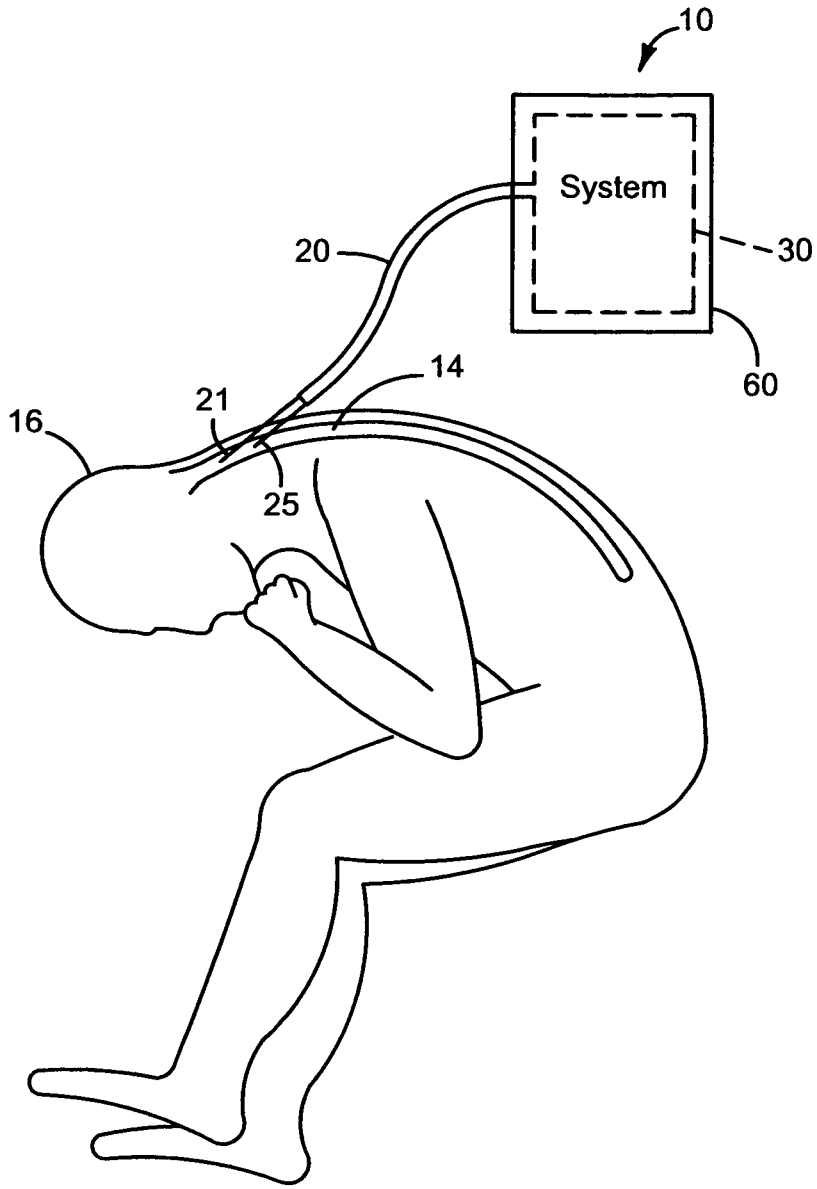

FIG. 3

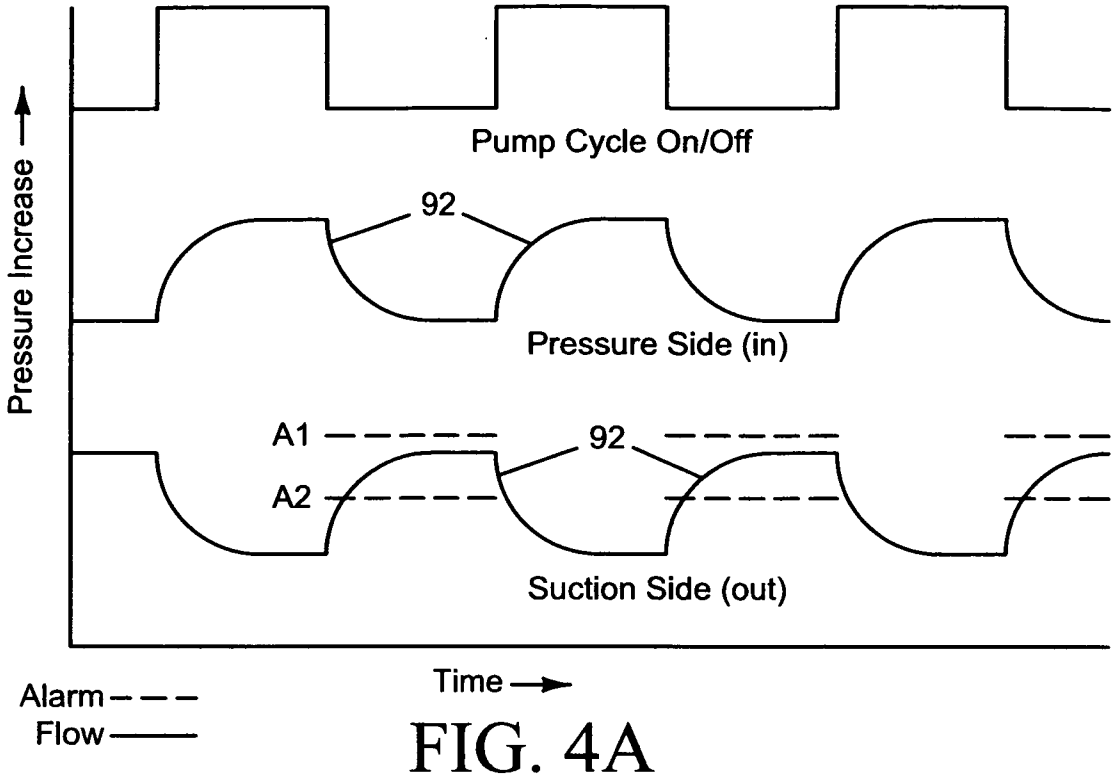
Pump Cycle On/Off
92
Pressure Side (in)
A1
92
A2
Suction Side (out)
Pressure Increase
Time
Alarm
Flow

FIG. 4A

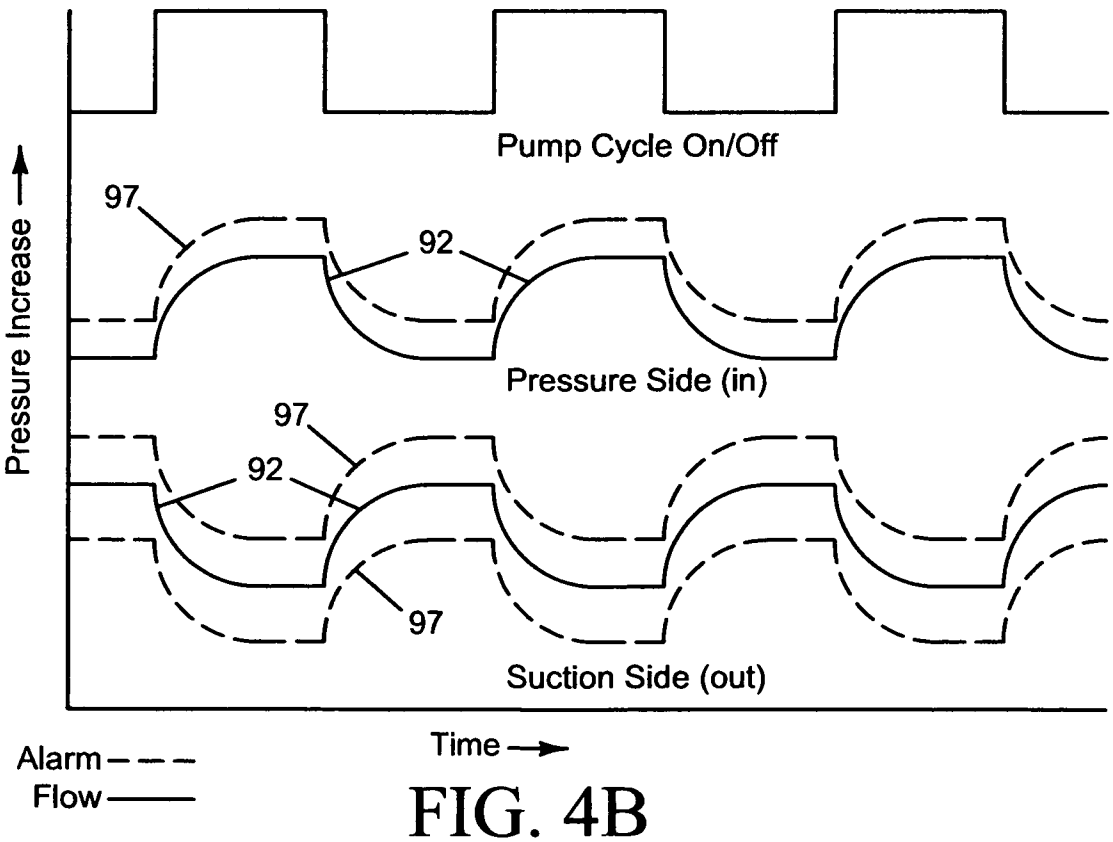
Pump Cycle On/Off
97
92
Pressure Side (in)
97
92
97
Suction Side (out)
Pressure Increase
Time
Alarm
Flow

FIG. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/01186

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 1/36 (2010.01)
USPC - 604/118
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61M 1/36 (2010.01)
USPC: 604/118

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): A61M 1/00, 5/00, 5/48 (2010.01)
USPC: 604/7, 8, 9, 19, 48, 65, 67, 93.01, 264, 317, 540, 541

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (DB=PGPB,USPT,USOC,EPAB,JPAB), Google Scholar: pressure, transducer, waveform, pump, filter, clean$4, fluid, pathogen, microb$, bacteria$, infect$, brain, condition$4, cerebrospinal, csf, composition, flow, static, dynamic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/105959 A2 (LAD et al.) 4 September 2008 (04.09.2008) para [0002], [0010]-[0014], [0082]-[0113] and [0136]	1-13a, 13b-15
Y	US 2004/0068221 A1 (SILVERBERG et al.) 8 April 2004 (08.04.2004) para [0048]-[0057]	1-13a, 13b-15
Y	US 2003/0032915 A1 (SAUL) 13 February 2003 (13.02.2003) para [0034]	2-7

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

* 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
9 June 2010 (09.06.2010)	21 JUN 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)