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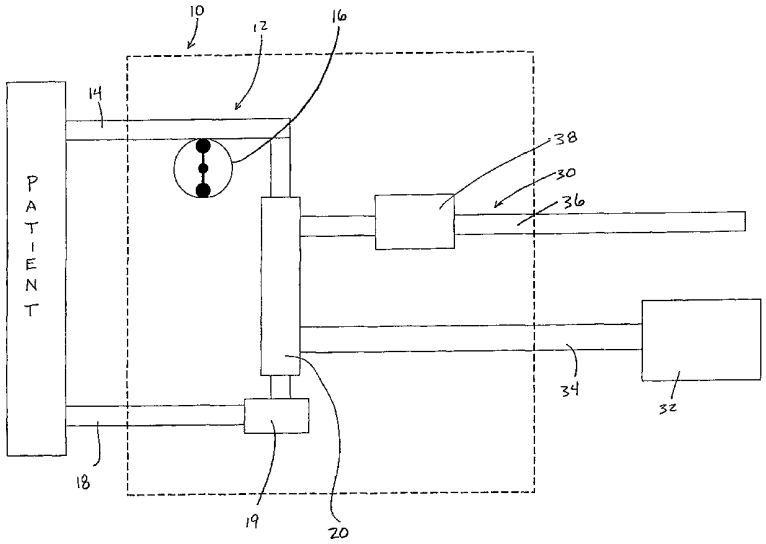
(54) Title: METHOD AND APPARATUS FOR TREATING RENAL DISEASE WITH HEMODIALYSIS UTILIZING PULSATILE PUMP



(57) Abstract: A method of removing toxins from blood from a patient in need of such toxin removal includes: providing a countercurrent dialysis filter (20) having a blood compartment and a dialysate compartment separated from the blood compartment by a semi-permeable membrane; conveying blood from the patient through the blood compartment of a countercurrent filter (20) an back to the patient; and drawing dialysate from a reservoir (32) through the dialysate compartment of the countercurrent filter (20). At least one of the blood or dialysate experiences pulsatile flow. The steps are carried out such that blood toxins are drawn from the blood compartment through the semi-permeable membrane into the dialysate compartment.

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METHOD AND APPARATUS FOR TREATING RENAL DISEASE WITH HEMODIALYSIS UTILIZING PULSATILE PUMP

FIELD OF THE INVENTION

The present invention is directed generally to treatment of renal disease, and more specifically to treatment of end stage renal disease (ESRD) with hemodialysis.

BACKGROUND OF THE INVENTION

Hemodialysis is a well-known treatment technique for ESRD, a condition in which the patient's renal system has essentially ceased to remove waste products and contaminants from the blood. Hemodialysis is a process that involves removing blood from the vasculature of a patient (usually a shunt or vein), purifying it with dialysate (a fluid that helps to remove toxins and return electrolytes to the blood), and returning the blood to the patient (usually through another vein).

Hemodialysis machines typically operate with separate compartments for blood and dialysate. In conventional systems, the compartments are separated by a semi-permeable membrane that allows selective diffusion; toxins are removed from the blood, and electrolytes are added to bring the electrolyte concentration of the blood to desired levels.

In many systems, the blood and dialysate compartments are arranged in a countercurrent flow exchange layout, with the blood traveling in one direction and the dialysate traveling in the opposite direction. One arrangement employs a large tube within which reside many smaller diameter tubules. Ordinarily, the large tube carries dialysate, and the smaller tubules carry blood. Blood is typically pumped through the

tubules with a positive pressure pump (exemplary is a roller head pump), and the dialysate is typically drawn through the large tube with a roller head pump.

There are some shortcomings with such an arrangement. The relatively constant flow of the blood and dialysate can create "dead" regions (where flow essentially stops) and regions of laminar flow within the tube. In each of these regions the component exchange between the blood and the dialysate can be adversely affected, as fluid in the dead regions and the regions of laminar flow tends to have less surface area contact with the membrane, thereby reducing the efficiency of exchange. Also, the constant flow of dialysate can create "shunting" of dialysate in certain regions, which can lead to blood/dialysate mismatch. As such, it would be desirable to provide a hemodialysis system with improved efficiency of exchange.

SUMMARY OF THE INVENTION

The present invention can address some of the shortcomings of prior systems by improving the efficiency of dialysis through the use of pulsatile flow. As a first aspect, the invention includes a method of removing toxins from blood from a patient in need of such toxin removal, comprising: providing a dialysis filter having a blood compartment and a dialysate compartment separated from the blood compartment by a semi-permeable membrane; conveying blood from the patient through the blood compartment of a filter and back to the patient; and drawing dialysate from a reservoir through the dialysate compartment of the countercurrent filter. At least one of the blood or dialysate experiences pulsatile flow. The steps are carried out such that blood toxins are drawn from the blood compartment through the semi-permeable membrane into the dialysate compartment.

As a second aspect, the invention includes an apparatus for performing hemodialysis on a subject in need of such treatment. The apparatus comprises: a dialysis filter having a blood compartment and a dialysate compartment separated from the blood compartment by a semi-permeable membrane; a first pump fluidly connected with the blood compartment that conveys blood from the patient through a blood compartment of a filter and back to the subject; and a second pump fluidly connected to the dialysate

compartment. At least one of the first and second pumps is configured to induce pulsatile flow.

It has been discovered that the use of pulsatile flow in the blood or dialysate circuits during hemodialysis can provide a number of advantages. These include increased efficiency of transport, reduction in dead regions, and intermittent increased transmembrane pressure.

Objects of the present invention will be appreciated by those of ordinary skill in the art from a reading of the figures and the detailed description of the preferred embodiments which follow, such description being merely illustrative of the present invention.

BRIEF DESCRIPTON OF THE FIGURES

The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate embodiments of the invention and, together with the description, serve to explain principles of the invention.

Figure 1 is a schematic diagram of a hemodialysis apparatus of the present invention.

Figure 2 is an enlarged schematic view of a hollow fiber artificial kidney (HFAK) included in the hemodialysis apparatus of **Figure 1**.

Figure 2A is a greatly enlarged schematic view of two blood tubules of the HFAK of **Figure 2**.

Figure 3 is a graph plotting urea concentration as a function of time in a two pool model of a dialysate.

Figure 4 is a graph plotting creatinine concentration as a function of time collected in a dialysis study on dogs.

Figure 5 is a graph plotting BUN concentration as a function of time collected in a dialysis study on a dog.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the

invention are shown and described. 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 so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like components throughout.

Referring now to **Figure 1**, a hemodialysis apparatus, designated broadly at **10**, is illustrated schematically. The hemodialysis apparatus **10** comprises a blood subsystem **12** and a dialysate subsystem **30**, each of which will be described in greater detail below.

The blood subsystem **12**, which as the name implies conveys blood through the hemodialysis apparatus **10**, includes a blood entry conduit **14** that leads from a patient's artery (usually in the wrist), a roller pump **16** fluidly connected with the blood entry conduit **14**, an HFAK **20** of conventional construction, and a blood exit conduit **18** leading from the HFAK **20** back to the patient's vein. A bubble trap **19** is located on the blood exit conduit **18** between the HFAK **20** and the vein of the patient to prevent bubbles created during the processing of the blood from entering the patient.

During operation, blood exits the patient through the blood entry conduit **14**. The roller pump **16** forces the blood to the HFAK **20**, wherein dialysis occurs as described below. The dialyzed blood then exits the HFAK **20** in the blood exit conduit **18**, passes through the bubble trap **19** and returns to the patient's body.

The dialysate subsystem **30**, which conveys dialysate into and from the HFAK **20**, includes a dialysate reservoir **32** that contains dialysate, a dialysate entry conduit **34** leading from the dialysate reservoir **32** to the HVAK **20**, a dialysate exit conduit **36** leading from the HFAK **20**, and an in-line pulsatile pump **38** located on the dialysate exit conduit **36**.

In operation, dialysate is pumped from the dialysate reservoir **32** through the dialysate entry conduit **34** and into the HFAK **20**, wherein countercurrent exchange of components of the blood and dialysate. The spent dialysate is then pumped via the pulsatile pump **38** back to the dialysate reservoir **32**.

An exemplary HVAK **20** is illustrated in **Figure 2**. The HVAK **20** includes a plurality of narrow blood tubules **22** that are enclosed within a dialysate casing **24**. As the

name implies, blood is conveyed through the blood entry conduit **14** into the blood tubules **22**, and dialysate is conveyed from the dialysate entry conduit **34** into the dialysate casing **24**. The blood tubules **22** are formed of a semi-permeable membrane material, such as polysulfone, that enables countercurrent exchange of components to occur between the blood and dialysate. The dialysate casing **24** is typically formed of an impervious material such as a plastic material.

The dialysate utilized in the dialysate subsystem **30** can be any dialysate known to those skilled in this art as being suitable for use in hemodialysis. An exemplary dialysate is available under the trade name Neutralyte from Fresenius Medical Care, Lexington, Massachusetts.

The use of the pulsatile pump **38** (which can be a piston pump, a modified roller head pump, or the like) in the dialysate subsystem **30** can have the effect of producing pulsatile flow of dialysate within the dialysate subsystem **30**. As used herein, "pulsatile flow" means flow that has a pulse pressure of 10 mm Hg or greater, and preferably when applied to blood means a pulse pressure of 30 mm Hg or greater. Preferably, the pulsatile flow is induced in the dialysate at a pulse rate of between about 30 and 100 cycles per minute, and more preferably at a rate of between about 50 and 80 cycles per minute. Those skilled in this art will recognize that the pulsatile pump may be used alone or in combination with a more constant flow pump.

Such pulsatile flow within the dialysate subsystem **30** can generate significant turbulence within the dialysate casing **24**, which can reduce or eliminate the number of "dead" regions, where flow stops and exchange is minimal. A typical flow pattern in blood tubules **22** and the blood casing **24** is shown in **Figure 2A** (darker areas represent regions of higher flow), with a dead region **25** being illustrated between two tubules **22**. Turbulence can increase the exchange efficiency between the blood and dialysate by increasing the amount of surface area contact between the dialysate and the blood tubules **22**. Also, the pulsation can produce bursts of increased transmembrane pressure, which additionally helps exchange. The increased energy introduced into the system can also enhance transport. Further, reduction of "dead" regions reduces the tendency of clotting, with secondary improvement in transport. As a result of these combined effects, the overall efficiency of hemodialysis (for example, increased clearance

of urea and creatinine) can be significantly increased over systems that lack a pulsatile dialysate flow.

It should also be noted that the pump **16** of the blood subsystem **12** may also be a pulsatile pump, with many of the advantages described above for the dialysate subsystem **30** also being achievable with pulsatile flow in the blood subsystem **12**. If a hemodialysis apparatus includes pulsatile pumps in both the blood and dialysate subsystems, the pulsatile pumps may be synchronous, such that they pump at the same rate and with matching amplitudes, or they may be dissynchronous, such that they pump at different rates and/or with mismatched amplitudes. Given that reduction of dead regions in the HFAK **20** can improve transport, it may be preferred to employ dissynchronous pulsatile pumps, as doing so may increase turbulence.

The invention and the advantages achievable therewith will now be described in greater detail in the following non-limiting examples.

EXAMPLE 1

In Vitro Analysis of Pulsatile Flow of Dialysate

In vitro dialysis experiments were conducted using a pair of pools filled with liquid and performing dialysis on these liquids. Experimental blood and dialysate circuits were created that each included a two-liter reservoir connected to a roller head pump (Sarns 7400 MDX, available from Sarns, Inc., Ann Arbor, Michigan). The roller head pump was connected to a dialysis filter, which was in turn connected to the two liter reservoir to form a closed loop. All connections were made with 3/8 inch plastic tubing.

For the control apparatus, the dialysis machine used was a Fresenius 2008H dialysis machine (available from Fresenius USA, Lexington, Massachusetts), which employs a relatively constant flow pump. The experimental system employed a Fresenius F7NR dialysis filter (available from Fresenius USA, Lexington, Massachusetts) and a Sarns roller head pump that operated at 50 cycles per minute and at a pulse pressure of 80 mm Hg.

For each system, the two liter reservoir was filled with a mixture of tap water and urea (2 liters water to 9.8-10 g of urea) to be used as experimental blood. This mixture had a measured level of 95-100 mg/dL urea. Tap water was used as the experimental dialysate. Experimental blood and dialysate were then allowed to flow through the system

at predetermined rates. Samples of fluid were drawn from the reservoir at 5 minute intervals for 35 minutes, and the urea level was measured with an Olympus AU640 instrument (available from Olympus Corp., Dallas, Texas).

The results of the procedures can be seen in **Tables 1** and **2** below and **Figure 3**.

Table 1 – Dialysate Flow –500cc/min
Pulsatile Experimental Blood Compartment Only

Blood Flow (cc/min)	Procedure	Urea Baseline	5 min	10 min	15 min	20 min
200						
	Control Dialysis	94	77 (18.1%)	53 (43.6%)	40 (57.4%)	28 (70.2%)
	Variable Speed Dialysis	97	65 (33%)	39 (59.8%)	23 (76.3%)	14 (85.6%)
	% Greater Efficiency		45	27	22	18
250						
	Control Dialysis	97	64 (34.0%)	42 (56.7%)	25 (74.2%)	15 (84.5%)
	Variable Speed Dialysis	95	57 (40.0%)	32 (66.3%)	18 (81.1%)	9 (6.6%)
	% Greater Efficiency		15	9.6	8.5	6.6
330						
	Control Dialysis	97	61 (37.0%)	33 (65.9%)	18 (81.4%)	10 (89.7%)
	Variable Speed Dialysis	94	56 (40.0%)	27 (71.3%)	14 (85.1%)	7 (92.6%)
	% Greater Efficiency		7.5	7.6	3.7	3.0
400						
	Control Dialysis	113	75 (33.6%)	53 (53.1%)	33 (70.8%)	20 (82.3%)
	Variable Speed Dialysis	114	55 (51.8%)	30 (73.7%)	14 (87.7%)	7 (93.9%)
	% Greater Efficiency		35.1	20.6	19.3	12.4

Table 2 – Dialysate Flow – 190cc/min Pulsatile Experimental Dialysate Compartment Only					
Blood Flow (cc/min)	Procedure	Urea Baseline	5 min	10 min	15 min
215					
	Control Dialysis	97	80 (17.5%)	62 (36.0%)	38 (60.8%)
	Variable Speed Dialysis	96	73 (23.9%)	54 (43.7%)	30 (68.8%)
	% Greater Efficiency		26.7	17.6	11.6

As can be seen from **Tables 1** and **2** and **Figure 3**, the efficiency of hemodialysis increases significantly (as much as 35 percent) with the employment of a variable speed pump for pumping blood or dialysate.

EXAMPLE 2

The experimental apparatus used in Example 1 was employed again to perform dialysis on a dog with the following changes. A HB 500 filter was employed with the Century System III dialysis machine (both available from Gambro Corp., Lakewood, Colorado). Also, rather than tap water, a standard 3K dialysate was used to hemodialyze the dog. Pulsatile flow was induced in the blood subsystem with a roller head pump operating at 50 cycles/minute. In addition, both blood urea nitrogen (BUN) and creatinine levels were measured (BUN was measured with a Olympus AU640 instrument and creatinine was measured by a Jaffe assay).

The results of the procedure are shown in **Tables 3** and **4** and **Figures 4** and **5**.

Table 3 – BUN Level				
Procedure	Baseline	60 min	120 min	Post 30 min
Control Dialysis	110	110 (0.0%)	80 (27.3%)	97
Variable Speed Dialysis	126	84 (33.3%)	69 (45.3%)	73
% Greater Efficiency			39.8%	

Table 4 – Creatinine Level				
Procedure	Baseline	60 min	120 min	Post 30 min
Control Dialysis	10.2	8.7 (14.7%)	7.3 (28.5%)	9.1
Variable Speed Dialysis	11.8	7.7 (34.7%)	6.3 (44.7%)	7.4
% Greater Efficiency		56.7%	36.3%	

These results again indicate that the variable speed dialysis procedure is significantly more efficient than the control apparatus.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

What is Claimed is:

1. A method of removing toxins from blood from a patient in need of such toxin removal, comprising:

providing a countercurrent dialysis filter having a blood compartment and a dialysate compartment separated from said blood compartment by a semi-permeable membrane;

conveying blood from the patient through the blood compartment of a filter an back to the patient; and

drawing dialysate from a reservoir through the dialysate compartment of the filter such that blood toxins are drawn from said blood compartment through the semi-permeable membrane into the dialysate compartment;

wherein at least one of the conveying and drawing steps is carried out with pulsatile flow.

2. The method defined in Claim 1, wherein said drawing step comprises drawing the dialysate through the dialysate compartment with a pulsatile pump.

3. The method defined in Claim 2, wherein said drawing step comprises drawing the dialysate through the dialysate compartment at a pulsatile pressure of greater than about 10 mm Hg.

4. The method defined in Claim 1, wherein said drawing step comprises drawing the dialysate through the dialysate compartment at between 30 and 100 pulses per minute.

5. The method defined in Claim 1, wherein said drawing step further comprises drawing the dialysate through the dialysate compartment with a roller head pump.

6. The method defined in Claim 1, wherein said conveying step comprises conveying blood from the patient through the blood compartment with a constant flow pump.

7. The method defined in Claim 1, wherein said providing step comprises providing a dialysis filter with a dialysate compartment comprising a dialysate casing and a blood compartment comprising a plurality of tubules that reside within the dialysate casing.

8. The method defined in Claim 1, wherein said conveying step comprises conveying blood with a pulsatile pump.

9. The method defined in Claim 1, wherein said conveying step comprises conveying the blood with a pulse pressure of greater than about 30 mm Hg.

10. An apparatus for performing hemodialysis on a subject in need of such treatment, comprising:

a dialysis filter having a blood compartment and a dialysate compartment separated from said blood compartment by a semi-permeable membrane;

a first pump fluidly connected with the blood compartment that conveys blood from the patient through a blood compartment of the filter and back to the subject; and

a second pump fluidly connected to the dialysate compartment;

wherein at least one of said first and second pumps is configured to induce pulsatile flow.

11. The apparatus defined in Claim 10, wherein said second pump comprises a pulsatile pump.

12. The apparatus defined in Claim 11, wherein said second pump is configured to induce a pulsatile pressure of greater than about 10 mm Hg in dialysate in the dialysate compartment.

13. The apparatus defined in Claim 10, wherein said dialysate compartment comprises a dialysate casing and said blood compartment comprises a plurality of blood tubules residing within said dialysate casing.

14. The apparatus defined in Claim 10, further comprising a third constant flow pump fluidly connected to said second pump.

15. The apparatus defined in Claim 10, wherein said second pump is configured to provide pulsatile flow at a rate of between about 30 and 100 cycles per minute.

16. The apparatus defined in Claim 10, wherein said first pump and said second pump are pulsatile pumps.

15. The apparatus defined in Claim 10, wherein the pulsatile pressure induced by said first or second pump is at least 30 mm Hg.

16. The apparatus defined in Claim 10, wherein the pulsatile pressure induced by said first pump is at least 30 mm Hg.

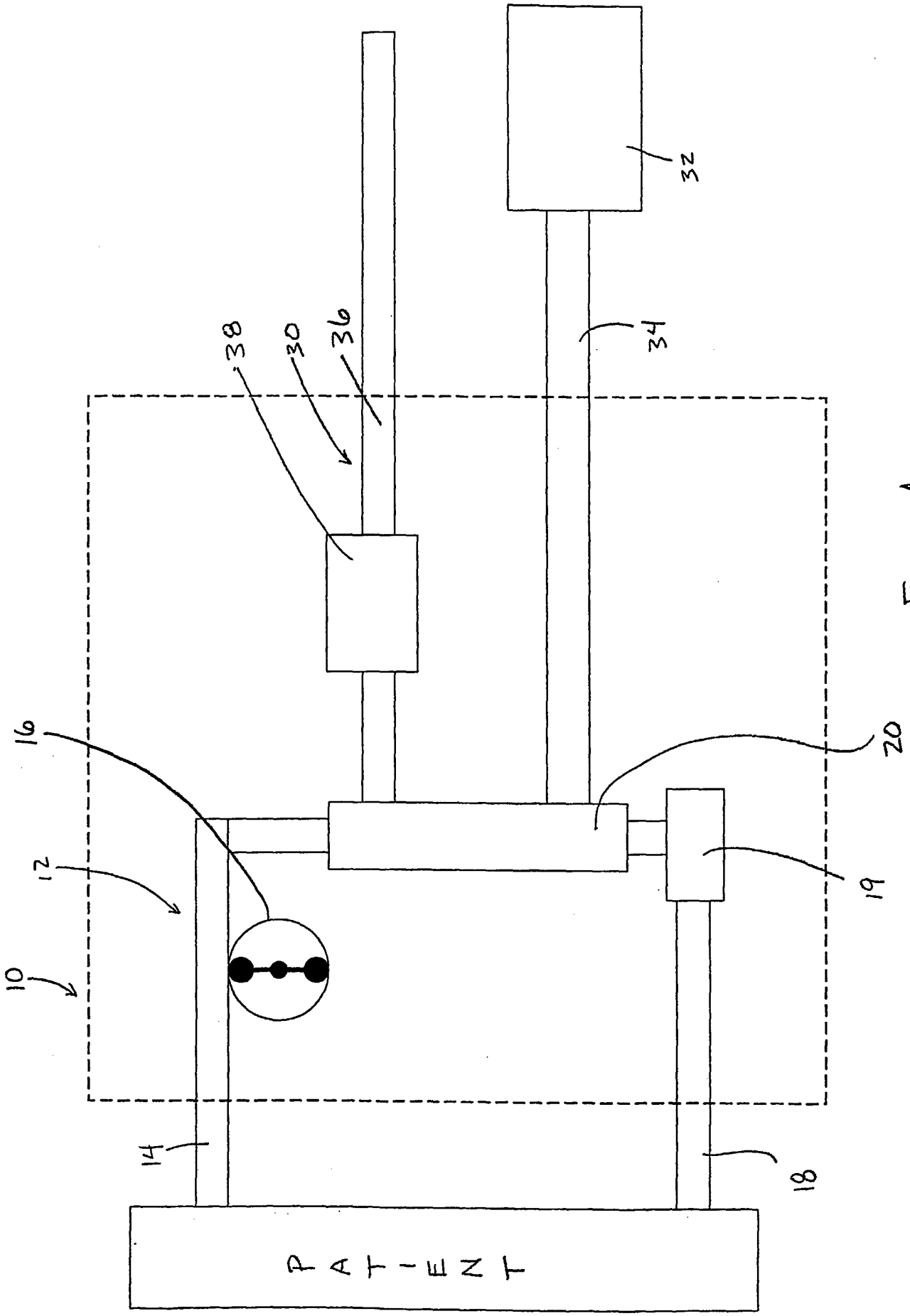

Figure 1

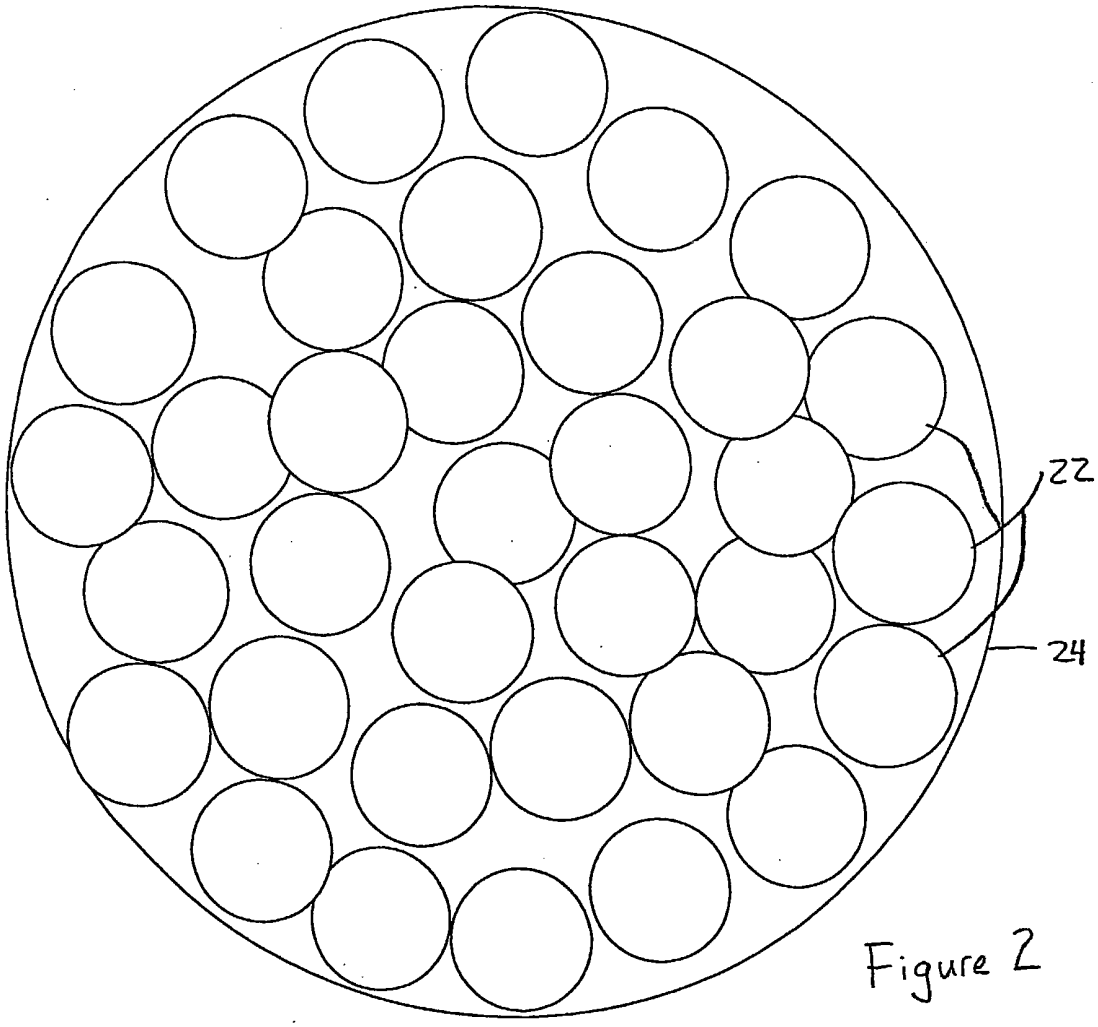

Figure 2

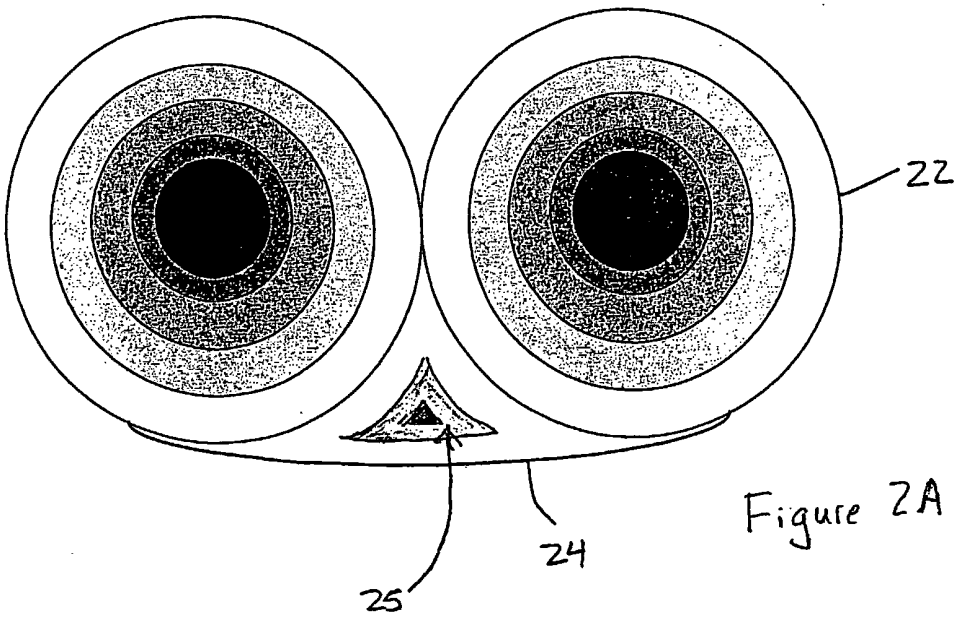

Figure 2A

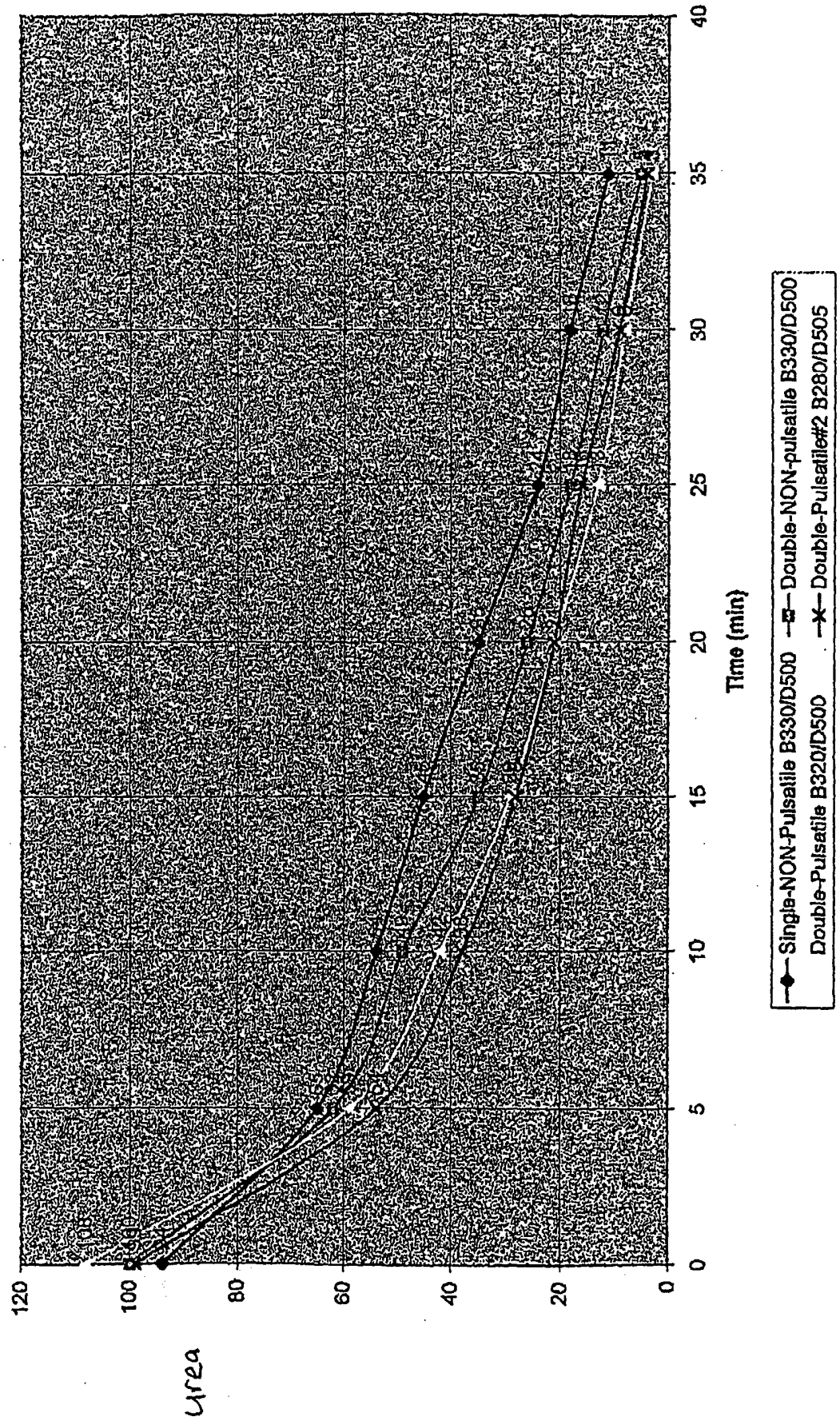
Pulsatile Blood/NON-Pulsatile Dialysate 2 Pool Model
Urea
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
Time (min)
Single-NON-Pulsatile B330/D500
Double-NON-pulsatile B330/D500
Double-Pulsatile B320/D500
Double-Pulsatile#2 B280/D505

Figure 3

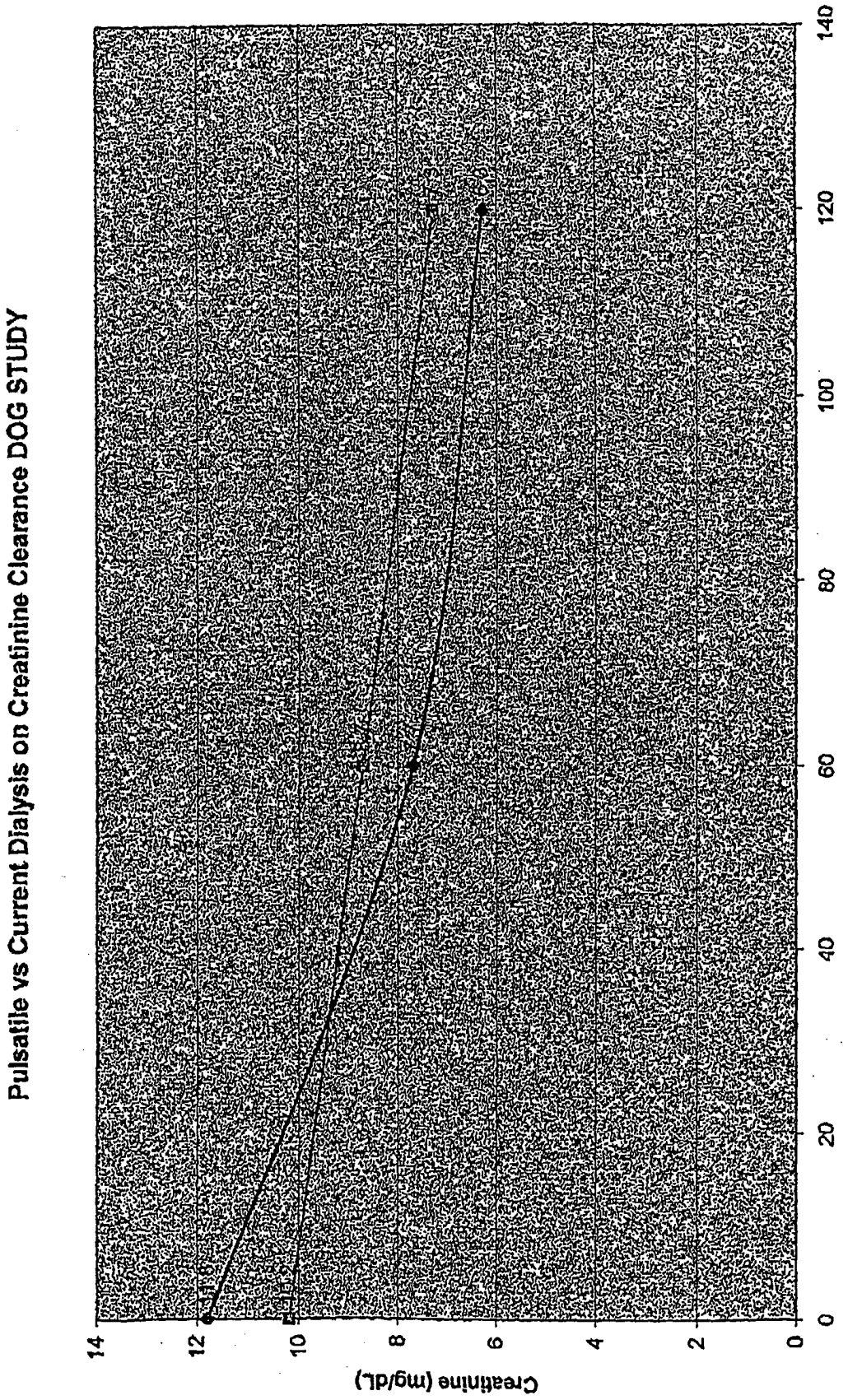
Pulsatile vs Current Dialysis on Creatinine Clearance DOG STUDY
Creatinine (mg/dL)
0
2
4
6
8
10
12
14
0
20
40
60
80
100
120
140
TIME (min)
Pulsatile
Current Dialysis

Figure 4

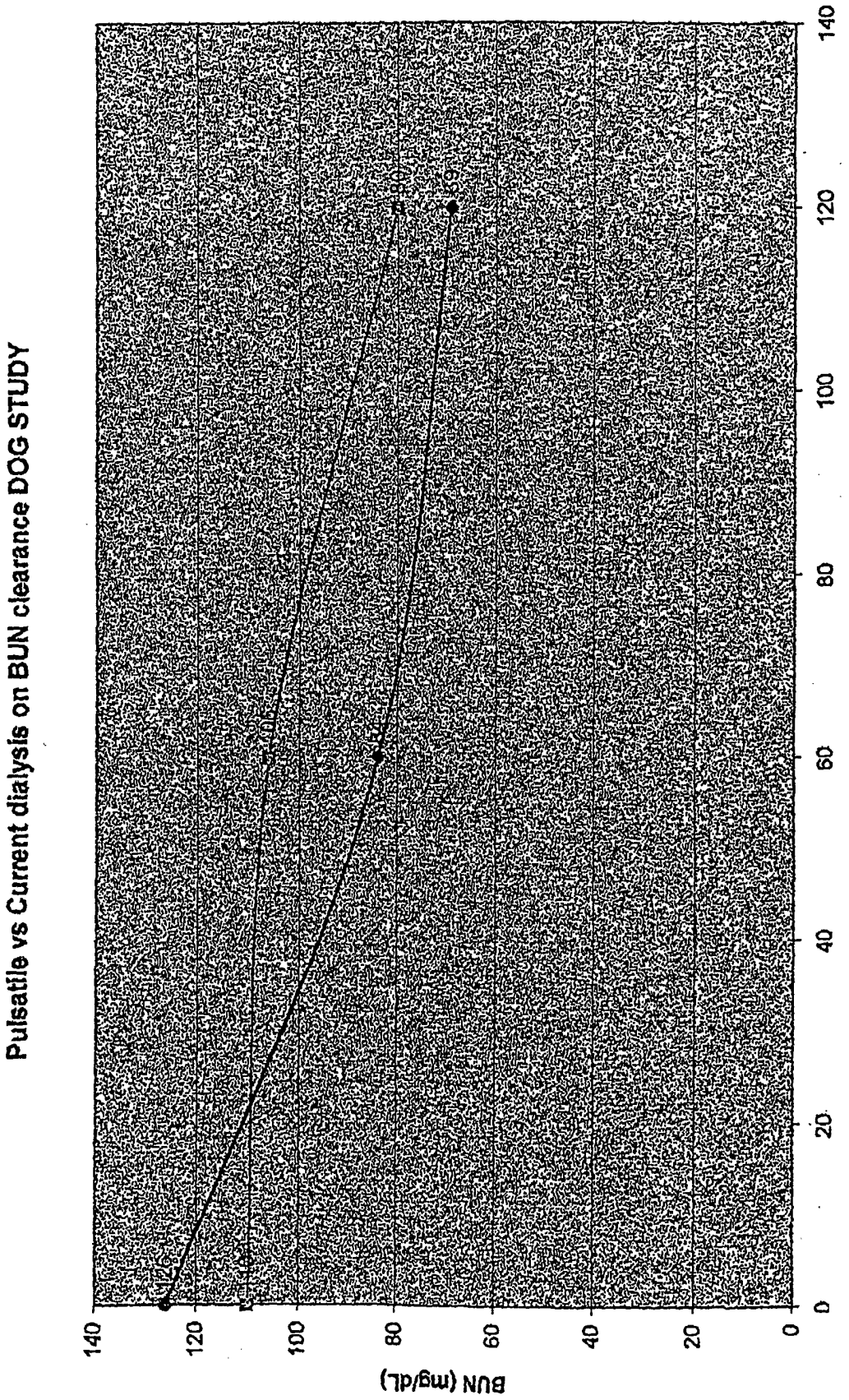
Pulsatile vs Current dialysis on BUN clearance DOG STUDY
BUN (mg/dL)
140
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
TIME (min)
Pulsatile
Current Dialysis

Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/03602

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B01D 61/24, 61/28
US CL :Please See Extra Sheet.
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)

U.S. : 210/321.6, 321.71, 321.72, 321.79, 321.8, 321.88, 321.89, 416.1, 645, 646, 650

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,083,777 A (HUTCHISSON) 11 April 1978, see abstract, figures 2-4; col. 3, line 34 - col. 5, line 57; col. 7, line 25 - col. 8, line 37; col. 9, line 66 - col. 11, line 12; col. 14, lines 6-65	10-13, 15-18 --- 1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 24 APRIL 2002	Date of mailing of the international search report 29 MAY 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DEBORAH THOMAS PATENT LEGAL SPECIALIST SUN UK KIM Telephone No. (703) 308-0661

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

210/321.6, 321.71, 321.72, 321.79, 321.8, 321.88, 321.89, 416.1, 645, 646, 650