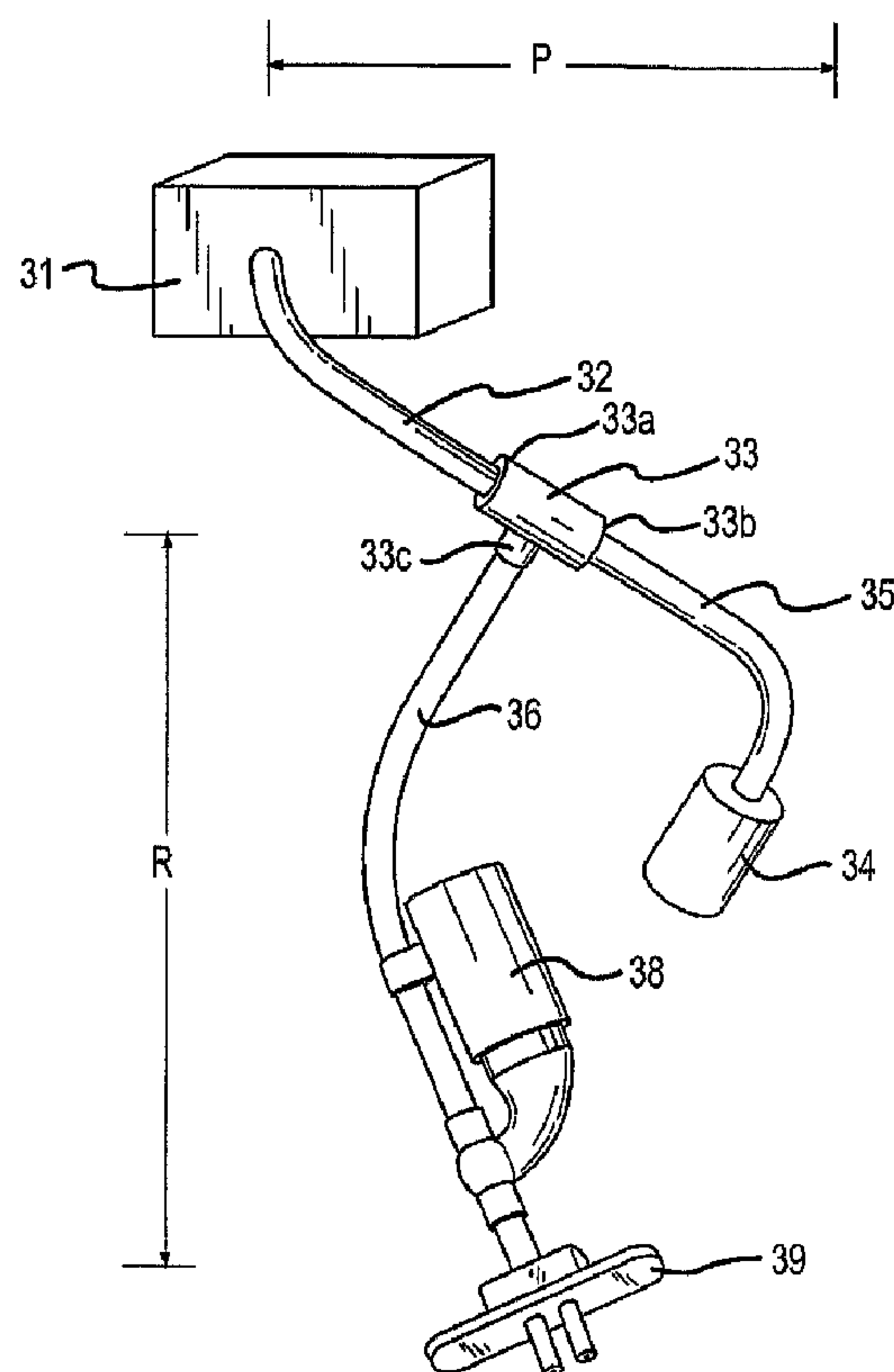




(86) Date de dépôt PCT/PCT Filing Date: 2005/04/20  
(87) Date publication PCT/PCT Publication Date: 2005/11/03  
(85) Entrée phase nationale/National Entry: 2006/09/27  
(86) N° demande PCT/PCT Application No.: US 2005/013488  
(87) N° publication PCT/PCT Publication No.: 2005/102431  
(30) Priorités/Priorities: 2004/04/20 (US10/828,765);  
2004/06/30 (US10/883,115); 2004/09/30 (US10/957,321);  
2005/03/14 (US11/080,279)

(51) Cl.Int./Int.Cl. **A61M 15/00** (2006.01),  
**A61M 16/00** (2006.01)  
(71) Demandeur/Applicant:  
AEROGEN, INC., US  
(72) Inventeurs/Inventors:  
FINK, JAMES, US;  
IVRI, YEHUDA, US  
(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : APPAREIL D'ADMINISTRATION EN AEROSOL, METHODES ET COMPOSITIONS POUR SYSTEMES DE  
RESPIRATION ASSISTEE EN PRESSION  
(54) Title: AEROSOL DELIVERY APPARATUS FOR PRESSURE ASSISTED BREATHING



(57) **Abrégé/Abstract:**

Improved pressure-assisted breathing systems are provided for the delivery of aerosolized medicaments. In addition, methods and compositions are provided for the treatment of respiratory diseases.



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

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
3 November 2005 (03.11.2005)

PCT

(10) International Publication Number  
**WO 2005/102431 A3**

## (51) International Patent Classification:

A61M 15/00 (2006.01) A61M 16/00 (2006.01)

## (21) International Application Number:

PCT/US2005/013488

(22) International Filing Date: 20 April 2005 (20.04.2005)

(25) Filing Language: English

(26) Publication Language: English

## (30) Priority Data:

|            |                                |    |
|------------|--------------------------------|----|
| 10/828,765 | 20 April 2004 (20.04.2004)     | US |
| 10/883,115 | 30 June 2004 (30.06.2004)      | US |
| 10/957,321 | 30 September 2004 (30.09.2004) | US |
| 11/080,279 | 14 March 2005 (14.03.2005)     | US |

(71) Applicant (for all designated States except US): **AERO-GEN, INC.** [US/US]; 2071 Stierlin Court, Mountain View, California 94043 (US).

## (72) Inventors; and

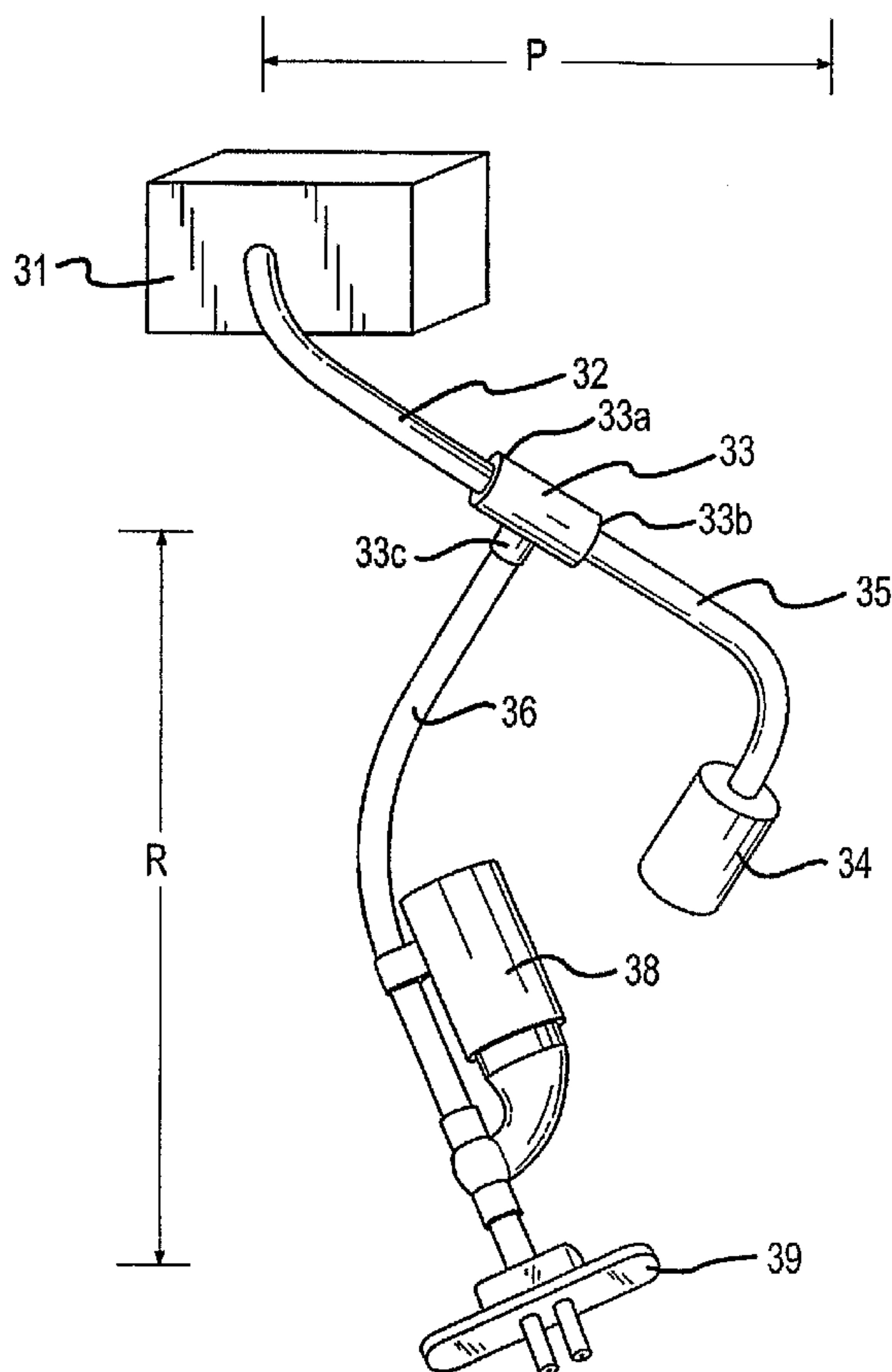
(75) Inventors/Applicants (for US only): **FINK, James** [US/US]; 1525 Seneca Lane, San Mateo, California 94402(US). **IVRI, Yehuda** [US/US]; 4 Tasman Sea, Newport Beach, California 92657 (US).(74) Agents: **GIBBY, Darin, J.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, California 94111-3834 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: AEROSOL DELIVERY APPARATUS FOR PRESSURE ASSISTED BREATHING



(57) Abstract: Improved pressure-assisted breathing systems are provided for the delivery of aerosolized medicaments. In addition, methods and compositions are provided for the treatment of respiratory diseases.

WO 2005/102431 A3

**WO 2005/102431 A3**



FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,  
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

**(88) Date of publication of the international search report:**  
22 June 2006

**Published:**

— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## AEROSOL DELIVERY APPARATUS, METHODS AND COMPOSITIONS FOR PRESSURE-ASSISTED BREATHING SYSTEMS

5

### BACKGROUND OF THE INVENTION

[0001] This invention relates to apparatus, methods and compositions for delivering medication to the respiratory system of a patient through a pressure-assisted breathing system. One aspect of the invention is directed to apparatus and methods for coupling an aerosol generator (preferably in a nebulizer) with a continuous positive airway pressure ("CPAP") system. Another aspect of the invention is directed to apparatus and methods for improving the delivery of an aerosolized medicament to a patient coupled to a pressure-assisted breathing system. Another aspect of the invention is directed to methods and compositions for treating respiratory diseases, particularly those diseases that are treated using lung surfactant replacement therapy.

[0002] The use of pressure-assisted breathing systems and therapies are conventional forms of ventilation treatment for respiratory disorders in adults and children. In particular, it has been reported that respiratory support with nasal CPAP ("nCPAP"), coupled with simultaneous treatment with nebulized drugs, preferably surfactants, has several advantages in the treatment of infant respiratory distress syndrome ("iRDS") in pre-term infants ("neonates"). For example, early application of nCPAP and early treatment with aerosolized surfactant in neonates with iRDS have been found to be effective in decreasing the need for mechanical ventilation, with its accompanying mechanical and infectious risks and pathophysiological effects. See, for example, "To the Editor: Surfactant Aerosol Treatment of Respiratory Distress Syndrome in Spontaneously Breathing Premature Infants"; *Pediatric Pulmonology* 24:22-224 (1997); "Early Use of Surfactant, NCPAP Improves Outcomes in Infant Respiratory Distress Syndrome"; *Pediatrics* 2004; 111:e560-e563 (as reported online by Medscape Medical News group, June 4, 2004); and "Nebulization of Drugs in a Nasal CPAP System"; *Acta Paediatr* 88: 89-92 (1999).

[0003] As used herein, the term "pressure-assisted breathing system" means any artificial ventilation system that applies continuous or intermittent pressure, usually positive (i.e. above

a certain baseline such as atmospheric pressure), to gas(es) in or about a patient's airway during inhalation as a means of augmenting movement of gas(es) into the lungs. Any pressure-assisted breathing system is contemplated as being useful in the present invention, and the term is intended to include, for example, standard CPAP, nCPAP and Bi-level CPAP systems as well as mechanical ventilators that perform the breathing function for the patient and/or provide CPAP to assist in spontaneous breathing by the patient. The term is also intended to include both invasive and non-invasive systems. Systems that utilize an endotracheal or tracheostomy tube are examples of invasive pressure-assisted breathing systems. Systems that utilize nasal prongs or a mask are examples of non-invasive pressure-assisted breathing systems.

[0004] Pressure-assisted breathing systems utilize positive pressure during inhalation to increase and maintain lung volumes and to decrease the work of breathing by a patient. The positive pressure effectively dilates the airway and prevents its collapse. The delivery of positive airway pressure may be accomplished through the use of a positive air flow source ("flow generator") that provides oxygen or a gas containing oxygen through a flexible tube connected to a patient interface device such as nasal prongs (cannula), nasopharyngeal tubes or prongs, an endotracheal tube, mask, etc. CPAP devices typically maintain and control continuous positive airway pressure by using a restrictive air outlet device, e.g. a fixed orifice or threshold resistor, or a pressure valve, which modulates the amount of gas leaving the circuit to which the patient interface device is attached. This pressure regulating device may be placed at, before or beyond the patient interface device and defines a primary pressure-generating circuit.

[0005] The tubes associated with commercially available pressure-assisted breathing systems create a "circuit" for gas flow by maintaining fluid communication between the elements of the circuit. Tubes may be made of a variety of materials, including but not limited to various plastics, metals and composites and can be rigid or flexible. Tubes can be attached to various elements of the circuit in a detachable mode or a fixed mode using a variety of connectors, adapters, junction devices, etc. These elements are sometimes collectively referred to herein as "junction devices".

[0006] As an example of one such junction device, a mechanical ventilator system may utilize a ventilator circuit comprising an inspiratory tube (sometimes referred to as a "inspiratory limb") that conducts a flow of gas from a ventilator and an expiratory tube (or

“limb”) that conducts a flow of gas back to the ventilator or to the atmosphere. This circuit (sometimes referred to herein as a “ventilator circuit”) is in fluid communication with a third tube (the “respiratory circuit”) that conducts a flow of gas to the patient interface device through a junction device, usually a tubular member in the shape of a “Y” or “T”. Such a junction device may comprise a first leg attachable to the inspiratory tube of the ventilator circuit, a second leg attachable to the expiratory tube of the ventilator circuit and a third leg attachable to the respiratory circuit. Other junction devices may be used, for example, to connect a nebulizer or a patient interface device to the appropriate circuit of the ventilator system.

10 [0007] During the course of conventional CPAP therapy, the patient may typically inhale only a fraction of the total flow of gas passing through the primary pressure-generating circuit. For example, it has been estimated that a CPAP gas flow of 8 L/min may typically result in a pharyngeal tube flow of about 2/L min. As a result, only 25% of aerosolized medicament introduced into the CPAP flow will enter the pharynx. In addition, from this 15 25% entering the pharynx, about two-thirds may be lost during expiration, assuming an inspiratory/expiratory ratio of 1:2. Thus, in conventional CPAP systems, only a small amount, e.g. 10%, of the nebulized drug may enter the patient interface device. This waste, particularly with extremely expensive surfactant medicaments, may make the cost of administering nebulized drugs through conventional CPAP systems unacceptably high for 20 routine clinical use. To reduce these costs, the prior art has identified the need for improvements in the method of delivery for aerosolized drugs, e.g. it has been suggested that a method and apparatus are needed for restricting nebulization to inspiration only.

[0008] Bi-level systems deliver continuous positive airway pressure but also have the capability to sense when an inspiratory and expiratory effort is being made by the patient. In response to those efforts, Bi-level systems deliver a higher level of inspiratory pressure 25 (IPAP) to keep the airway open and augment inspiratory volumes as a patient breathes in to reduce the work of inhalation, and deliver a lower expiratory pressure (EPAP) as the patient exhales to keep the airway and lungs open during exhalation. Thus, a Bi-level device employs pressure sensors and variable pressure control devices to deliver at least two levels 30 of air pressure that are set to coincide with the patient’s inspiratory and expiratory efforts. Bi-level has been found to be useful for a wider range of respiratory disorders than using CPAP alone, particularly in infants and small children.

[0009] An aerosol generator in a nebulizer has been used to deliver an aerosol of medication through a ventilation device into the respiratory system of a patient. For example, U.S. Pat. No. 6,615,824, issued September 9, 2003, and in co-pending U.S. Patent Application Ser. Nos. 10/465,023, filed June 18, 2003, and 10/284,068, filed October 30, 2002 describe apparatus and methods for connecting a nebulizer to a ventilator circuit to emit an aerosolized medicament directly into the flow of gas being delivered to a patient's respiratory system.

[0010] It is imperative that a therapeutically effective amount of aerosolized medicament reach the desired sites in the patient's lungs to achieve a successful treatment, yet it is also desirable that the medicament be delivered in as efficient a manner as possible to minimize losses and waste. Although effective amounts of medicament delivered to a patient's airways in aerosol form, e.g. by the using a nebulizer connected to a ventilator system, are considerably less than the amounts needed to deliver a therapeutically effective amount of medicament systemically, current systems still exhibit inefficiencies. For example, aerosol particles being carried in the circuits of ventilator systems and other pressure-assisted breathing systems may be trapped on the inner walls of the tubes, deposited at irregular surfaces and obstructions in the tubes or other elements in the circuits, impact the interconnection between tubes of different diameters, or be diverted by sharply angled paths in the circuits. As one specific example, aerosol particles have to "turn corners" when traveling at relatively high flow rates through the sharply angled conduits presented by the "Y", "T", and "V"- shaped junction devices currently used in conventional pressure-assisted breathing system circuits. As a result, the aerosol particles may impact the walls of the junction device, and a portion of the particles may be diverted from the primary aerosol flow into various ports or branches in the circuits. As another example, aerosol particles may be deposited at the junction of a patient interface device and the respiratory tube connecting it to the ventilator circuit, or may be diverted or deposited within the patient interface device itself.

[0011] An important feature in all mammalian lungs is the presence of surface active lining material in the alveoli. These surface active materials are lung surfactants comprised of protein-lipid compositions, e.g. surface active proteins and phospholipids, which are produced naturally in the lungs and are essential to the lungs' ability to absorb oxygen. They facilitate respiration by continually modifying surface tension of the fluid normally present within the air sacs, or alveoli, that line the inside of the lungs. In the absence of sufficient

lung surfactant or when lung surfactant functionality is compromised, these air sacs tend to collapse, and, as a result, the lungs do not absorb sufficient oxygen.

[0012] Insufficient or dysfunctional surfactant in the lungs results in a variety of respiratory illnesses in both infants and adults. For example, insufficient lung surfactant may manifest itself as iRDS in premature infants, i.e. those born prior to 32 weeks of gestation, who have not fully developed a sufficient amount of natural lung surfactant. Diseases involving dysfunctional lung surfactant may include adult respiratory disorders such as acute respiratory distress syndrome (ARDS), asthma, pneumonia, acute lung injury (ALI), etc., as well as infant diseases such as meconium aspiration syndrome (MAS), wherein full-term babies have their first bowel movement in the womb and aspirate the meconium into their lungs. In these cases, the amount of lung surfactant may be normal, but surfactant properties have been disrupted by foreign matter, trauma, sepsis and other infection, etc.

[0013] Diseases involving surfactant deficiency and dysfunction have historically been treated by the administration of surface active materials to the lungs, sometimes referred to as surfactant (replacement) therapy. For example, surfactant therapy is at present an established part of routine clinical management of newborn infants with iRDS. Usually these surface active materials are naturally-occurring or synthetically engineered lung surfactants, but may also be nonphospholipid substances such as perfluorocarbons. As used herein, the terms "lung surfactant" and "surfactant" contemplate all of these surface active materials suitable for use in surfactant therapy. These lung surfactants can be administered in a variety of ways, the simplest being direct instillation of a liquid solution of lung surfactant into the lungs. An initial dose of about 100 mg/kg body weight (BW) is usually needed to compensate for the deficiency of lung surfactant in these babies, and repeated treatment is required in many cases.

[0014] An alternative approach is treatment with aerosolized lung surfactant. Aerosol delivery of surfactant to the lungs is usually less efficient than direct instillation, mainly because of large losses of aerosol in the delivery system. In conventional delivery systems, the amount of aerosol reaching the lungs can be further reduced if particle sizes are too large, i.e.  $> 5 \mu\text{m}$  mass median aerodynamic diameter (MMAD), if aerosol delivery is not coordinated with slow inspiration and breath-hold, or if airways (especially artificial airways) are long and narrow. Estimates of lung delivery of aerosolized surfactants with most

conventional delivery systems have been generally less than 1-10% of amount the liquid surfactant placed in the nebulizer.

[0015] However, animal work with improved aerosol delivery systems has shown some promise of increased efficiency. The gas exchange and mechanical benefits that have been seen in animal lung models with the aerosol approach were comparable to those seen with the instillation technique, but those benefits were achieved with only a fraction of the conventional 100 mg/kg of body weight (BW) instilled dose (MacIntyre, N.R., "Aerosolized Medications for Altering Lung Surface Active Properties". *Respir Care* 2000;45(3) 676-683). As an example of improved aerosol delivery methods in the prior art, increased deposition of aerosolized surfactant has been achieved in animal models using ultrasonic nebulizers instead of jet nebulizers. Lung surfactant deposition of only 0.15 – 1.6 mg/kg BW/ hour has been reported using jet nebulization, whereas deposition of about 10 mg/kg BW/hour (7-9 mg/kg BW with 50 minute nebulization) has been achieved with ultrasonic nebulization. See, for example, Schermuly R et al; "Ultrasonic Nebulization for Efficient Delivery of Surfactant in a Model of Acute Lung Injury – Impact on Gas Exchange." *Am. J. Respir. Crit. Care Med.*; 1997 156 (2) 445-453.

[0016] It has been reported that respiratory support with nCPAP systems, coupled with early instillation of lung surfactants, may have several advantages in the treatment of neonates with iRDS. This treatment has been found to be effective in decreasing the need for mechanical ventilation, with its accompanying mechanical and infectious risks and pathophysiological effects, but still requires intubation for surfactant treatment. See, for example, "Early Use of Surfactant, NCPAP Improves Outcomes in Infant Respiratory Distress Syndrome"; *supra*.

[0017] Opportunities for aerosol delivery of lung surfactants to infants weighing less than 5 kg. have been limited, largely due to the low minute volumes required and the relatively high flow rates of nebulizers and ventilatory support devices that have been available. It has been demonstrated that pre-term infants, both on and off the ventilator, received less than 1% of the nebulizer dose to their lungs. See "Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia". *Pediatr. Pulmonol.* 1996 May;21; (5):301-9. There has been little empirical data to suggest that nCPAP would be any more efficient since most animal and in vitro CPAP models have demonstrated less than 3% deposition.

[0018] Simultaneous administration of surfactant aerosol therapy (using a jet nebulizer) in conjunction with a CPAP system has been found to be clinically feasible and to result in improved respiratory parameters. See, for example, Jorch G et al; "To the Editor: Surfactant Aerosol Treatment of Respiratory Distress Syndrome in Spontaneously Breathing  
5 Premature Infants"; *Pediatric Pulmonology* 24:22-224 (1997); and Smedsaas-Lofvenberg A; "Nebulization of Drugs in a Nasal CPAP System"; *Acta Paediatr* 88: 89-92 (1999).

However, the losses of aerosolized lung surfactant and other aerosolized medicaments used in CPAP systems were found to be unacceptably high, mainly because of the continued inefficiency of the delivery system. The authors suggest that as much as 10% of the  
10 nebulized surfactant might be expected to enter the pharyngeal tube coupled to the patient's respiratory system, but they did no testing to quantify that delivery estimate. (Jorch G et al, *supra*).

[0019] A number of studies have tried to combine aerosolized surfactant with high-frequency ventilation of the infant with iRDS, and aerosolized surfactants have also been  
15 tried in the treatment of airway diseases, e.g. cystic fibrosis and chronic bronchitis, both with mixed success, again because of the inefficiency of the delivery systems used. (McIntyre, *supra*).

[0020] Accordingly, it is desirable to find ways to improve the delivery, and decrease the losses, of aerosol particles within pressure-assisted breathing systems. In particular,  
20 increasing the efficiency in the delivery of aerosolized medicaments and the resulting smaller amounts of medicament required for treatment, can represent a substantial advantage in surfactant replacement therapy, wherein scarce and expensive lung surfactants are employed.

#### BRIEF SUMMARY OF THE INVENTION

[0021] In one embodiment, the present invention provides a pressure-assisted  
25 breathing system comprising a pressure-generating circuit for maintaining a positive pressure within the system, a patient interface device, and a respiratory circuit for providing gas communication between the pressure-generating circuit and the patient interface device, wherein a nebulizer is coupled to the respiratory circuit rather than to the pressure-generating  
30 circuit. The pressure-generating circuit may comprise a conduit that couples a flow generator that produces a high volume flow of gas through the conduit with a pressure-regulating device that maintains the CPAP. The respiratory circuit may provide a lower-volume

positive pressure air flow from the pressure generating-circuit to the patient interface device for inhalation by the patient. The respiratory circuit may comprise a conduit connected at one end to the pressure-generating circuit and at the other end to the patient interface device.

[0022] The nebulizer is coupled to the respiratory circuit and is adapted to emit an aerosolized medicament directly into the portion of the total gas flow that is inhaled by the patient, preferably in the direct vicinity of the patient's nose, mouth or artificial airway, thereby eliminating the dilution effect caused by introducing the aerosolized medicament into the high-volume gas flow of the pressure-generating circuit. Nebulizers suitable for the practice of the present invention preferably comprise a reservoir for holding a liquid medicament to be delivered to a patient's respiratory system, a vibrating aperture-type aerosol generator for aerosolizing the liquid medicament and a connector for connecting nebulizer to the respiratory circuit. Particularly preferred nebulizers of the invention are small and light-weight. Such "miniature" nebulizers may have a small reservoir that holds one unit dose of medicament and a light-weight aerosol generator, e.g. on the order of about 1 gm in weight. In addition, preferred nebulizers are quiet in operation, e.g. producing less than 5 decibels of sound pressure, so that they can conveniently be placed very close to the patient's airway.

[0023] The present invention also provides a method of respiratory therapy comprising the steps of providing a pressure-assisted breathing system having a pressure-generating circuit for providing positive airway pressure and a respiratory circuit coupled to the pressure-generating circuit for providing a flow of gas to a patient's respiratory system, and introducing an aerosolized medicament only into the flow of gas in the respiratory circuit. The present invention also provides a method of delivering a surfactant medicament to a patient's respiratory system.

[0024] In one embodiment of the invention, the efficiency of delivery of aerosolized medicaments can be significantly increased by eliminating the sharp angles or corners encountered by the flow of aerosol particles in the circuits of pressure-assisted breathing systems. Specifically, the present invention provides apparatus and methods that increase the efficiency of the delivery of aerosolized medicament to the patient by providing a straight or gently angled path for the flow of aerosol particles from the point at which the aerosol generator introduces aerosol particles into the gas flow to the point at which the aerosol particles enter the patient's respiratory system.

[0025] In a preferred embodiment, the present invention provides a pressure-assisted breathing system comprising a flow generator, a circuit connecting the flow generator to a patient's respiratory system and an aerosol generator for emitting aerosol particles of medicament into the circuit, wherein the circuit defines a path for said aerosol particles having a change in angle no greater than  $15^{\circ}$ , preferably no greater than  $12^{\circ}$ , and most preferably no change in angle at all.

[0026] In another embodiment, the present invention provides a junction device for connecting the various flexible tubes comprising the circuits of a pressure-assisted breathing system. For example, the present invention provides a junction device comprising (i) a tubular main body member having a straight longitudinal lumen extending its entire length for conducting a first flow of gas carrying aerosol particles; and (ii) a tubular branch member in fluid communication with the longitudinal lumen for conducting a second flow of gas substantially free of said aerosol particles into or out of the longitudinal lumen. The junction device may further comprise: (iii) a port for attaching an aerosol generator to the main body member so as to introduce the aerosol particles into the first flow of gas. Preferably a vibrating aperture-type aerosol generator is positioned in the port so that the vibrating plate is flush with the internal surface ("wall") of the longitudinal lumen so that the emitted aerosol particles will not drag against the walls of the lumen. The invention also provides a ventilator system employing such junction device. Still another embodiment provides improved nasal prongs (cannula) for delivering aerosolized medicament to a patient.

[0027] In another embodiment, the present invention provides a ventilator system comprising a ventilator circuit and a patient interface device attached to the ventilator circuit, wherein a nebulizer is positioned between the patient interface device and the ventilator circuit. In still another embodiment, a second nebulizer is positioned in the ventilator circuit on a junction device of the present invention.

[0028] In one embodiment, the present invention provides a method of delivering aerosolized medicament to a subject's respiratory system comprising the steps of attaching the subject to pressure-assisted breathing system comprising a gas flow generator, a circuit connecting the gas flow generator to the subject's respiratory system and an aerosol generator for emitting aerosol particles of medicament into the circuit, the circuit defining a path for said aerosol particles having a change angle no greater than  $15^{\circ}$ ; preferably no greater than

12°, and most preferably no change in angle at all, and then administering the aerosol particles of medicament to the subject via the pressure-assisted breathing system.

[0029] In other embodiments, the present invention provides a pressure-assisted breathing system, e.g. a CPAP system, comprising a pressure-generating circuit for  
5 maintaining a positive pressure within the system, a patient interface device coupled to a patient's respiratory system, a respiratory circuit for providing gas communication between the pressure-generating circuit and the patient interface device, means for introducing aerosol particles, e.g. an aerosolized medicament, into the gas flow in the respiratory circuit and means for discontinuing the introduction of aerosol particles into the respiratory circuit when  
10 the patient exhales. The means for discontinuing the introduction of aerosol particles may comprise a flow sensor disposed in an auxiliary circuit in fluid communication with the respiratory circuit and electronically coupled with the means for introducing the aerosol particles into the respiratory circuit flow. A small portion of the gas flow in the respiratory circuit is diverted through the flow sensor by the auxiliary circuit. Preferably, the flow rate in  
15 the auxiliary circuit is adjusted to be commensurate with the middle of the flow rate range detected by the flow sensor. Preferred flow sensors are adapted to detect small changes in the volumetric flow rate of gas in the auxiliary circuit and send a corresponding electronic signal to the means for introducing aerosol particles into the respiratory circuit.

[0030] In one embodiment of the invention, the means for introducing aerosol  
20 particles comprises a nebulizer, most preferably, a nebulizer having a reservoir for holding a liquid medicament to be delivered to the patient's respiratory system, a vibrating aperture-type aerosol generator for aerosolizing the liquid medicament and a connector for connecting the nebulizer to the respiratory circuit so as to entrain the aerosolized medicament from the aerosol generator into the gas flowing through the respiratory circuit. As previously  
25 mentioned, the nebulizer is preferably electronically coupled to the flow sensor through the electronic circuitry of the CPAP system.

[0031] As with conventional CPAP operation, a constant flow of gas is maintained in the respiratory circuit by the CPAP system of the present invention during inhalation by the patient (hereinafter referred to as "inspiratory flow"). In the practice of the present invention,  
30 a flow corresponding to the inspiratory flow, but at a lesser flow rate, is diverted to the auxiliary circuit. An adjustable valve, e.g. an orifice valve, is preferably provided in the auxiliary circuit to regulate the flow of gas through the flow sensor. This valve may be used

to reduce the flow of gas in the respiratory circuit to a range that can be measured by the flow sensor, and preferably in the middle of this range. Particularly preferred flow sensors have a flow range of from 0 to 1 liter/minute ("L/min").

[0032] When the patient exhales, the flow of gas in the respiratory circuit (and correspondingly in the auxiliary circuit) increases as a result of the additional flow of gas generated by the patient's lungs (hereinafter referred to as "expiratory flow"). In a preferred embodiment, the flow sensor detects the change in the flow rate of gas in the auxiliary circuit corresponding to the expiratory flow in the respiratory circuit, and sends an electronic signal to turn off the aerosol generator of the nebulizer. When the expiratory flow ceases, the flow sensor detects the decrease in flow rate in the auxiliary circuit and discontinues the electronic signal to the nebulizer. As a result, the nebulizer turns on and resumes the introduction of aerosol particles into the respiratory circuit. In this way, the system of the present invention stops the delivery of aerosol particles during exhalation by the patient so that aerosol particles are introduced into the respiratory circuit only when the patient inhales.

[0033] A disposable filter is preferably positioned in the auxiliary circuit up-stream to the flow sensor. Since a portion of the expiratory flow is diverted into the auxiliary circuit, bacterial, viral or other contaminants emanating from the diseased patient's respiratory system may be present in the auxiliary circuit flow. The filter removes these contaminants before the air flow passes through the flow sensor and is preferably replaced with every new patient using the apparatus. This feature allows the flow sensor to be permanently connected to the electronic circuitry of the CPAP system and remain in place without contamination when the apparatus is used by different patients.

[0034] The present invention also provides a method of respiratory therapy wherein an aerosolized medicament is introduced into a pressure-assisted breathing system only when the patient inhales. In another embodiment, the invention provides a method of delivering an aerosol to a patient's respiratory system which comprises the steps of: (a) providing a pressure-assisted breathing system having a respiratory circuit wherein a constant inspiratory flow is provided to a patient during inhalation and an additional expiratory flow is generated by the patient during exhalation, (b) providing an auxiliary circuit to divert a portion of the total flow in the respiratory circuit to a flow sensor; (c) measuring the flow rate in the auxiliary circuit with the flow sensor when the total flow in the respiratory circuit comprises only the inspiratory flow, thereby producing a first electronic signal; (d) measuring the flow

rate in the auxiliary circuit with the flow sensor when the total flow in the respiratory circuit comprises the sum of the inspiratory flow and the expiratory flow, thereby producing a second electronic signal; (e) providing a nebulizer electronically coupled to the flow sensor and adapted to introduce aerosol particles of medicament into the respiratory circuit when the first electronic signal is detected, and to stop the introduction of aerosol particles of medicament into the respiratory circuit when the second electronic signal is detected.

[0035] The present invention also provides an improved method of treating a disease involving surfactant deficiency or dysfunction in a patient's lungs. In one embodiment, the method of the present invention comprises the steps of providing a liquid lung surfactant composition; aerosolizing the lung surfactant composition with a vibrating aperture-type aerosol generator to form a lung surfactant aerosol; and introducing the lung surfactant aerosol into the gas flow within a circuit of a pressure-assisted breathing system, preferably a CPAP system, coupled to the patient's respiratory system, whereby a therapeutically effective amount of the lung surfactant is delivered to the patient's lungs. Preferred lung surfactants comprise natural surfactants derived from the lavage of animal lungs and synthetically engineered lung surfactants.

[0036] In one embodiment, the vibrating aperture-type aerosol generator of the present invention allows the use of a liquid surfactant composition, e.g. a lung surfactant composition having a concentration from 20 mg/ml to 120 mg/ml. The diluent may be any pharmaceutically acceptable diluent, e.g. water or a saline solution.

[0037] In another embodiment, 10-90%, preferably greater than 30%, of the active lung surfactant provided to the aerosol generator is delivered to the patient's airway and is inhaled by the patient. Preferably, 5-50% of the active lung surfactant is actually deposited in the patient's lungs. In the practice of the present invention, a therapeutically effective amount of lung surfactant delivered to the patient's lungs (a "unit dose") may be in the range of 2-400 mg. Flow rates of vibrating aperture-type aerosol generators of the present invention may be in the range of 0.1-0.5 ml/min, which is considerably higher than the flow rate of comparable aerosol generators. Preferred delivery rates of active surfactant to the patient's airway are in the range of 2-800 mg/hr. Preferably, the aerosol generator may be adjusted to produce a surfactant particle size of less than 5  $\mu\text{m}$  MMAD, most preferably 1-3  $\mu\text{m}$  MMAD.

[0038] In one embodiment, the aerosol generator may be positioned so as to introduce surfactant aerosol into a plenum chamber located outside the direct breathing circuit of the

CPAP system, thereby collecting a concentration of surfactant aerosol higher than generated by the aerosol generator alone, prior to discharging the surfactant aerosol into the respiratory circuit.

5 BRIEF DESCRIPTION OF THE DRAWINGS

[0039] Fig. 1 is a schematic illustration of one embodiment of a CPAP system with a nebulizer.

[0040] Fig. 2 is a schematic illustration of another embodiment of a CPAP system of the present invention.

10 [0041] Fig. 3 is a perspective view of a CPAP apparatus of the present invention.

[0042] Fig. 4 is a perspective view of a nebulizer apparatus of the present invention.

[0043] Fig. 5 is a side, cross-sectional view of the nebulizer apparatus of Fig. 4.

[0044] Fig. 6 is a perspective view of a mask CPAP apparatus of the present invention.

15 [0045] Fig. 7 is a perspective view of an alternative CPAP arrangement in accordance with the present invention.

[0046] Fig. 8 is a schematic illustration of a pressure-assisted breathing system with a "Y"-shaped junction device.

[0047] Fig. 9 is a cross-sectional view of the "Y"-shaped junction device of Fig. 8.

20 [0048] Fig. 10 is a schematic illustration of a pressure-assisted breathing system with a junction device of the present invention.

[0049] Fig. 11 is a cross-sectional view of a junction device of the present invention.

[0050] Fig. 12 is a cross-sectional view of another junction device of the present invention.

25 [0051] Fig. 13 is a perspective view of the ventilator and respiratory circuits of a pressure-assisted breathing system of the present invention.

[0052] Fig. 14 is a cross-sectional view of the respiratory circuit shown in Fig. 13.

[0053] Fig. 15 is a perspective view of a portion of a nCPAP system of the present invention.

[0054] Fig. 16 is a perspective view of the nasal cannula shown in Fig. 15.

[0055] Fig. 17 is a schematic illustration of one embodiment of a CPAP system according to the present invention with an auxiliary circuit containing a flow sensor.

[0056] Fig. 18 is a cross-sectional view of the CPAP system of Fig. 17.

[0057] Fig. 19 is a schematic illustration of a CPAP system as described in Example 2.

[0058] Fig. 20 is a diagrammatic representation of an embodiment of the present invention employing a plenum chamber.

[0059] Figs. 21a and 21b are diagrammatic representations of models used for measuring aerosol delivery with simulated infant breathing pattern during nCPAP.

[0060] Fig. 22 is a graphic representation showing the range of inhaled mass of three types of nebulizers with nCPAP during simulated infant ventilation using the models of Figs. 21a and 21b.

#### DETAILED DESCRIPTION OF THE INVENTION

[0061] Fig. 1 of the drawings is a schematic illustration of a CPAP system 100 employing a nebulizer. The CPAP system 100 includes a primary pressure-generating circuit P and a respiratory circuit R. Circuit P includes a flow generator 2 in fluid communication with a pressure-regulating device 3. Respiratory circuit R includes a patient interface device 4 in fluid communication with circuit P at intersection 5. Nebulizer 6 is in fluid communication with circuit P at intersection 7 upstream to intersection 5. In operation, a high volume flow of gas 8 is introduced into circuit P from flow generator 2 and passes to and through pressure-regulating device 3 so as to maintain a positive pressure in the system. Nebulizer 6 emits an aerosolized medicament 9 into gas flow 8 at intersection 7 to produce combined gas flow 10 containing medicament 9. Gas flow 10 is transported through intersection 5 to pressure-regulating device 3 and ultimately to the atmosphere as part of gas flow 12.

[0062] Upon inspiratory effort by the patient through patient interface device 4, the transient decrease in pressure in respiratory circuit R produces an inspiratory flow 13 to be drawn from circuit P into circuit R and ultimately into the patient's respiratory system through patient interface 4. As shown, inspiratory flow 13 contains at least a portion of the medicament 9 that is entrained in gas flow 10. Expiratory effort by the patient through patient interface 4 produces a transient increase in pressure in respiratory circuit R that moves expiratory flow 14 from the patient interface device through circuit R to circuit P at intersection 5. Expiratory flow 14 joins gas flow 10 in pressure-generating circuit P at intersection 5 to form gas flow 11, which in turn passes through pressure-regulating device 3 to the atmosphere as gas flow 12.

[0063] A Bi-level system is similar to system 100, but may employ variable flow valves coupled with pressure sensors to vary the pressure in respiratory circuit R to coincide with the respiratory cycle of the patient. An invasive CPAP system is also similar to system 100, but would employ, for example an endotracheal tube, as the patient interface device 4.

[0064] In the embodiment of Fig. 1, the aerosolized medicament may be diluted by the high volume gas flow passing through the pressure-generating circuit, and a portion of the medicament may be ultimately lost to the atmosphere and never reach the patient. The higher the volume of gas flow in the pressure-generating circuit, the smaller the percentage of aerosolized medicament included in the respiratory gas flow to the patient's respiratory system through the patient interface device. For example, an infant breathing a respiratory flow of 0.2 to 0.6 liters/minute from a total flow of 10 liters/minute through the pressure-generating circuit may not be able to inhale more than a small percentage, e.g. from 2-6%, of the aerosolized medicament carried by the flow of gas in the primary pressure-generating circuit.

[0065] In one aspect of the present invention, the delivery of aerosolized medicament to a pressure-assisted breathing system is achieved in an efficient manner without the previously-described substantial dilution or loss of medicament. One arrangement may involve an improved CPAP or Bi-level system that introduces an aerosolized medicament directly into the air flow being inhaled by the patient during respiratory therapy and outside the air flow in the primary pressure-generating circuit. Such a CPAP or a Bi-level system may also be configured to employ small amounts of liquid medicament per treatment, for example a unit dose of 4 ml or less. Also, such CPAP or Bi-level systems may utilize a

nebulizer having a small, low volume reservoir, thereby providing to smaller patients an efficient method of respiratory therapy using a CPAP or Bi-level system.

[0066] Referring now to Fig. 2, one embodiment of an apparatus for applying CPAP in accordance with the present invention will be described. Elements in Fig. 2 that are similar to those in Fig. 1 are assigned the same reference numerals.

[0067] CPAP system 200 includes a primary pressure-generating circuit P and a respiratory circuit R. As used herein, the term "circuit" is intended to mean a gas (or other fluid) communication path between two points. Circuit P includes a flow generator 2 in gas communication with a pressure regulating device 3. Circuit R includes a patient interface device 4 in gas communication with circuit P at junction 5. In contrast to the CPAP system 100 illustrated in Fig. 1, nebulizer 6 of CPAP system 200 communicates with circuit R at intersection 15 outside pressure-generating circuit P. During operation of CPAP system 200, a high volume flow of gas 8 is introduced into circuit P from flow generator 2 and passes to and through pressure regulating device 3 so as to maintain a positive pressure in the system.

[0068] Upon inspiratory effort by the patient through patient interface device 4, there is a transient decrease in pressure in circuit R that causes a inspiratory flow 18 to be drawn from circuit P into circuit R and ultimately into the patient's respiratory system through patient interface 4. Nebulizer 6 emits aerosolized medicament 9 into inspiratory flow 18 at junction 15 to produce gas flow 19 in which medicament 9 is entrained and which is carried through patient interface device 4 into the patient's respiratory system. In this way, medicament 9 is emitted only into the flow of gas being inhaled by the patient, thereby greatly increasing the efficiency of delivery of medicament 9 to the patient. Expiratory effort by the patient through patient interface 4 produces a transient increase in pressure that moves expiratory flow 14 from the patient interface device through circuit R to circuit P at junction 5. Expiratory flow 14 joins gas flow 8 at junction 5 to form gas flow 16, which in turn passes through pressure-regulating device 3 as gas flow 17 to the atmosphere. As graphically illustrated in Fig. 2, a greater proportion of medicament 9 is delivered directly to the patient by CPAP system 200 with a lesser amount of dilution and loss into the atmosphere than in CPAP system 100.

[0069] Fig. 3 illustrates an embodiment of the present invention that is particularly suited for use in neo-natal and infant CPAP therapies. Referring now to Fig. 3, the primary pressure-generating circuit P may comprise a gas conduit, e.g. flexible tube 32, which

receives the high-volume flow of gas generated by flow generator 31. Flexible tube 32 conducts the flow of gas through junction unit 33 to flexible tube 35, which continues to transport the flow of gas to pressure-regulating device 34. Pressure-regulating device 34 may be connected to a controller (not shown) that regulates the pressure in the system to the  
5 desired CPAP. Respiratory circuit R may comprise a gas conduit, e.g. flexible tube 36, that connects with nebulizer 38, which is connected to patient interface device 39, either directly (as shown) or through a short section of flexible tube 36. As previously described, nebulizer 38 is preferably placed in close proximity to patient interface device 39.

[0070] Flexible tube 36 is preferably relatively thin, smaller in diameter and more  
10 flexible than flexible tubes 32 and 35. For example, flexible tube 36 may be commercially available silicone tubing having an outside diameter of about 5mm. The more flexible nature of flexible tube 36 allows the patient's head to more freely move about without disconnecting the patient interface device 39 from the patient.

[0071] Flow generator 31 may conveniently comprise any of the known sources of  
15 pressurized gas suitable for use with pressure-assisted breathing systems such as CPAP or Bi-level. Typically, the flow generator is capable of supplying a flow of high-volume gas, which includes at least some portion of oxygen, at slightly greater than atmospheric pressure. For example, the source of pressurized gas may be an air blower or a ventilator (as shown in Fig. 3), or the pressurized gas may originate from a wall supply of air and/or oxygen, such as that  
20 found within hospitals and medical facilities, or may originate from a pressurized cylinder or cylinders. The pressurized gas may comprise various known mixtures of oxygen with air, nitrogen, or other gases and may be provided in a single stream or flow to circuit R, for example, as shown by element 8 of Fig. 2.

[0072] Pressure-regulating device 34 may comprise any of the known devices for  
25 controlling and maintaining air pressure within a CPAP or Bi-level system at the desired level. Typically, pressure-regulating device 34 may comprise a restrictive air outlet device such as a pressure valve or threshold resistor that modulates the flow of gas leaving the pressure-regulating circuit P. This resistance to air flow may be varied so that the continuous positive airway pressure conducted by respiratory circuit R to patient interface device 39 will  
30 suit the needs of the particular patient using the apparatus. Although pressure-regulating device 34 is typically placed downstream of junction unit 33, it may also be placed at or upstream to junction 33.

[0073] Junction unit 33 is the point at which respiratory circuit R is in gas communication with primary pressure-generating circuit P. Junction unit 33 may comprise a "T" or "Y"-shaped hollow unit (sometimes referred to as the "WYE") to which flexible tubes 32, 35 and 36 are coupled. As shown in Fig. 3, junction unit 33 may comprise an inlet arm 33a and an outlet arm 33b, which together define a primary gas conduit through the body of junction unit 33. Respiratory arm 33c defines a branch gas conduit that depends from and is in gas communication with the primary gas conduit. Flexible tube 32 from flow generator 31 is coupled to the upstream opening in inlet arm 33a and flexible tube 35 leading to pressure-regulating device 34 is coupled to the downstream opening in outlet arm 33b to form pressure-generating circuit P. Flexible tube 36 is coupled to the downstream opening of respiratory arm 33c and, together with patient interface device 39, forms respiratory circuit R.

[0074] Patient interface device 39 is coupled to nebulizer 38, either directly or through a short section of flexible tube of the same size and material as tubing 36. Patient interface device 39 may include any of the known devices for providing gas communication between the CPAP device and the patient's respiratory system. By way of example, the patient interface device may include nasal prongs (as shown), an oral/nasal mask, a nasal mask, nasopharyngeal prongs, an endotracheal tube, a tracheotomy tube, a nasopharyngeal tube, and the like.

[0075] Nebulizer apparatus 38 is disposed in respiratory circuit R between primary pressure-generating circuit P and patient interface device 39 so as to emit an aerosolized medicament into the flow of gas in respiratory circuit R that is inhaled by the patient. Vibrating aperture-type nebulizer apparatus are preferred for the practice of this invention, for example, as described in detail in U.S. Pat. No. 6,615,824, 5,164,740; 5,586,550; 5,758,637; and 6,085,740, and in copending U.S. Patent Application Ser. Nos. 10/465,023, filed June 18, 2003, and 10/284,068, filed October 30, 2002. The entire disclosures of said patent and applications are incorporated herein.

[0076] A particularly preferred nebulizer apparatus is a "miniature" nebulizer 38, such as illustrated in Fig. 4, or as embodied in the latest version of the Pulmonary Drug Delivery System (PDDS) nebulizer marketed by Aerogen, Inc.. As shown in Fig. 4, nebulizer 38 may comprise a cylindrical body 41 having relatively small dimensions, e.g. about 15mm in outside diameter and about 20mm in length. Body 41 may have an upper medicament port 42 at one end and may be coupled to a generally L-shaped arm 43 at the

other end. At its distal end, arm 43 includes a generally "T"-shaped connector unit 44 having an inlet nipple 45 and outlet nipple 46. As illustrated in Fig. 3, connector 44 may be used to connect nebulizer 38 to respiratory circuit R by slipping the downstream end of tube 36 over inlet nipple 45 and attaching the patient interface device 39 directly to outlet nipple 46 or through a short section of tube 36. Body 41 may also include a clip holder 47 including notched channel 48, which is adapted to clip over flexible tube 36 to further secure and support nebulizer 38 on tube 36. Nebulizer 38 is preferably light-weight, for example, having a net weight (without contained liquid) of 5 gms or less, most preferably 3 gms or less. Particularly preferred nebulizers of the present invention have a net weight of 1-2 gms.

10 [0077] Referring now to Fig. 5, nebulizer 38 may comprise a reservoir 51 within cylindrical body 41 for holding a liquid medicament to be delivered to patient's respiratory system and a vibrating aperture-type aerosol generator 52 for aerosolizing the liquid medicament. Upper medicament port 42 may be provided for delivering the liquid medicament into reservoir 51 and a removable plug (not shown) may be provided to seal  
15 medicament port 42. Reservoir 51 may be sized to accommodate a small volume of medicament; e.g. a volume of 4 ml or less, and preferably a volume of 1-3 ml. Aerosol generator 52 may be positioned at lower medicament outlet 54 of reservoir 51 so that the liquid medicament flows by gravitational action from the reservoir 51 to aerosol generator 52 (Flow G).

20 [0078] Aerosol generator 52 may comprise a piezoelectric element and a vibratable member having a plurality of tapered apertures extending between a first surface and a second surface thereof. Representative vibratable aperture-type aerosol generators are described in detail in previously cited U.S. Pat. Nos. 5,164,740; 5,586,550; 5,758,637; and 6,085,740, the entire disclosures of which are incorporated herein by reference. In general,  
25 the first surface of the vibratable member, which faces upwardly, receives the liquid medicament from reservoir 51, and the aerosolized medicament is generated at the second surface of the vibratable member when droplets of medicament are ejected from the apertures upon vibration of the vibratable member. Aerosol generators of the present invention are preferably small and light-weight, for example, about 1 gm.

30 [0079] Aerosol generator 52 is positioned so as to facilitate flow of liquid medicament from the reservoir 51 to the aerosol generator 52 and to facilitate passage of the aerosolized medicament from the aerosol generator 52 into arm 42. Arm 42 may comprise a

supply conduit 55 in fluid communication with aerosol generator 52 at one end and connector unit 93 at the other end so as to conduct a flow of aerosolized medicament (Flow A) toward connector 93. Connector 93 may comprise a gas conduit 56, which is defined on one end by inlet conduit 57 in inlet nipple 45 and at the other end by outlet conduit 58 in outlet nipple 46.

5 The gas conduit 56 of connector 93 may be quit small, e.g. less than 10 cc in volume for infant applications, thereby decreasing dead space in the respiratory circuit.

[0080] The downstream end of flexible tubing 36 (Fig. 3) may be coupled to inlet nipple 45 of connector 93 to conduct gas flow B in the respiratory circuit into inlet conduit 57 to gas conduit 56 of connector 93. Flow A of aerosolized medicament in supply conduit 55  
10 passes into gas conduit 56 of connector 96 and the aerosolized medicament is entrained in gas conduit 56 with Flow B. The entrained mixture of aerosolized medicament and gas (Flow AB) then passes out of the gas conduit 56 through outlet conduit 58 in outlet nipple 46 and on to the respiratory system of the patient.

[0081] Nebulizer apparatus 38 may be connected to a controller (not shown) for  
15 controlling operation of and to supply power to the aerosol generator. Preferably, the controller and other electronic components are connected with wires, cables and connectors that are small and flexible. Examples of other components that may also be associated with nebulizer apparatus 38 are a timer, status indication means, liquid medicament supply nebule or syringe, etc., all as known by those skilled in the art and described in detail in the  
20 aforementioned patent and patent applications.

[0082] The miniature vibrating aperture-type nebulizer apparatus of the present invention is so small and quiet that it may be placed in very close proximity to the mouth, nose or artificial airway of the patient. This placement further ensures that the aerosolized medicament is introduced directly into the flow of gas being inhaled by the CPAP patient (i.e.  
25 into the respiratory circuit) and eliminates the dilution effect caused by introducing the medicament into the high-volume flow of gas from the flow generator (i.e. in the pressure-generating circuit). Fig. 6 illustrates a typical adult CPAP/Bi-level system comprising a flow generator 501 attached by a single flexible tube 502 to a nasal or full face mask 503. Pressure is maintained by a flow of gas escaping through a fixed orifice located in swivel  
30 valve 504 between the tube 502 and the mask 503. In an alternative embodiment, a fixed orifice 505 may be located at the top (above the bridge of the nose) of the mask 503. In both embodiments, the entire respiratory circuit R is contained within the patient interface device.

Nebulizer apparatus 506 is coupled to mask 503 so that the aerosolized medicament exits the nebulizer apparatus into the respiratory circuit directly in the vicinity of the mouth and nose of the patient. In this manner, the efficiency of the system is increased by decreasing the distance which the aerosolized medicament must travel, i.e. by decreasing the length of the respiratory circuit. In an alternative embodiment, the aerosol generator can be operated only during patient inspiration, further improving the efficiency of the system.

[0083] Fig. 7 illustrates another alternative embodiment of the invention suitable for adults. CPAP apparatus 700 comprises flexible tube 701 conducting gas flow F from a flow generator (not shown) through “Y”-shaped junction unit 703 and flexible tubing 702 to a pressure-regulating device (not shown) to form pressure-generating circuit P. Elbow-shaped junction unit 704 connects pressure-generating circuit P to respiratory circuit R at junction unit 703. Respiratory circuit R comprises a smaller flexible tubing 705 which conducts gas flow I from elbow unit 704 to a patient interface device (not shown). Nebulizer apparatus 706 is disposed on tubing 705 so as to entrain aerosolized medicament into gas flow I being inhaled by the patient, as previously described above.

[0084] Fig. 8 of the drawings is a schematic illustration of a ventilator system employing a nebulizer. The ventilator system 800 includes a ventilator circuit V in fluid communication with a respiratory circuit R. One element is in “fluid communication” with another element when it is attached through a channel, port, tube or other conduit that permits the passage of gas, vapor and the like.

[0085] Circuit V includes a ventilator 802 in fluid communication with inspiratory tube 803 and expiratory tube 804 converging at “Y”- shaped junction device 805. Respiratory circuit R includes a patient interface device 806 in fluid communication with circuit V at junction device 805. Nebulizer 807 is in fluid communication with circuit V at intersection 808 upstream to junction device 805. In operation, a pressurized flow of gas 809 is introduced into inspiratory tube 803 from ventilator 802 and passes to and through intersection 808. Nebulizer 807 emits an aerosolized medicament 810 into gas flow 809 at intersection 808 to produce combined gas flow 811 containing aerosolized medicament 810. Gas flow 811 is transported through junction device 805 to patient interface device 806 and ultimately to the respiratory system of the patient upon inspiratory effort by the patient through patient interface device 806. Expiratory effort by the patient through patient

interface device 806 produces expiratory flow 812 which flows from patient interface device 806 through junction device 805 to expiratory tube 804 and back to ventilator 802.

[0086] Referring now to Fig. 9, junction device 905 comprises inspiratory leg 921 attachable to inspiratory tube 903, expiratory leg 922 attachable to expiratory tube 904 and  
5 respiratory leg 923 attachable to respiratory circuit R. Gas flow 911 (containing aerosol particles of medicament) passes from inspiratory tube 903 into inspiratory leg 921 and encounters a sharp change in the angle of its path (represented by  $\Delta_1$ ) at intersection 924. As gas flow 911 attempts to turn the sharp corner at intersection 924, a portion of gas flow 911 impacts the wall and ridges encountered at intersection 924. As a result, a portion 911a of  
10 gas flow 911 (and the aerosol particles of medicament entrained therein) is diverted to expiratory leg 922 and is lost through expiratory tube 904. The remainder of gas flow 911 continues through respiratory leg 923 to respiratory circuit R. Upon expiratory effort by the patient, expiratory gas flow 912 follows a path from respiratory circuit R through respiratory leg 923, expiratory leg 922 and expiratory tube 904 back to the ventilator (not shown).

15 [0087] Referring now to Fig. 10, one embodiment of a mechanical ventilator system in accordance with the present invention will be described. Ventilator system 1000 includes a ventilator circuit V and a respiratory circuit R. Ventilator circuit V includes a ventilator 1002 in fluid communication with inspiratory tube 1003 and expiratory tube 1004, which converge at junction device 1035 of the present invention. Respiratory circuit R includes a  
20 patient interface device 1006 in fluid communication with circuit V at junction device 1035. Nebulizer 1007 may be attached to and in fluid communication with junction device 1035. Alternatively, nebulizer 1007' may be attached to and in fluid communication with inspiratory tube 1003. During operation of ventilator system 1000, a pressurized flow of gas 1009 is introduced into inspiratory tube 1003 from ventilator 1002 and passes to and through  
25 junction device 1035. Nebulizer 1007 (or 1007') emits an aerosolized medicament 1010 into gas flow 1009 to produce combined gas flow 1011 containing aerosol particles of medicament 1010. Gas flow 1011 is transported through junction device 1035 to patient interface device 1006 and ultimately to the respiratory system of the patient. Expiratory effort by the patient through patient interface 1006 produces expiratory gas flow 1012 which  
30 flows from the patient interface device through junction device 1035 to expiratory tube 1004 back to ventilator 1002.

[0088] As illustrated in Fig. 11, one embodiment of junction device 1135 may comprise a tubular main body member 1141 having a straight longitudinal lumen 1142 connecting an opening in a first end 1143 attachable to inspiratory tube 1103 and an opening in a second end 1144 attachable to respiratory circuit R. Junction device 1135 may further  
5 comprise a tubular branch member 1145 having a lumen 1146 that communicates with lumen 1142 at intermediate opening 1147. Gas flow 1111 (which contains aerosol particles of medicament emitted by nebulizer 1007' into gas flow 1009 in inspiratory tube 1003 - see Fig. 10), passes from inspiratory tube 1103 into lumen 1142 through the opening in first end 1143. In contrast to the "Y"-shaped junction device 905 shown in Fig. 9, junction device 1135  
10 provides for gas flow 1111 (containing aerosolized medicament) to follow a straight unobstructed path to respiratory circuit R without any portion being diverted into branch member 1145. In other words, there is virtually no change in the angle of the path of gas flow 1111. As a result, the full amount of aerosol particles of medicament contained in gas flow 1111 is efficiently delivered through respiratory circuit R to the patient. Upon  
15 expiratory effort by the patient, expiratory gas flow 1112 follows a path from respiratory circuit R through lumen 1142 to lumen 1146 of branch member 1145 and through expiratory tube 1104 back to the ventilator (not shown).

[0089] Another embodiment of the present invention is shown in Fig. 12, wherein junction device 1250 comprises tubular main body member 1251 having a first end 1252  
20 (attachable to an inspiratory tube 1103 in Fig. 11) and a second end 1253 (attachable to respiratory circuit R in Fig. 11), a tubular branch member 1254 (attachable to the expiratory tube 1104 in Fig. 11), and a port 1255 attachable to a nebulizer (not shown). Gas flow 1209 from the ventilator 1002 (Fig. 10) passes into lumen 1258 through the opening in first end 1252 of main body 1251. Nebulizer 1007 (Fig. 10) introduces aerosolized medicament 1210  
25 into gas flow 1209 in lumen 1258 through port 1255 located in close proximity to first end 1252 of lumen 1258. It has been found that any protrusion into lumen 1258 causes turbulence in gas flow 1209, which may result in the deposition of aerosol particles on the walls of lumen 1258. Therefore, if a vibrating aperture-type nebulizer is used, the vibrating plate of the nebulizer is preferably positioned completely within nebulizer port 1255, and  
30 most preferably flush with the internal surface (wall) of lumen 1258. Aerosolized medicament 1210 is entrained in gas flow 1209 to produce gas flow 1211 containing aerosolized medicament 1210. Gas flow 1211 travels an unobstructed straight path through lumen 1258 out the opening in second end 1253 to respiratory circuit R. Upon expiratory

effort by the patient, expiratory gas flow 1212 follows a path from respiratory circuit R through lumen 1258 and intermediate opening 1256 to lumen 1257 of branch member 1254 and through the expiratory tube back to the ventilator.

[0090] The respiratory circuit of the present invention may comprise a patient interface and optionally, such customary tubes and connectors as are required to provide fluid communication between the ventilator circuit and the patient interface device. The patient interface device may include any of the previously described known devices for providing gas communication to the patient's respiratory system, e.g. nasal prongs, an oral/nasal mask, a nasal mask, nasopharyngeal prongs, an endotracheal tube, a tracheostomy tube, a nasopharyngeal tube, and the like.

[0091] In the embodiments of the invention shown in Figs. 8-16, the nebulizer used in the present invention may be any of the aerosol generators suitable for creating aerosols as liquid droplets or dry particles (referred to herein as "aerosol particles"), for example, atomizers, atomizing catheters, vibrating aperture-type nebulizers, ultrasonic nebulizers, jet nebulizers, etc. Nebulizers may comprise a reservoir for holding a liquid medicament to be delivered to a patient's respiratory system and an aerosol generator for aerosolizing the liquid medicament. The nebulizer is positioned so as to direct aerosol particles into a circuit of the pressure-assisted breathing system. For example, the nebulizer may be connected to a circuit of a ventilator system through a separate connector, a connector integrated with the nebulizer body or a connector integrated with a junction device. However, as stated above, particularly preferred "vibrating aperture-type" nebulizers comprise a vibrational element and dome-shaped aperture plate with tapered holes. When the plate vibrates at a rate of about 100 thousand times per second, a micro-pumping action causes liquid to be drawn through the tapered holes, creating a low-velocity aerosol with a precisely defined range of droplet sizes. Such nebulizers are commercially available from Aerogen Inc., Mountain View, California.

[0092] As previously stated, due to the increased efficiency of the present invention, the reservoir of the nebulizer may be sized to accommodate a smaller amount of medicament. For example, the reservoir of the nebulizer may have a capacity equal to a single unit dose of medicament, i.e. an amount sufficient for one treatment, and substantially all of the medicament may be delivered to the patient without the need to replenish the reservoir. This is particularly beneficial in respiratory therapies that utilize phospholipid surfactants since these medicaments are scarce, expensive and, because of their high viscosity, are difficult to

deliver. The present invention may also eliminate the need to pump medicament from an outside container to the nebulizer, although in some applications of the invention this may be desirable.

[0093] As stated in connection with Fig. 3 above, the nebulizer may be connected to a controller for controlling operation of, and to supply power to, the aerosol generator and may be associated with other electronic components. In one embodiment, the controller may be integrated in the same enclosure with a CPAP system controller. In this case, the two systems may use the same power supply and communicate electronically.

[0094] When used in a mechanical ventilator system, the nebulizer may be conveniently positioned in the ventilator circuit or in the respiratory circuit. As one example, the nebulizer may be attached to the inspiratory tube of the ventilator circuit using a separate connector or using a connector integrated with the body of the nebulizer. Such connectors are adapted to provide a conduit for aerosol particles to travel from the aerosol generator of the nebulizer to the gas flow in the ventilator circuit so that the aerosol particles are entrained in the gas flow. As another example, the nebulizer may be attached to a port in a junction device of the present invention, as previously described above in connection with Fig. 12.

[0095] For example, Fig. 13 illustrates junction device 1350 (corresponding to junction device 1250 of Fig. 12) connecting inspiratory tube 1363 and an expiratory tube 1364 of ventilator circuit V with respiratory tube 1369 of respiratory circuit R. When a nebulizer in the ventilator circuit is desired, it may be attached to port 1355 of junction device 1350, as described in connection with Fig. 12. Alternatively, the nebulizer may be attached to inspiratory tube 1363 using one of the previously described connectors.

[0096] In other embodiments, it may be advantageous to have a nebulizer positioned in the respiratory circuit. For example, placement of the nebulizer in close proximity to the patient's nose, mouth or artificial airway, e.g. directly adjacent to the point of intake of an endotracheal (ETT) tube or in close proximity to a nasal cannula or mask, may further improve the efficiency and control of the delivery of the aerosolized medicament to the patient. Since significant deposition of aerosol particles may occur at the connection of patient interface device when the aerosol particles impact the edges of the connector as they try to enter the device, placing the nebulizer as close as possible to the patient interface device makes the "dead space" between the aerosol generator and the patient interface device

as small as possible. This reduction or elimination of dead space may significantly reduce the loss of aerosol particles entering the patient interface device.

[0097] Fig. 13 shows one example of how a nebulizer may be positioned in the respiratory circuit R of a ventilator system. Nebulizer 1361 is located between ETT tube 1367 and ventilator circuit V, which are connected to each other through connector 1365, respiratory tube 1369 and junction device 1350. In those embodiments wherein a first nebulizer is desired in the respiratory circuit R and a second nebulizer is desired in the ventilator circuit V, the second nebulizer may be optionally attached to junction device 1350 using port 1355 in the manner described above. Connector 1365 is particularly suited for this application because branch member 1368 of connector 1365 defines an arcuate path for aerosol particles coming through respiratory tube 1369 from the second nebulizer attached to junction device 1350. This arcuate path minimizes the impact of aerosol particles on the walls of branch member 1368 as they travel to ETT tube 1367 and, as a result, the loss of aerosol particles at this point is minimized. Connector 1365 may also have a port 1362 for administering liquids to the patient when such administration is needed.

[0098] Referring now to Fig.14, which illustrates an enlarged cross-section of respiratory circuit R in Fig. 13, nebulizer 1461 may comprise a reservoir 1471 in the shape of a rectangle with rounded corners and connector base 1473. Reservoir 1471 is adapted to hold liquid medicament for delivery to a patient's respiratory system. Vibrating aperture-type aerosol generator 1472 is in fluid communication with reservoir 1471 and is adapted to aerosolize liquid medicament that is gravity-fed from reservoir 1471. Reservoir 1471 is preferably rotatably mounted on connector base 1473 so that reservoir 1471 can be moved, for example, around an axis represented by A. In this way, reservoir 1471 can be readily positioned for optimum gravity feeding of liquid medicament to aerosol generator 1472 regardless of varied positions of the patient and/or the other components of the respiratory circuit. For example, when the patient is lying down and ETT tube 1467 is in a substantially vertical position, reservoir 1471 may be positioned above aerosol generator 1472 so that liquid medicament is gravity-fed to aerosol generator 1472. If the patient then assumes a sitting position and ETT tube 1467 is placed in a substantially horizontal position, reservoir 1471 may be rotated 90° to maintain its optimum position above aerosol generator 1472 so that liquid medicament continues to be gravity-fed to aerosol generator 1472.

[0099] Connector base 1473 may further comprise main body member 1474 having inlet 1475 adapted to interconnect with connector 1465 on one end and outlet 1476 adapted to interconnect with endotracheal tube 1467 on the opposite end. Longitudinal lumen 1477 extends from inlet 1475 through main body member 1474 to outlet 1476 to form a straight path for the flow of gas from connector 1465 to endotracheal tube 1467. The vibrating plate of aerosol generator 1472 is positioned in port 1478 of connector base 1473, preferably flush with the internal wall of lumen 1477, so as to emit aerosol particles of medicament produced by aerosol generator 1472 directly into the gas flow within lumen 1477 with a minimum amount of turbulence.

[0100] Fig. 15 illustrates a neo-natal or infant nCPAP system employing nasal cannula according to the present invention. The primary pressure-generating circuit of the nCPAP system may comprise flexible tubes 1581 and 1583 for conducting the high-volume flow of gas generated by a conventional air flow generator (not shown); junction device 1582 for connecting tubes 1581 and 1583 to the respiratory circuit of the nCPAP system; and pressure-regulating device 1584. Pressure-regulating device 1584 may be connected to a controller (not shown) that regulates the level of CPAP in the system. Nebulizer 1585 is connected to nasal cannula 1586 through respiratory tube 1587 and is positioned to emit aerosol particles of medicament into the flow of gas from junction device 1582 to nasal cannula 1586. Respiratory tube 1587 is preferably relatively thin, smaller in diameter and more flexible than flexible tubes 1581 and 1583. For example, respiratory tube 1587 may be commercially available silicone tubing having an outside diameter of about 5mm. The more flexible nature of respiratory tube 1587 allows the patient's head to more freely move about without disconnecting the nasal cannula 1586 from the patient. The flow of gas 1588 containing aerosol particles is carried through respiratory tube 1587 to nasal cannula 1586 and ultimately to the patient's nostrils and respiratory system.

[0101] Referring now to Fig. 16, nasal cannula 1686 of the present invention may comprise a tubular inlet section 1691 connected to a pair of nasal cannula 1692 by a tubular forked section 1693. Lumen 1694 in inlet section 1691 is in fluid communication with substantially parallel lumens 1695 and 1696 in each prong of forked section 1693 to provide a gently forked conduit extending from inlet section 1691 to nasal cannula 1692. Air flow 1688 containing aerosol particles emitted by nebulizer 1585 (Fig. 15) is conducted by respiratory tube 1687 through lumen 1694 in inlet section 1691 to intersection 1697, where the path of aerosol particles is split so as to follow lumens 1695 and 1696 to cannula 1692. In

accordance with the present invention, the change in angle between the path for aerosol particles defined by lumen 1694 and each of the lumens 1695 and 1696 at intersection 1697 is relatively small; i.e. angles  $\Delta_2$  and  $\Delta_3$  are no greater than about  $15^\circ$ . As a result, substantially all of the aerosol particles of medicament contained in gas flow 1688 reach the nasal cannula 1692 and ultimately the patient's nostrils. Because there is minimal loss of aerosol particles in the nasal cannula of the present invention, the efficiency of delivery of the aerosolized medicament is significantly enhanced.

[0102] The embodiment shown in Figs. 15 and 16 is particularly useful for treatment of iRDS, discussed in more detail later. This embodiment of the present invention provides an efficient way to integrate a vibrating aperture-type aerosol generator with a nCPAP system capable of delivering surfactant medication simultaneously with the CPAP treatment. As a result, the administration of surfactant medication by means of extubation may be eliminated, thereby decreasing the risk of airway damage and secondary infection.

[0103] One embodiment of the present invention provides a method of delivering aerosolized medicament to a subject, preferably a human patient that exhibits one or more symptoms of infection or other respiratory disease or disorder. The method generally comprises attaching the subject to a pressure-assisted breathing system comprising a gas flow generator, a circuit connecting the gas flow generator to the subject's respiratory system and an aerosol generator for emitting aerosol particles of medicament into the circuit, wherein the circuit defines a path for the emitted aerosol particles having a change in angle of no greater than  $15^\circ$ . The larger changes of path angle, e.g. about  $12^\circ$ - $15^\circ$ , are most suited to pressure-assisted breathing systems employing nasal cannula, particularly when used with surfactant medications. In other applications, smaller changes of path angle may be preferred, i.e. a change in path angle of no greater than  $12^\circ$  and most preferably no change in path angle (a straight path).

[0104] Medicaments useful in the practice of the invention may be any of those commonly used in aerosol form for treating the above-described symptoms, for example, various antibiotics or combinations of antibiotics (preferably used in ventilator systems) and surfactant medicaments (preferably used in CPAP systems). Examples of antibiotics include anti-gram-positive agents such as macrolides, e.g. erythromycin, clarithromycin, azithromycin, and glycopeptides, e.g. vancomycin and teicoplanin, as well as any other anti-gram-positive agent capable of being dissolved or suspended and employed as a suitable

aerosol, e.g. oxazolidinone, quinupristin/dalfopristen, etc.. Antibiotics useful as anti-gram-negative agents may include aminoglycosides, e.g. gentamicin, tobramycin, amikacin, streptomycin, netilmicin, quinolones, e.g. ciprofloxacin, ofloxacin, levofloxacin, tetracyclines, e.g. oxytetracycline, doxycycline, minocycline, and cotrimoxazole, as well as  
5 any other anti-gram-negative agents capable of being dissolved or suspended and employed as a suitable aerosol. Surfactant medications are discussed in detail later.

[0105] The pressure-assisted breathing systems of the present invention may include any of the other elements conventionally found in such systems such as, for example, humidifiers, filters, gauges, traps for sputum and other secretions and controllers that control  
10 the breathing cycle, the nebulizer and/or other components. A humidifier in the system is particularly advantageous since control of the humidity may affect the efficiency of aerosol particle delivery. For examples, the aerosol particles should be prevented from undergoing significant hygroscopic enlargement since particles enrobed in water will tend to condense on the walls of system tubes. Breathing cycle controllers may also be particularly useful in the  
15 practice of the invention since they may be used to actuate the administration of aerosol only during the inspiration phase of the breathing cycle or when the humidifier is not active, thereby further enhancing the efficiency of the system.

[0106] As shown in Fig. 17, one preferred embodiment of the invention comprises a CPAP system 1700 having a primary pressure-generating circuit P, a respiratory circuit R and  
20 an auxiliary circuit A. As previously mentioned, the tubes associated with commercially available pressure-assisted breathing systems create a "circuit" for gas flow by maintaining fluid communication between the elements of the circuit. Tubes can be made of a variety of materials, including but not limited to various plastics, metals and composites and can be rigid or flexible. Tubes can be attached to various elements of the circuit in a detachable  
25 mode or a fixed mode using a variety of connectors, adapters, junction devices, etc. Circuit P includes a flow generator 1702 in fluid communication through conduit 1701 with a pressure-regulating device 1703.

[0107] Respiratory circuit R includes a patient interface device, namely nasal cannula 1704, which communicates with circuit P at "T"-shaped junction unit 1705 through tube  
30 1706. Tube 1706 is preferably a flexible tube having a smaller diameter than conduit 1701, e.g. tube 1706 may have an outside diameter of 5-8 mm or less. Nebulizer 1707 (comprising an aerosol generator) is in fluid communication with tube 1706 at junction 1708. Nebulizer

1707 is adapted to emit an aerosolized medicament directly into the gas flow that is inhaled by the patient, i.e. the gas flow in respiratory circuit R, and is preferably located in the direct vicinity of the patient's nose, mouth or artificial airway (e.g. an endotracheal tube).

Nebulizer 1707 itself may comprise a built-in connector for connecting to tube 1706 (as shown), or may be connected using a separate tube or connector.

[0108] Auxiliary circuit A includes flexible tube 1711, preferably having the same outside diameter as tube 1706, which connects flow sensor 1709 with tube 1706 at "T"-shaped junction unit 1710. Junction unit 1710 is preferably positioned close to nasal cannula 1704, but upstream to nebulizer 1707 so that aerosol particles emitted by nebulizer 1707 are not diverted into tube 1711. Adjustable orifice valve 1712 may be positioned in tube 1711 between junction 1710 and flow sensor 1709 to adjust the flow rate of gas passing through flow sensor 1709, preferably to the middle of the optimal flow range for sensor 1709. Disposable filter 1713 may be positioned in tube 1711 between junction 1710 and flow sensor 1709 to remove any bacterial, viral and/or other contaminants from the patient's diseased respiratory system that may be carried by the exhaled air passing through flow sensor 1709.

[0109] The operation of CPAP system 1700 will be illustrated by referring to Fig. 18, which is an enlarged, cross-section view of CPAP system 1700. A high volume flow of gas 1820 is introduced into circuit P from flow generator 1802 and passes through conduit 1801 to pressure-regulating device 1803 which maintains a continuous positive pressure throughout the system. Inspiratory flow 1821, which may typically be about 10% of flow 1820, flows from conduit 1801 of pressure-generating circuit P into tube 1806 of respiratory circuit R to provide a relatively constant inspiratory flow rate of air to the patient's respiratory system, thereby assisting in the patient's inspiratory efforts in accordance with conventional CPAP system principles. At junction 1810, a portion 1821a of inspiratory flow 1821 proceeds through tube 1806 to nasal cannula 1804, and a portion 1821b of inspiratory flow 1821 is diverted through tube 1811 to flow sensor 1809.

[0110] Flow 1821a passes through junction 1808, at which point aerosolized medicament particles 1822 produced by the aerosol generator of nebulizer 1807 are introduced into flow 1821a. Resulting flow 1823 containing entrained aerosol particles 1822 ultimately passes into the patient's respiratory system through nasal cannula 1804, thereby delivering the aerosolized medicament to the patient's respiratory system. Flow 1821b

passes through tube 1811 and adjustable orifice valve 1812, which may be adjusted to reduce the rate of flow 1821b to a reduced flow 1821c, e.g. a flow rate that may be about 20% of the flow rate of flow 1821b. Reduced flow 1821c then proceeds through disposable filter 1813 to flow sensor 1809, and is ultimately released to the atmosphere. As flow 1821c passes through flow sensor 1809, flow sensor 1809 measures the volumetric flow rate of flow 1821c and generates a first electronic signal, e.g. a certain output voltage, in electronic circuitry 1825 of CPAP system 1700 that is characteristic of flow 1821c. Since flow 1821c is directly proportional to inspiratory flow 1821, the first electronic signal caused by flow 1821c may be used by the system to identify when the patient is inhaling and continue the delivery of aerosolized medicament.

[0111] When the patient exhales, expiratory flow 1824 passes through nasal cannula 1804 to tube 1806 and is diverted through tube 1811 at junction unit 1810. Expiratory flow 1824 is combined with inspiratory flow 1821b in tube 1811 to produce a flow rate equal to the sum of the flow rates of flow 1824 and 1821b. The combination of flow 1824 and flow 1821b passes through adjustable orifice valve 1812 and the total flow rate is reduced in the same manner as previously described for flow 1821b alone (identified in Fig. 18 as a combination of flow 1821c and 1824a). Disposable filter 1813 removes any bacterial, viral or other contaminants that may have been present in the combined air flow as a result of flow 1824a and the combined air flow then passes through flow sensor 1809. When the combination of flow 1821c and 1824a passes through flow sensor 1809, the change (increase) in flow rate over that of flow 1821c alone is detected by flow sensor 1809. As a result, flow sensor 1809 generates a second electronic signal in electronic circuitry 1825 that is different than the first electronic signal produced by flow 1821c alone. The second electronic signal is transmitted by electronic circuitry 1825 to nebulizer 1807 and causes it to turn off its aerosol generator. This inactivation of the aerosol generator stops the introduction of aerosol particles 1822 into flow 1821a. Since the second electronic signal is generated by the volumetric flow rate of the combination of flow 1821c and 1824a, it indicates the presence of expiratory flow 1824. Therefore, the second electronic signal may be used by the system to identify when the patient is exhaling and stop the introduction of aerosolized medicament. In this way, no aerosol is introduced into tube 1806 when the patient exhales, and therefore, no aerosolized medicament is entrained in expiratory flow 1824, which is ultimately released to the atmosphere and lost.

[0112] When expiratory effort by the patient stops and inhalation commences again, expiratory flow 1824 discontinues and only inspiratory flow 1821 is present in the system. As a result, only flow 1821c passes through tube 1811. Flow sensor 1809 detects this change (decrease) in flow rate and generates the first electronic signal, which is transmitted to  
5 nebulizer 1807. The first electronic signal causes nebulizer 1807 to turn on the aerosol generator and resume the introduction of aerosol particles 1822 into flow 1821a. The turning on and off of the aerosol generator of nebulizer 1807 in concert with the patient's respiratory cycle allows aerosolized medicament to be introduced into the CPAP system of the present invention only when the patient is inhaling. This results in a dramatic increase in the  
10 efficiency of delivery of the medicament and a corresponding reduction in losses of medicament to the atmosphere.

[0113] As previously described, pressure-regulating device 1803 may comprise any of the known devices for controlling and maintaining air pressure within a CPAP system at the desired constant level. Typically, pressure-regulating device 1803 may comprise a  
15 restrictive air outlet device such as a pressure valve or threshold resistor that modulates the flow of gas leaving the pressure-regulating circuit P. In other applications, the modulation of the gas flow may be provided by releasing the air flow into a standardized vessel containing a predetermined quantity of water, with the pressure in the system being expressed in terms of the height to which the water rises in the vessel. Regardless of the pressure-regulating device  
20 used, the resistance to air flow in the pressure-generating circuit may be varied so that the continuous positive airway pressure conducted by respiratory circuit R to patient interface device 1804 will suit the needs of the particular patient using the apparatus.

[0114] Although junction unit 1805 may typically comprise a "T" or "Y"-shaped hollow unit (sometimes referred to as the "WYE"), it may take other shapes. As shown in  
25 Fig. 18, flexible tube 1806 is connected to junction unit 1805 and defines a branch gas conduit that depends from and is in gas communication with pressure-generating circuit P. Tube 1806 is ultimately connected to a patient interface device, e.g. nasal cannula 1804, to form respiratory circuit R. Flexible tube 1806 is preferably relatively thin, smaller in diameter and more flexible than conduit 1801 comprising pressure-generating circuit P. For  
30 example, flexible tube 1806 may be commercially available silicone tubing having an outside diameter of about 5-8 mm.

[0115] Nebulizer 1807 may be any of the known devices for nebulizing (aerosolizing) drugs that are suitable for use with a CPAP system, but as described above, is preferably a small, light weight nebulizer having a vibrating aperture-type aerosol generator.

[0116] The flow sensor 1809 of the present invention may be a known flow sensor device that is adapted to detect small changes in the volumetric flow rate of fluid passing through it and is capable of generating an electronic signal, e.g. an output voltage, which is characteristic of that flow rate. A particularly preferred flow sensor for the practice of the present invention is commercially available from Omron Corporation of Japan, and is identified as "MEMS Flow Sensor, Model D6F-01A1-110". The Omron flow sensor is capable of detecting a flow rate in the range of 0 to 1 L/min (at 0° C. and 101.3kPa pressure). The relationship of measured flow rate and resulting output voltage for the Omron flow sensor is summarized in Table 1 below:

TABLE 1

|                                 |      |      |      |      |      |      |
|---------------------------------|------|------|------|------|------|------|
| Flow rate (L/min)               | 0    | 0.2  | 0.4  | 0.6  | 0.8  | 1.0  |
| Output voltage (VDC $\pm$ 0.12) | 1.00 | 2.31 | 3.21 | 3.93 | 4.51 | 5.00 |

[Note: measurement conditions for Table 1 are as follows: power-supply voltage of 12VDC, ambient temperature of 25°C and ambient humidity of 25-75%RH.]

[0117] Nebulizer apparatus 1807 may be connected to flow sensor 1809 through the electronic circuitry 1825 of the CPAP system. For example, nebulizer 1807 may be connected to a controller (not shown) that turns the aerosol generator off and on in response to signals from flow sensor 1809. Preferably, the controller and other electronic components of the CPAP system are connected with wires, cables and connectors that are small and flexible. Examples of other components that may also be associated with nebulizer apparatus 1807 are a timer, status indication means, liquid medicament supply nebule or syringe, etc., all as known by those skilled in the art and described in detail in the aforementioned patent and patent applications.

[0118] The following examples will illustrate the present invention using the Omron flow sensor described above, but is not intended to limit the invention to the particular details set forth therein:

### EXAMPLE 1

[0119] A CPAP system of the present invention such as illustrated in Fig. 18 may be used for respiratory treatment of an infant. The system may be pressurized to a pressure of 5 cm H<sub>2</sub>O and a constant flow of air may be supplied by a flow generator 1802 into pressure-generating circuit P at a rate of 10 L/min. About 1 L/min (10%) of the air flow in the pressure-generating circuit may flow into flexible tube 1806 as flow 1821. During inhalation by the infant through nasal cannula 1804, about 20% of flow 1821 (identified in Fig. 18 as flow 1821b) may be diverted into tube 1811 at junction 1810 by appropriately adjusting orifice valve 1812 to produce a flow rate for flow 1821c of about 0.2L/min (0.2 x 1L/min). Flow 1821c may also pass through a disposable filter 1813, but since flow 1821c contains only inhalation air containing very little, if any, contamination, nothing significant should be removed from flow 1821c by the filter. Flow 1821c then may pass through the Omron flow sensor described above at a flow rate of 0.2 L/min, which according to Table 1 above, results in the generation of an output voltage of about 2.31 VDC. The electronic circuitry of the CPAP system may be configured to have the aerosol generator of nebulizer 1807 turned on when the flow sensor is transmitting this output voltage to nebulizer 1807. Turning on the aerosol generator introduces aerosolized medicament into the respiratory circuit R of the CPAP system so it can be inhaled by the infant.

[0120] During exhalation, the infant may exhale about 0.6 L/min of air flow through nasal cannula 1804 to produce expiratory flow 1824, which combines in tube 1811 with flow 1821b. As previously described for flow 1821b alone, orifice valve 1812 has been adjusted to reduce the flow rate of gas in tube 1806 to about 20% of the original flow rate. Accordingly, flow 1821b may be reduced to flow 1821c having a flow rate of about 0.20 L/min (0.2 x 1 L/min) and flow 1824 may be reduced to flow 1824a having a flow rate of about 0.12 L/min (0.2 x 0.6 L/min). The combined expiratory flow rate of the combination of flow 1821c and 1824a therefore equals about 0.32 L/min. This combined expiratory flow rate may then pass through disposable filter 1813 to remove any contaminants that may be present as a result of expiratory flow 1824a, and then pass through the Omron flow sensor. Again referring to Table 1 above, it can be seen that the Omron pressure sensor generates an output voltage of about 3.0 VDC at the combined exhalation flow rate of 0.32 L/min. The electronic circuitry of the CPAP system may be configured to have the aerosol generator of nebulizer 1607 turned off when this output voltage is transmitted to nebulizer 1807 by electronic circuitry 1825. Turning off the aerosol generator ceases the introduction of aerosolized medicament particles 1822 into the respiratory circuit R of the CPAP system

during the presence of expiratory flow 1824. As a result, a minimum amount of aerosol is entrained in expiratory flow 1824 and ultimately lost to the atmosphere. In some cases, electronic circuitry 1825 may include a phase shift circuit which can slightly advance or delay the inactivation of the aerosol generator, if desired.

5 [0121] When the flow rate through the Omron flow sensor returns to 0.2 L/min during inhalation, the output voltage of the Omron flow sensor returns to 2.31 VDC. Since this voltage is characteristic of the inhalation phase of the patient's respiratory cycle, it may be used by electronic circuitry 1825 as a signal to turn on the aerosol generator again so that the introduction of aerosolized medicament into the respiratory circuit of the CPAP system is  
10 resumed during inhalation. The cycle of turning the nebulizer on and off depending on what phase of the patient's respiratory cycle is occurring may be repeated during the period that the CPAP system is used for respiratory treatment of the infant, thereby significantly reducing the amount of medicament needed for such treatment.

### EXAMPLE 2

15 [0122] Referring to Fig. 19, CPAP system 1900 was attached to a breathing simulation piston pump 1930 (commercially available from Harvard Apparatus, Holliston, MA 01746) to simulate an infant's breathing cycle. CPAP system 1900 included auxiliary circuit A comprising pressure valve 1938, disposable filter 1939 and flow sensor 1940 connected to respiratory circuit 1942 through tube 1943 in accordance with the present  
20 invention. A removable filter 1931 was placed at the inlet of pump 1930. An adapter 1932 with two orifices 1933 representing infant nares (Argyle nasal prong commercially available from Sherwood Medical, St. Louis, MO 63013) was connected to filter 31. Nebulizer 1937 (Aeroneb® Professional Nebulizer System commercially available from Aerogen, Inc., Mountain View, CA) was placed in respiratory circuit 1942 near adapter 1932 so as to deliver  
25 an aerosolized drug into the air flow passing through orifices 1933. During the operation of pump 1930, air containing the entrained aerosolized drug flowed back and forth through filter 1931, which collected the drug from the air flow. The amount of drug collected on filter 1931 after each test was measured by high-pressure liquid chromatography (HPLC) and compared to the total amount that was nebulized to provide a measure of the efficiency of  
30 aerosol delivery to the system.

[0123] Pump 1930 was set to infant ventilatory parameters with a tidal volume of 10 ml and a respiratory rate of 40 breaths per minute. A constant air flow 1934 of 10 L/min was

provided through CPAP inlet 1935 and resistance pressure regulator 1936 was set to generate a pressure of 5 cm H<sub>2</sub>O. Nebulizer 1937 was filled with 3 ml of a solution of albuterol sulfate ("albuterol"). In order to study the effect of synchronized nebulization (i.e., nebulization during inhalation only) versus continuous nebulization, two separate sets of 4 tests were conducted. In the first set of tests, nebulizer 1937 ran continuously during both the inhalation and exhalation cycles of pump 1930. In the second set of tests, the operation of nebulizer 1937 was stopped during the exhalation cycle of pump 1930 using the input from flow sensor 1940 in accordance with the present invention. After each test, the amount of albuterol collected on filter 1931 was measured by HPLC and compared with the amount of albuterol nebulized to obtain a percent efficiency. The results are summarized in Table 2 below:

**Table 2**Continuous Nebulization:

|    | <u>Test No.</u>     | <u>Efficiency</u> |
|----|---------------------|-------------------|
|    | 1                   | 26%               |
| 15 | 2                   | 24%               |
|    | 3                   | 22%               |
|    | 4                   | 27%               |
|    | Average Efficiency: | 24.75%            |

20 Synchronized Nebulization:

|    | <u>Test No.</u>     | <u>Efficiency</u> |
|----|---------------------|-------------------|
|    | 1                   | 40%               |
|    | 2                   | 44%               |
|    | 3                   | 51%               |
| 25 | 4                   | 43%               |
|    | Average Efficiency: | 44.5%             |

[0124] The above results demonstrate that synchronized nebulization according to the present invention may deliver an order of magnitude more albuterol through nasal prongs during CPAP than continuous nebulization.

5 [0125] The high efficiency of delivery of aerosolized medicaments according to the present invention is particularly valuable in respiratory therapies that utilize expensive or scarce medicaments, such as the aforementioned nCPAP treatment of iRDS using aerosolized surfactants. Since most surfactants are animal-based, the current supply is limited, and although synthetic surfactants are available, their manufacture is both inexact and expensive. In addition, the surfactant medicaments are typically high in viscosity and are difficult to  
10 deliver to the patient's respiratory system. The increased efficiency of the pressure-assisted breathing system of the present invention, and the smaller amount of medicament required for a treatment according to the present invention, can be a substantial advantage when such scarce and expensive medicaments are employed.

[0126] In a preferred embodiment, the nebulizer of the present invention has a  
15 reservoir capacity equal to a unit dose of medicament. As an example, one dose of a liquid phospholipid surfactant medicament is typically achieved by instilling about 100 mg of the surfactant into an infant's lung. However, the required aerosol dose appears to be considerably less. For example, animal researchers have determined that an inhaled dose of about 4.5 mg/kg of surfactant is sufficient to substantially improve oxygenation in animal  
20 models. This suggests that a sufficient unit dose of surfactant to deliver to the lungs of a 1 kg. infant in aerosolized form may be about 5-10 mg. Since liquid surfactant is typically dispensed in a dilute solution having a concentration of 25 mg/ml, about 2/5 ml (10/25 ml) of liquid surfactant may be required to obtain 10 mg of active surfactant. A neonate CPAP system may be designed according the present invention to deliver about 6-18% of the total  
25 aerosolized medicament to an infant's lungs with a normal breathing pattern. If, for example, the nebulizer efficiency is 10%, the amount of surfactant solution required in the nebulizer reservoir to deliver a unit dose of aerosolized surfactant would have to be increased by a factor of 10, i.e. 10 x 2/5 ml or 4 ml. Therefore, a nebulizer reservoir having a capacity of 4 ml may be sufficient to provide a unit dose of surfactant to a 1 kg infant in accordance with  
30 the present invention without the need to replenish the reservoir.

[0127] The unit dose and the corresponding nebulizer reservoir size may vary depending on the efficiency of the nebulizer, the weight of the patient and the amount of

surfactant needed. For example, if the infant in the above example weighs 3 kg, a unit dose (and corresponding reservoir size) would be about 12 ml of liquid surfactant (i.e. 3 kg x 4 ml/kg). Similarly, if 5 mg of active surfactant is needed in the above example, a unit dose would be about 2 ml of liquid surfactant (i.e. 5/25 ml x 10), and if the efficiency of the nebulizer in the above example is 15%, a unit dose would be about 2 2/3 ml (i.e. 2/5 ml x 100/15).

[0128] A nebulizer according to the present invention may administer a unit dose by aerosol in less than 20 minutes, and possibly in as little as 5 minutes. Aerosol generation can be continuous or phasic, and can be timed to titrated dose delivery rate over time; for example, a 4 ml maximum dose with nebulization for 1 second out of every 10, 20 or 30 seconds.

[0129] In one embodiment, the present invention is directed to a method of treating diseases involving surfactant deficiency (also known as “surfactant depletion syndromes”) or diseases involving surfactant dysfunction (also known as “surfactant dysfunction syndromes”). Such diseases include, but are not limited to, infant respiratory distress syndrome (iRDS), acute respiratory distress syndrome (ARDS), meconium aspiration syndrome (MAS), asthma, pneumonia (all kinds, including ventilator associated pneumonia), persistent pulmonary hypertension of the newborn (PPHN), congenital diaphragmatic hernia (CDH), sepsis, acute lung injury (ALI), bronchiolitis, COPD-chronic bronchitis, cystic fibrosis, lung transplantation diseases and respiratory syncytial virus (RSV). Since methods for treating such diseases generally involve the administration to the patient’s lung of a naturally-occurring (animal-derived) or synthetic (engineered) lung surfactant, the subject methods are sometimes referred to in the art as “surfactant (replacement) therapies”.

[0130] Generally, the method of the present invention comprises the steps of providing a liquid lung surfactant composition; aerosolizing the lung surfactant composition with an aerosol generator, preferably a vibrating aperture-type aerosol generator, to form an aerosolized lung surfactant (also referred to herein as “surfactant aerosol”); and introducing the surfactant aerosol into the gas flow within a circuit of a pressure-assisted breathing system such as described above, preferably a CPAP system, which is coupled to the patient’s respiratory system, whereby a therapeutically effective amount of surfactant is delivered to the patient’s lungs.

[0131] Lung surfactants are complex and highly surface-active materials, generally composed of lipids and/or proteins. Their principal property is to reduce the surface tension in the lungs and protect the lungs from injuries and infections caused by inhaled particles and microorganisms. The composition of naturally-occurring lung surfactant may vary with various factors such as species, age, and general health of the subject. Therefore, the definition of what a natural lung surfactant is or what should be included in a synthetic lung surfactant composition is dependent on the situation. Surfactant isolated from lung lavage of healthy mammals contain about 10% protein and 90% lipids, of which about 80% are phospholipids and about 20% are neutral lipids, including about 10% unesterified cholesterol.

10 [0132] Lung surfactants are typically high in viscosity and difficult to administer. The lung surfactant may be admixed with a pharmaceutically acceptable diluent, e.g. water or a saline solution, to provide a liquid surfactant composition. In the practice of the present invention, liquid lung surfactant compositions are preferred, for example, liquid surfactant compositions having a concentration of from 20-120 mg/ml, preferably 20-80 mg/ml.

15 Commercially available lung surfactants may already be presented as ready-mixed liquids, and are contemplated as also being useful in the present invention. Examples of commercially available lung surfactant compositions are natural surfactant compositions marketed under the trademarks CUROSURF (Chiesi Pharmaceuticals), ALVEOFACT (Boehringer Ingelheim) and SURVANTA (Abbott Laboratories); and synthetic surfactant

20 compositions marketed under the trademarks EXOSURF (Glaxo Wellcome) and SURFAXIN (Discovery Laboratories).

[0133] Aerosol generators permit aerosol formation in a wide variety of ways, e.g. single-substance jet, atomization by centrifugal force, condensation, vaporization, dispersion, ultrasound, jet nebulization, etc. As mentioned, vibrating aperture-type aerosol generators are preferred in the practice of the present invention. Vibrating aperture-type aerosol generators comprise a unique dome-shaped aperture plate containing over 1000 precision-formed tapered holes, surrounded by a vibrational element. When energy is applied, the aperture plate vibrates over 100,000 times per second. This rapid vibration causes each aperture to act as a micropump, drawing liquid in contact with the plate through the holes to

25 form consistently sized droplets. The result is a low-velocity liquid aerosol optimized for maximum lung deposition. Preferred vibrating aperture-type aerosol generators aerosolize liquids very efficiently, leaving virtually no residual liquid, and operate without using propellants or generating heat, thereby preserving a surfactant's molecular integrity.

30

Representative vibrating aperture-type aerosol generators are described in detail in the aforementioned U.S. Pat. Nos. 5,164,740; 5,586,550; 5,758,637; and 6,085,740, the entire disclosures of which are incorporated herein by reference.

[0134] Apertures in the aperture plate may be shaped to enhance the rate of droplet production while maintaining droplets within a specified size range, e.g. as described in co-  
5 pending U.S. Patent Application Ser. No. 09/822,573, filed March 30, 2001, incorporated by reference herein. Such apertures may be particularly useful for aerosolizing viscous surfactant compositions in accordance with the present invention. Preferred vibrating aperture-type aerosol generators are commercially available from Aerogen, Inc., Mountain  
10 View, California.

[0135] In general, the apparatus described above comprise a nebulizer containing an aerosol generator that is positioned so as to introduce the surfactant aerosol produced by the aerosol generator directly into the gas flow within a circuit of a pressure-assisted breathing system coupled to the subject patient's respiratory system.

[0136] As described above, CPAP systems support spontaneous breathing by the patient and typically comprise a pressure-generating circuit for maintaining a positive pressure within the system, a patient interface device coupled to a patient's respiratory system and a respiratory circuit for providing gas communication between the pressure-generating circuit and the patient interface device. CPAP systems utilize a constant positive pressure  
20 during inhalation to increase and maintain lung volumes and to decrease the work by a patient during spontaneous breathing. The positive pressure effectively dilates the airway and prevents its collapse. Use of such CPAP systems in combination with a vibrating aperture-type aerosol generator considerably enhances the efficiency of delivery of the surfactant aerosol to the patient's lungs.

[0137] Vibrating aperture-type aerosol generators have several aerosol delivery characteristics that make them uniquely suited for aerosolized medicaments in general, and in particular, for surfactant replacement therapy in accordance with the present invention. Vibrating aperture-type aerosol generators are extremely efficient at producing aerosol particles, aerosolizing nearly 100% of the liquid surfactant that comes into direct contact with  
30 the aperture plate. This characteristic virtually eliminates one source of surfactant loss in the system.

[0138] In addition, vibrating aperture-type aerosol generators deliver a low-velocity aerosol of precisely defined average particle size. Aerosol particle size distribution and drug output can be modified by changing aperture size in the vibrating plate to meet the needs of a particular patient or situation. Preferably, aerosol particle size is adjusted to less than 5  $\mu\text{m}$  mass median aerodynamic diameter (MMAD), and most preferably 1-3  $\mu\text{m}$  MMAD, so as to maintain optimum efficiency. These smaller aerosol particles contribute to enhanced delivery and peripheral pulmonary deposition of the surfactant aerosol, thereby reducing aerosol loss in the system. Vibrating aperture-type aerosol generators also do not create significant heat or shear that can change the characteristics and properties of the surfactant composition.

[0139] Aerosol output (flow rate) for vibrating aperture-type aerosol generators of the present invention is considerably higher than other types of nebulizers, and as a result, treatment times for the method of the present invention are considerably shorter than conventional surfactant therapies. For example, a therapeutic amount ("unit dose") of aerosolized surfactant deposited in a patient's lung may be in the range of 2-400 mg. In the practice of the invention, liquid surfactant composition may comprise a solution having a concentration of 20-120 mg/ml. Flow rates for vibrating aperture-type aerosol generators of the present invention are in the range of 0.1-0.5 ml/min, which is considerably higher than the flow rate of comparable aerosol generators, e.g. jet nebulizers typically have a flow rate of less than 0.2 ml/min. If a unit dose of aerosolized surfactant for treatment of surfactant deficiency in a 1 kg neonate is 40 mg (e.g. 1.0 ml of a 40 mg/ml liquid surfactant composition), the method of the present invention using a vibrating aperture-type aerosol generator with a flow rate of 0.4 ml/min will generate 90% of the unit dose in less than 3 minutes, whereas a comparable jet nebulizer would require a fill volume of 3 ml and may deliver the same unit dose in more than 6 minutes. The lower dose requirement and shorter treatment times achieved by the method of the present invention considerably improves the likelihood that the patient will receive benefit prior to direct instillation, or require a treatment protocol with a much lower amount of liquid surfactant placed in the nebulizer. In preferred embodiments, the delivery rate of active surfactant delivered to the lungs of the patient is preferably in the range of 2-800 mg/hr.

[0140] In preferred embodiments, the small diameter and size of the reservoir holding the liquid surfactant composition in the nebulizer having a vibrating aperture-type aerosol generator allows the nebulizer to be placed directly into the respiratory circuit without adding a large "rebreathed volume". For example, preferred vibrating aperture-type aerosol

generators of the present invention may not add more than about 5 ml of rebreathed volume. As used herein, "rebreathed volume" is the volume of gas required in the system to produce the desired amount of aerosolized surfactant in a confined space. Pneumatic and jet nebulizers typically have reservoir volumes of 6-20 ml, so that placement of one of these  
5 nebulizers in the respiratory circuit of a CPAP system between the main flow and the patient's airway adds an undesirable increase in rebreathed volume in the circuit. This increase in rebreathed volume has a dilutive effect on the aerosolized surfactant and reduces the efficiency of the delivery system.

[0141] In one preferred embodiment that may be used for any aerosolized  
10 medicament, and is particularly useful in surfactant therapy, surfactant aerosol from a vibrating aperture-type aerosol generator may be generated into a plenum chamber of 5-400 ml internal volume located outside the direct breathing circuit (e.g. respiratory circuit R in Fig. 20). The plenum chamber allows a concentration of surfactant aerosol to be collected that is higher than the concentration that is generated by the aerosol generator alone, prior to  
15 being discharged into the respiratory circuit. It has been found that the use of the plenum chamber provides an inhaled mass of aerosol surfactant that is comparable to a breath actuated nebulizer, e.g. an inhaled mass of 80% of the surfactant provided to the nebulizer, in less than 25% of the time required for the breath actuated nebulizer to deliver the same inhaled mass.

[0142] As one example of apparatus using a plenum chamber according to the present invention, Fig. 20 illustrates a CPAP system 2000, wherein a main gas flow 2071 is carried in pressure-generating circuit P and respiratory flow 2072 is carried in respiratory circuit R from circuit P to patient 2073. A vibrating aperture-type aerosol generator 2074 is located above plenum chamber 2075 so as to collect surfactant aerosol 2076 generated by aerosol generator  
25 2074 in plenum chamber 2075. Plenum chamber 2075 is sized so that the plume of surfactant aerosol 2076 does not impact the wall or bottom of plenum chamber 2075, thereby reducing any resulting impactive losses of surfactant aerosol. A controlled secondary gas flow 2077 may be introduced into plenum chamber 2075 through inlet 2078 to drive a flow 2079 of concentrated surfactant aerosol from plenum chamber 2075 into respiratory flow 2072  
30 through conduit 2080, which intersects respiratory circuit R at a point 2081 proximal to the airway of patient 2073. Conduit 2080 may have a one-way valve or solenoid 2082 that controls flow 2079 to respiratory circuit R so as to isolate the volume of gas in plenum chamber 2075 from being rebreathed volume; i.e. so that gas flow 2079 from plenum

chamber 2075 is a small percentage of respiratory flow 2072. Flow 2079 may be continuous or intermittent, with surfactant aerosol being introduced into respiratory circuit R during a discrete part of the respiratory cycle.

[0143] As the result of the unique combination of an aerosol generator, preferably a vibrating aperture-type aerosol generator, with a pressure-assisted breathing system, preferably a CPAP system having one or more of the efficiency-improving features set forth above and in the aforementioned co-pending patent applications, from 10-80% of the lung surfactant may be inhaled by the patient in the method of the present invention. In particularly preferred embodiments, greater than 30% of the lung surfactant may be delivered to the patient's lungs.

[0144] The following example will illustrate the increase in efficiency resulting from the practice of the present invention, but the present invention is not limited to the details set forth therein. For example, the following example is not limited to the delivery of any particular aerosolized medicament.

### EXAMPLE 3

[0145] Figs. 21a and 21b are diagrams of nCPAP systems 2100 and 2200 that may be used for measuring aerosol delivery with a simulated infant breathing pattern during nCPAP. The nCPAP systems 2100 and 2200 comprise breath simulators 2101 and 2201, consisting of adapters with orifices representing infant size nasal prongs 2102 and 2202 (Argyle; n=3) connected to absolute filters 2103 and 2203, attached to reciprocating pump animal ventilators 2104 and 2204 (Harvard Apparatus) to form a nCPAP system. Lung simulators 2100 and 2200 may be set to infant ventilatory parameters (VT 10 ml, respiratory rate 40 breaths per minute). A constant oxygen flow of 10 L/min from ventilators 2104 and 2204 may be used to generate a CPAP of 5 cm H<sub>2</sub>O regulated by threshold resistors 2105 and 2205.

[0146] In both systems, a liquid medicament (0.5 mL of 0.5% albuterol sulfate) may be aerosolized with a nebulizer 2106 and 2206 placed in a circuit of the nCPAP system. Drug may be collected on filters 2103 and 2104 placed distal to the nasal prongs 2102 and 2202, and the collected drug may be assayed using High Pressure Liquid Chromatography (HPLC). Care should be taken to assure that only aerosol reaches the filters, and that condensate remains in the breathing circuit, nebulizer or adapter. This may be accomplished by tilting the system so that nebulizers 2106 and 2206 are lower than respective filter elements 2103 and 2203. The efficiency of the nCPAP system may then be measured by

expressing the amount of drug collected on the filter as a percentage of the drug dose placed in the nebulizer.

[0147] In Test 1, nebulizer 2106 may comprise a standard jet nebulizer placed so as to discharge aerosolized medicament into the main air flow in the pressure-generating circuit of nCPAP system 2100, as shown in Fig. 21a. In Test 2, nebulizer 2106 may comprise a nebulizer having a vibrating aperture-type aerosol generator (Aeroneb® Pro from Aerogen, Inc.), also placed so as to discharge aerosolized medicament into the main air flow in the pressure-generating circuit of nCPAP system 2100. In Test 3, nebulizer 2206 may comprise a small, lightweight nebulizer designed to be suitable for placement proximal to an infant's airway and employing a vibrating aperture-type aerosol generator [Pulmonary Drug Deliver System (PDDS) nebulizer from Aerogen, Inc.], in accordance with one embodiment of the present invention. As shown in Fig. 21b (and in Fig. 2), nebulizer 2206 may be placed so as to continuously discharge aerosolized medicament into the lower air flow in the respiratory circuit of nCPAP system 2200 between the main air flow and the simulated patient airway, in accordance with another embodiment of the present invention. In Test 4, aerosolized medicament may be generated intermittently from PDDS nebulizer 2206 with aerosol generation interrupted during exhalation, in accordance with another embodiment of the present invention.

[0148] As illustrated in Fig. 22, when the Aeroneb® Pro nebulizer incorporating a vibrating aperture-type aerosol generator of the present invention is placed in the pressure-generating circuit of the nCPAP system, it is typically more efficient than a standard jet nebulizer. In addition, when the PDDS nebulizer with a vibrating aperture-type aerosol generator of the present invention is placed between the primary gas flow through the nCPAP system and the simulated patient airway, it typically delivers an order of magnitude more medicament through the nasal prongs to the filter. For example, PDDS nebulizer 2206 in the position shown in Fig. 21b typically results in deposition of  $26 \pm 9\%$  (mean + standard deviation) of the medicament dose placed in the nebulizer with continuous generation of aerosol, and  $40 \pm 9\%$  of the medicament dose placed in the nebulizer with intermittent generation of aerosol. During continuous generation of aerosol, there is typically a visible amount of aerosol that is driven from the nebulizer into the expiratory limb of the pressure-generating circuit in the nCPAP system. Interrupting aerosol generation during expiration in accordance with one aspect of the present invention eliminates the visual losses and may result in close to a 50% improvement in the percentage of dose inhaled. The relatively low

deposition achieved in Test 2, even with a higher efficiency vibrating aperture-type aerosol generator nebulizer, is believed to be due in large part to the dilution of the aerosol output of the nebulizer by the high total flow of gas passing through the nebulizer when the nebulizer is placed in the position shown in Fig. 21a.

5    **[0149]**       As the above examples demonstrate, a nebulizer incorporating a vibrating aperture-type aerosol generator in accordance with the present invention is generally more efficient than a standard jet nebulizer when used to deliver aerosolized surfactant and other medicaments to a patient's airway through a typical CPAP system. In one embodiment of the invention, that efficiency can be even more dramatically improved by placing a particularly  
10   preferred small nebulizer including vibrating aperture-type aerosol generator in the lower-flow respiratory circuit of the CPAP system, most preferably in close proximity to the patient's airway. In still another embodiment of the invention, even more efficiency may be achieved by generating the aerosol intermittently, for example, only during inhalation and interrupting generation during exhalation.

15   **[0150]**       It is understood that while the invention has been described above in connection with preferred specific embodiments, the description and drawings are intended to illustrate and not limit the scope of the invention, which is defined by the appended claims and their equivalents.

WHAT IS CLAIMED IS

- 1           1.       A pressure-assisted breathing system comprising:  
2                   a pressure-generating circuit for maintaining a positive pressure within the  
3 system;  
4                   a patient interface device coupled to a patient's respiratory system;  
5                   a respiratory circuit for providing gas communication between the pressure-  
6 generating circuit and the patient interface device; and  
7                   a nebulizer coupled to the respiratory circuit.
- 1           2.       A system according to claim 1 wherein the pressure-generating circuit  
2 comprises a conduit that couples a flow generator with a pressure-regulating device.
- 1           3.       A system according to claim 1 wherein the pressure-generating circuit  
2 comprises a first flexible tube and the respiratory circuit comprises a second flexible tube,  
3 and wherein the second flexible tube has a smaller diameter than the first flexible tube.
- 1           4.       A system according to claim 3 wherein the second flexible tube is a silicone  
2 tube having an outside diameter of 5 mm or less.
- 1           5.       A system according to claim 1 wherein the nebulizer comprises a reservoir for  
2 holding a liquid medicament to be delivered to the patient's respiratory system, a vibrating  
3 aperture-type aerosol generator for aerosolizing the liquid medicament and a connector for  
4 connecting the nebulizer to the respiratory circuit so as to entrain the aerosolized medicament  
5 from the aerosol generator into the gas flowing through the respiratory circuit.
- 1           6        A system according to claim 5 wherein the reservoir has a capacity equal to  
2 one unit dose of medicament.
- 1           7.       A system according to claim 6 wherein the reservoir has a capacity of 4 ml or  
2 less.

1           8.       A system according to claim 5 wherein the nebulizer has a net weight of 5 gms  
2 or less.

1           9.       A system according to claim 8 wherein the nebulizer produces 5 decibels or  
2 less of sound pressure.

1           10.      A system according to claim 5 wherein the aerosol generator has a weight of  
2 about 1 gm.

1           11.      A system according to claim 1 wherein the nebulizer is located in the direct  
2 vicinity of the patient's nose, mouth or artificial airway.

1           12.      A system according to claim 11 wherein the respiratory circuit comprises a gas  
2 conduit contained within the patient interface device and the nebulizer is integrated with the  
3 patient interface device.

1           13.      A system according to claim 1 wherein the patient interface device comprises  
2 nasal prongs, a mask, nasopharyngeal prongs, a nasopharyngeal tube, a tracheotomy tube or  
3 an endotracheal tube.

1           14.      Apparatus for the delivery of an aerosolized medicament to a patient  
2 comprising:

3                   a first gas conduit connecting a gas flow generator to a pressure-regulating  
4 device to provide a first high-volume gas flow for generating a continuous positive airway  
5 pressure;

6                   a patient interface device coupled to a patient's respiratory system;

7                   a second gas conduit connecting the first gas conduit to the patient interface  
8 device for providing a second gas flow to the patient's respiratory system that is lower  
9 volume than the first gas flow; and

10                  a nebulizer coupled to the second gas conduit for emitting an aerosolized  
11 medicament into the second gas flow.

1           15.      Apparatus according to claim 14 wherein the second gas conduit has an  
2 outside diameter less than the first gas conduit.

1           16.     Apparatus according to claim 15 wherein the second gas conduit is a flexible  
2 silicone tube having an outside diameter less than 5 mm.

1           17.     Apparatus according to claim 14 wherein the nebulizer has a net weight less  
2 than 5 gm and produces less than 5 decibels of sound pressure.

1           18.     Apparatus according to claim 17 wherein the nebulizer comprises a reservoir  
2 having a capacity equal to one unit dose of medicament.

1           19.     A CPAP device comprising:  
2                   a source of pressurized gas;  
3                   a mask coupled to the respiratory system of a patient;  
4                   a flexible tube connecting the source of pressurized gas to the mask; and  
5                   a nebulizer coupled to the mask and adapted to emit aerosolized medicament  
6 in close proximity to the patient's nose and/or mouth.

1           20.     A method of respiratory therapy comprising the steps of:  
2                   providing a pressure-assisted breathing system having a pressure-generating  
3 circuit and a respiratory circuit coupled to a patient interface device, the pressure-generating  
4 circuit having a higher volume flow of gas than the respiratory circuit; and  
5                   introducing an aerosolized medicament only into the flow of gas in the  
6 respiratory circuit to deliver the medicament to the patient's respiratory system.

1           21.     A method according to claim 20 wherein the aerosolized medicament is  
2 introduced by a vibrating aperture-type nebulizer coupled to the respiratory circuit.

1           22.     A method according to claim 21 wherein the nebulizer comprises a reservoir  
2 having a capacity equal to one unit dose of medicament and substantially all of the contents  
3 of the reservoir is delivered to the patient's respiratory system without the need to replenish  
4 the reservoir.

1           23.     A method according to claim 22 wherein the dose is 4 ml or less of  
2 medicament.

1           24.     A method of delivering a surfactant medicament to a patient's respiratory  
2 system which comprises the steps of:

3           providing a pressure-assisted breathing system having a pressure-generating circuit, a  
4 respiratory circuit coupled to a patient interface device and a vibrating aperture-type  
5 nebulizer coupled to the respiratory circuit;

6           introducing a liquid surfactant into the nebulizer;

7           aerosolizing the surfactant in the nebulizer ; and

8           entraining the aerosolized surfactant into the respiratory circuit, whereby the patient  
9 breathes the aerosolized surfactant through the patient interface device.

1           25.     The method of claim 24 wherein the surfactant is a phospholipid.

1           26.     The method of claim 24 wherein 6-18% of the aerosolized surfactant is  
2 delivered to the patient.

1           27.     The method of claim 24 wherein one unit dose of medicament is introduced  
2 into the nebulizer and the entire dose is delivered to the patient.

1           28.     The method of claim 24 wherein the dose is equal to 10 mg or less of  
2 surfactant.

1           29.     A pressure-assisted breathing system comprising:  
2           an air flow generator;  
3           a circuit connecting the air flow generator to a patient's respiratory system; and  
4           an aerosol generator for emitting aerosol particles into the circuit;  
5           wherein the circuit defines a path for the emitted aerosol particles having a  
6 change in angle of no greater than 15°.

1           30.     A system according to claim 1 wherein the change in path angle is no greater  
2 than 12°.

1           31.     A system according to claim 1 wherein the circuit defines a straight path for  
2 the emitted aerosol particles.

1           32.     A system according to claim 1 wherein the circuit comprises a ventilator  
2 system.

1           33.     A system according to claim 1 wherein the circuit comprises a CPAP system.

1           34.     A system according to claim 1 wherein the aerosol generator comprises a  
2 nebulizer.

1           35.     A system according to claim 6 wherein the nebulizer comprises a reservoir for  
2 holding a liquid medicament to be delivered to the patient's respiratory system and a vibrating  
3 aperture-type aerosol generator for aerosolizing the liquid medicament.

1           36.     A system according to claim 7 wherein the reservoir has a capacity equal to  
2 one unit dose of medicament.

1           37.     A system according to claim 7 wherein the reservoir is rotatable to maintain  
2 optimum gravity feeding of liquid medicament to the aerosol generator during varied  
3 positions of the patient and/or the other components of the circuit.

1           38.     A system according to claim 1 wherein the circuit comprises a ventilator  
2 circuit having a inspiratory tube and a expiratory tube converging on a junction device  
3 connected to a respiratory circuit, the junction device having: (a) a tubular main body  
4 member having a straight longitudinal lumen extending from a first end attached to the  
5 inspiratory tube to a second end attached to the respiratory circuit; and (b) a tubular branch  
6 member having a lumen extending from the longitudinal lumen to a third end attached to the  
7 expiratory tube.

1           39.     A system according to claim 10 wherein the aerosol generator is positioned to  
2 emit aerosol particles into the inspiratory tube.

1           40.     A system according to claim 10 wherein the aerosol generator is positioned to  
2 emit aerosol particles into the longitudinal lumen of the junction device.

1           41.     A system according to claim 1 wherein said circuit comprises a ventilator  
2 circuit and a patient interface device attached to the ventilator circuit.

1           42.     A system according to claim 13 wherein the aerosol generator is a nebulizer  
2 positioned to emit aerosol particles into the circuit between the ventilator circuit and the  
3 patient interface device.

1           43.     A system according to claim 14 wherein the aerosol generator is located in the  
2 direct vicinity of the patient's nose, mouth or artificial airway.

1           44.     A system according to claim 13 wherein the patient interface device comprises  
2 a tubular inlet section connected to a pair of nasal cannula by a tubular forked section,  
3 wherein a lumen in the inlet section is in fluid communication with lumens in each prong of  
4 the forked section so as to provide two substantially parallel paths for aerosol particles  
5 passing there through, each path having a change of angle no greater than 15°.

1           45.     A junction device for connecting the tubes of a pressure-assisted breathing  
2 system, said junction device comprising:

3                 a tubular main body member having a substantially straight longitudinal lumen  
4 extending its entire length for conducting a first flow of gas carrying aerosol particles from a  
5 first tube attached to one end of the longitudinal lumen to a second tube attached to the  
6 opposite end of the longitudinal lumen; and

7                 a tubular branch member in fluid communication with the longitudinal lumen  
8 at one end of the branch member and attached to a third tube at the opposite end of the branch  
9 member for conducting a second flow of gas substantially free of said aerosol particles into or  
10 out of the longitudinal lumen.

1           46.     A junction device according to claim 17 further comprising:

2                 a nebulizer port for attaching a nebulizer to the main body member so as to  
3 introduce said aerosol particles into the first flow of gas.

1           47.     A patient interface device for the delivery of aerosol particles to a patient  
2 comprising:

3                 a tubular inlet section having a longitudinal lumen;

4 a pair of nasal cannula; and  
5 a tubular forked section connecting the inlet section to the nasal cannula;  
6 wherein the longitudinal lumen is in fluid communication with lumens in each prong of the  
7 forked section so as to define two substantially parallel paths for the aerosol particles, each  
8 path having a change of angle no greater than 15°.

1 48. An nCPAP system comprising:

2 (a) a pressure-generating circuit;

3 (b) a patient interface device connected to the pressure-generating circuit for  
4 conducting a pressurized flow of gas from the pressure-generating circuit to a patient; said  
5 patient interface device comprising:

6 (i) a tubular inlet section having a longitudinal lumen;

7 (ii) a pair of nasal cannula; and

8 (iii) a tubular forked section connecting the inlet section to the nasal  
9 cannula; wherein the longitudinal lumen is in fluid communication with  
10 lumens in each prong of the forked section so as to conduct the flow of gas  
11 along two substantially parallel paths to the nasal cannula, each path having a  
12 change of angle no greater than 15°; and

13 (c) a nebulizer positioned between the pressure-generating circuit and the  
14 patient interface device so as to emit aerosol particles of medicament into the flow of  
15 gas to the patient interface device.

1 49. A method of delivering an aerosolized medicament to a subject's respiratory  
2 system comprising the steps of:

3 attaching the subject to a pressure-assisted breathing system comprising  
4 an air flow generator; a circuit connecting the air flow generator to the subject's respiratory  
5 system; and an aerosol generator for emitting aerosol particles of medicament into the circuit;  
6 wherein the circuit defines a path for the emitted aerosol particles having a change in angle of  
7 no greater than 15°; and

8 administering the aerosol particles of medicament to said subject via the  
9 pressure-assisted breathing system.

1 50. A method according to claim 21 wherein the pressure-assisted breathing  
2 system is a mechanical ventilator system comprising a ventilator circuit having an inspiratory

3 tube and a expiratory tube converging on a junction device connected to a respiratory circuit  
4 comprising a patient interface device; the junction device comprising:

5 (a) a tubular main body member having a straight longitudinal lumen  
6 extending from a first end attached to the inspiratory tube to a second end attached to the  
7 respiratory circuit; and

8 (b) a tubular branch member having a lumen extending from the longitudinal  
9 lumen to a third end attached to the expiratory tube.

1 51. A method according to claim 22 wherein the aerosol particles of medicament  
2 are introduced into the inspiratory tube of the ventilator circuit or into the longitudinal lumen  
3 of the junction device.

1 52. A method according to claim 22 wherein the aerosol particles of medicament  
2 are introduced into the respiratory circuit in direct proximity to the patient's mouth, nose or  
3 artificial airway.

1 53. A method according to claim 22 wherein the subject is a patient exhibiting one  
2 or more symptoms of infection and the medicament is an antibiotic.

1 54. A method according to claim 21 wherein the pressure-assisted breathing  
2 system is a nCPAP system comprising:

3 (a) a pressure-generating circuit;  
4 (b) a patient interface device connected to the pressure-generating circuit for  
5 conducting a pressurized flow of gas from the pressure-generating circuit to a patient; said  
6 patient interface device comprising:

7 (i) a tubular inlet section having a longitudinal lumen;  
8 (ii) a pair of nasal cannula; and  
9 (iii) a tubular forked section connecting the inlet section to the nasal  
10 cannula; wherein the longitudinal lumen is in fluid communication with  
11 lumens in each prong of the forked section so as to conduct the flow of gas  
12 along two substantially parallel paths to the nasal cannula, each path having a  
13 change of angle no greater than 15°; and

14 (c) a nebulizer positioned between the pressure-generating circuit and the  
15 patient interface device so as to emit aerosol particles of medicament into the flow of gas to  
16 the patient interface device.

1 55. A method according to claim 26 wherein the patient is an infant exhibiting one  
2 or more symptoms of infant respiratory distress syndrome and the medicament is a surfactant.

1 56. A method of treating infant respiratory distress syndrome comprising the steps  
2 of:

3 (a) attaching the infant to a nCPAP system comprising:

4 (i) a pressure-generating circuit;

5 (ii) a respiratory circuit that conducts a pressurized gas flow from the  
6 pressure-generating circuit to a nasal cannula patient interface device,  
7 and

8 (iii) a vibrating aperture-type nebulizer in fluid communication with  
9 the respiratory circuit so as to introduce aerosol particles of surfactant  
10 medication into the pressurized gas flow in the respiratory circuit;  
11 wherein the nasal cannula interface device defines a path for the  
12 emitted aerosol particles that has a change in angle no greater than 15°;  
13 and

14 (b) administering the aerosol particles of surfactant medicament to the infant  
15 via the nasal cannula interface device.

1 57. A pressure-assisted breathing system comprising:

2 a pressure-generating circuit for maintaining a positive pressure within the  
3 system;

4 a patient interface device coupled to a patient's respiratory system;

5 a respiratory circuit for providing gas communication between the pressure-  
6 generating circuit and the patient interface device;

7 means for introducing aerosol particles into the gas flow in the respiratory  
8 circuit; and

9 means for discontinuing the introduction of aerosol particles into said  
10 respiratory circuit gas flow when the patient exhales.

1           58.     A system according to claim 1 wherein the means for discontinuing the  
2 introduction of aerosol particles comprises a flow sensor disposed in an auxiliary circuit in  
3 fluid communication with the respiratory circuit and electronically coupled with the means  
4 for introducing the aerosol particles into the respiratory circuit flow, wherein said flow sensor  
5 is adapted to detect a change in the volumetric flow rate of gas in the auxiliary circuit when  
6 the patient exhales and send a first electronic signal that causes the means for introducing  
7 aerosol particles to turn off upon such detection.

1           59.     A system according to claim 2 wherein the flow sensor is further adapted to  
2 detect a change in the volumetric flow rate of gas in the auxiliary circuit when the patient  
3 stops exhaling and send a second electronic signal that causes the means for introducing  
4 aerosol particles to turn on upon such detection.

1           60.     A system according to claim 2 wherein the auxiliary circuit further comprises  
2 a pressure valve for reducing the flow of gas through the flow sensor.

1           61.     A system according to claim 2 wherein the auxiliary circuit further comprises  
2 a disposable filter for trapping contaminants in the flow of gas before it passes through the  
3 flow sensor.

1           62.     A system according to claim 1 wherein the means for introducing aerosol  
2 particles comprises a nebulizer.

1           63.     A system according to claim 6 wherein the nebulizer comprises a reservoir for  
2 holding a liquid medicament to be delivered to the patient's respiratory system, a vibrating  
3 aperture-type aerosol generator for aerosolizing the liquid medicament and a connector for  
4 connecting the nebulizer to the respiratory circuit so as to entrain the aerosolized medicament  
5 from the aerosol generator into the gas flowing through the respiratory circuit.

1           64.     CPAP apparatus for the delivery of an aerosolized medicament to a patient's  
2 respiratory system comprising:

3                   a pressure-generating circuit that maintains continuous positive pressure  
4 within the system;

5                   a patient interface device coupled to a patient's respiratory system;

6 a respiratory circuit that provides gas communication between the pressure-  
7 generating circuit and the patient interface device;

8 a nebulizer that introduces aerosolized medicament into the gas flow in the  
9 respiratory circuit;

10 a flow sensor disposed in an auxiliary circuit in gas communication with the  
11 respiratory circuit; and

12 electronic circuitry connecting the flow sensor to the nebulizer, whereby the  
13 flow sensor sends a first electronic signal that causes the nebulizer to turn off when the flow  
14 sensor detects an increase in the volumetric flow rate of gas in the auxiliary circuit as the  
15 result of the patient commencing exhalation.

1 65. Apparatus according to claim 8 wherein the flow sensor sends a second signal  
2 that causes the nebulizer to turn on when the flow sensor detects a decrease in the volumetric  
3 flow rate of gas in the auxiliary circuit as the result of the patient ceasing exhalation.

1 66. Apparatus according to claim 9 wherein each signal is a certain output voltage  
2 generated by the flow sensor.

1 67. Apparatus according to claim 8 further comprising a valve for regulating the  
2 flow of gas to the flow sensor.

1 68. Apparatus according to claim 11 wherein the flow sensor has a flow range of 0  
2 to 1 L/min and the valve regulates the flow of gas to about the middle of said range.

1 69. Apparatus according to claim 8 further comprising a disposable filter for  
2 trapping contaminants prior to passing through the flow sensor.

1 70. Apparatus according to claim 8 wherein the nebulizer comprises a reservoir  
2 for holding a liquid medicament to be delivered to the patient's respiratory system, a  
3 vibrating aperture-type aerosol generator for aerosolizing the liquid medicament and a  
4 connector for connecting the nebulizer to the respiratory circuit so as to entrain the  
5 aerosolized medicament from the aerosol generator into the gas flowing through the  
6 respiratory circuit.

1 71. Apparatus according to claim 14 wherein said liquid medicament is a  
2 surfactant.

1           72.     In a CPAP system comprising a respiratory circuit whereby an aerosolized  
2 medicament is delivered to a patient's respiratory system, the improvement which comprises  
3 a flow sensor disposed in an auxiliary circuit that is in fluid communication with the  
4 respiratory circuit, said flow sensor being adapted to detect an increase in the volumetric flow  
5 rate of gas in the auxiliary circuit when the patient exhales and stop the delivery of  
6 aerosolized medicament in response thereto.

1           73.     A CPAP system according to claim 16 wherein the flow sensor is further  
2 adapted to detect a decrease in the volumetric flow rate of gas in the auxiliary circuit when  
3 the patient stops exhaling and resume the delivery of aerosolized medicament in response  
4 thereto.

1           74.     A method of respiratory therapy comprising the steps of:  
2                   providing a CPAP system having a respiratory circuit coupled to a patient's  
3 respiratory system; and  
4                   introducing an aerosolized medicament into the respiratory circuit only when  
5 the patient inhales.

1           75.     A method according to claim 18 wherein the aerosolized medicament is  
2 introduced into the respiratory circuit by a nebulizer.

1           76.     A method according to claim 19 wherein the nebulizer is electronically  
2 connected to a flow sensor disposed in an auxiliary circuit that is in fluid communication with  
3 the respiratory circuit, the flow sensor causing the nebulizer to turn off when the flow sensor  
4 detects a change in the volumetric flow rate of gas in the auxiliary circuit that corresponds to  
5 the presence of an expiratory flow in the respiratory circuit, and to turn on when the flow  
6 sensor detects a change in the volumetric flow rate of gas in the auxiliary circuit that  
7 corresponds to the absence of an expiratory flow in the respiratory circuit.

1           77.     A method of delivering an aerosol to a patient's respiratory system which  
2 comprises the steps of :  
3                   providing a CPAP system having a pressure-generating circuit, a respiratory  
4 circuit coupled to a patient interface device and a nebulizer coupled to the respiratory circuit;  
5                   introducing a liquid into the nebulizer;

6 turning on the nebulizer during patient inhalation so that aerosol particles  
7 formed by the nebulizer are introduced into the respiratory circuit and inhaled by the patient  
8 through the patient interface device; and

9 turning off the nebulizer during patient exhalation so that aerosol particles  
10 formed by the nebulizer are not introduced into the respiratory circuit during such exhalation.

1 78. The method according to claim 21 wherein a flow sensor disposed in an  
2 auxiliary circuit in gas communication with the respiratory circuit causes the nebulizer to turn  
3 on and off depending on the changes in volumetric flow rate of gas that the flow sensor  
4 detects in the auxiliary circuit.

1 79. A method of treating a disease involving surfactant deficiency or dysfunction  
2 in a patient's lungs, comprising the steps of:

3 providing a liquid lung surfactant composition;  
4 aerosolizing the lung surfactant composition with a vibrating aperture-type  
5 aerosol generator to form a surfactant aerosol; and  
6 introducing the surfactant aerosol into the gas flow within a circuit of a  
7 pressure-assisted breathing system coupled to the patient's respiratory system, whereby a  
8 therapeutically effective amount of said lung surfactant is delivered to the patient's lungs.

1 80. A method according to claim 1 wherein the lung surfactant is a natural  
2 surfactant derived from animal lungs or a synthetically engineered lung surfactant.

1 81. A method according to claim 1 wherein the liquid lung surfactant composition  
2 has a concentration of from 20-120 mg/ml.

1 82. A method according to claim 1 wherein 10-80% of the active lung surfactant  
2 is inhaled by the patient.

1 83. A method according to claim 4 wherein 5-50% of the active lung surfactant is  
2 delivered to the patient's lungs.

1 84. A method according to claim 1 wherein said therapeutically effective amount  
2 of lung surfactant is in the range of 2-400 mg.

1           85.     A method according to claim 6 wherein the delivery rate of lung surfactant to  
2 the patient's lungs is in the range of 2-800 mg/hr .

1           86.     A method according to claim 1 wherein the aerosol output of the vibrating  
2 aperture-type aerosol generator is in the range of 0.1-0.5 ml/min.

1           87.     A method according to claim 1 wherein said pressure-assisted breathing  
2 system is a CPAP system.

1           88.     A method according to claim 1 wherein the particle size of the lung surfactant  
2 aerosol is less than 5  $\mu$ m MMAD.

1           89.     In a surfactant replacement therapy wherein a liquid lung surfactant  
2 composition is aerosolized and delivered to the lungs of a patient having lung surfactant  
3 deficiency or dysfunction, the improvement which comprises:  
4                   aerosolizing the lung surfactant with a vibrating aperture-type aerosol  
5 generator; and  
6                   introducing the aerosolized lung surfactant into the gas flow within a circuit of  
7 a pressure-assisted breathing system coupled to the patient's respiratory system.

1           90.     A surfactant replacement therapy according to claim 11 wherein the circuit of  
2 the pressure-assisted breathing system provides a straight or gently angled path for the flow  
3 of aerosol particles from the point at which the aerosol generator introduces the aerosolized  
4 lung surfactant into the gas flow to the point at which the aerosolized lung surfactant enters  
5 the patient's respiratory system.

1           91.     A surfactant replacement therapy according to claim 11 wherein the pressure-  
2 assisted breathing system is a CPAP system.

1           92.     A surfactant replacement therapy according to claim 13 wherein the  
2 aerosolized lung surfactant is introduced into the respiratory circuit of the CPAP system.

1           93.     A surfactant replacement therapy according to claim 14 wherein a higher  
2 concentration of aerosolized lung surfactant than generated by the aerosol generator is first

3 collected in a plenum chamber located outside the respiratory circuit, and then discharged  
4 into the respiratory circuit.

1 94. A surfactant replacement therapy according to claim 15 wherein the plenum  
2 chamber has an internal volume of 5-400 ml.

1 95. A surfactant replacement therapy according to claim 15 wherein the mass of  
2 surfactant inhaled by the patient is at least 80% of the surfactant provided to the aerosol  
3 generator.

1 96. A surfactant replacement therapy according to claim 17 wherein the inhaled  
2 mass is provided in at least 25% of the time required for a breath actuated nebulizer to  
3 provide the same inhaled mass.

1 97. A surfactant replacement therapy according to claim 13 wherein the CPAP  
2 system comprises means for discontinuing the introduction of aerosolized lung surfactant into  
3 the gas flow when the patient exhales.

1 98. A surfactant replacement therapy according to claim 11 wherein the  
2 rebreathed volume is no more than 5 ml.

1 99. Apparatus for the delivery of an aerosolized medicament to a patient  
2 comprising:

3 a pressure-generating circuit having a first gas flow that maintains a positive  
4 pressure within the apparatus;

5 a patient interface device coupled to a patient's respiratory system;

6 a respiratory circuit for providing gas communication between the pressure-  
7 generating circuit and the patient's respiratory system, wherein the gas flow in the respiratory  
8 circuit is lower volume than the first gas flow;

9 a plenum chamber located outside of and in gas communication with the  
10 respiratory circuit;

11 a vibrating aperture-type aerosol generator positioned so as to generate  
12 aerosolized medicament into the plenum chamber, wherein a concentration of aerosolized

13 medicament is collected in the plenum chamber that is higher than the concentration  
14 generated by the aerosol generator;  
15 a conduit from the plenum chamber to a point in the respiratory circuit  
16 proximal to the patient's airway; and  
17 means for introducing a controlled secondary gas flow into the plenum  
18 chamber to drive concentrated aerosolized medicament through the conduit into the  
19 gas flow in the respiratory circuit.

1 100. Apparatus according to claim 21 wherein the plenum chamber has an internal  
2 volume of 5-400 ml.

1 101. Apparatus according to claim 21 wherein the plume of aerosolized  
2 medicament generated by the aerosol generator does not impact the bottom or walls of the  
3 plenum chamber.

1 102. Apparatus according to claim 21 wherein the conduit has a one-way valve or  
2 conduit that controls the flow of concentrated aerosolized medicament to the respiratory  
3 circuit so as to isolate the volume of gas in the plenum chamber from being rebreathed  
4 volume.

1 103. Apparatus according to claim 21 wherein the aerosolized medicament is a lung  
2 surfactant.

1/21

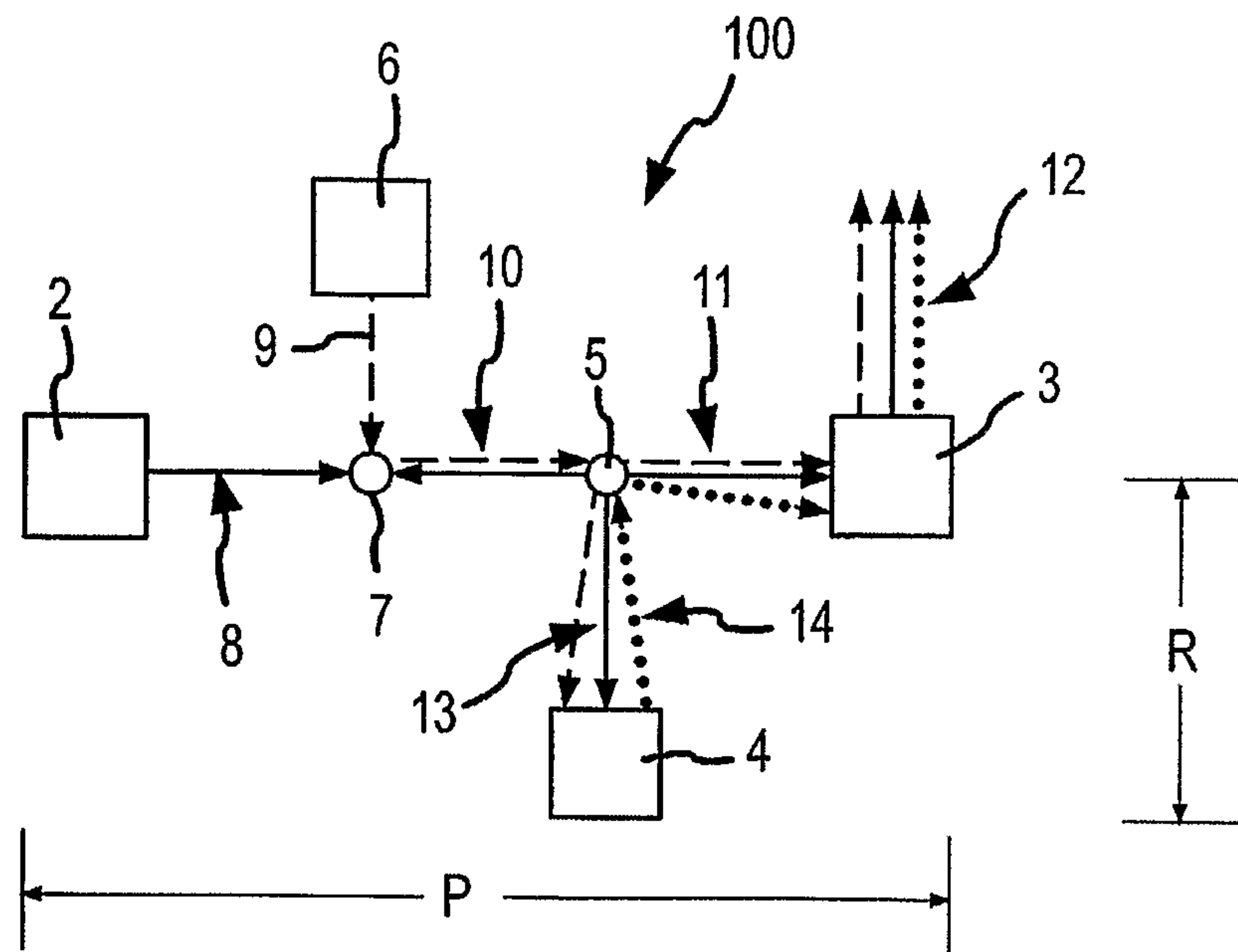


FIG.1

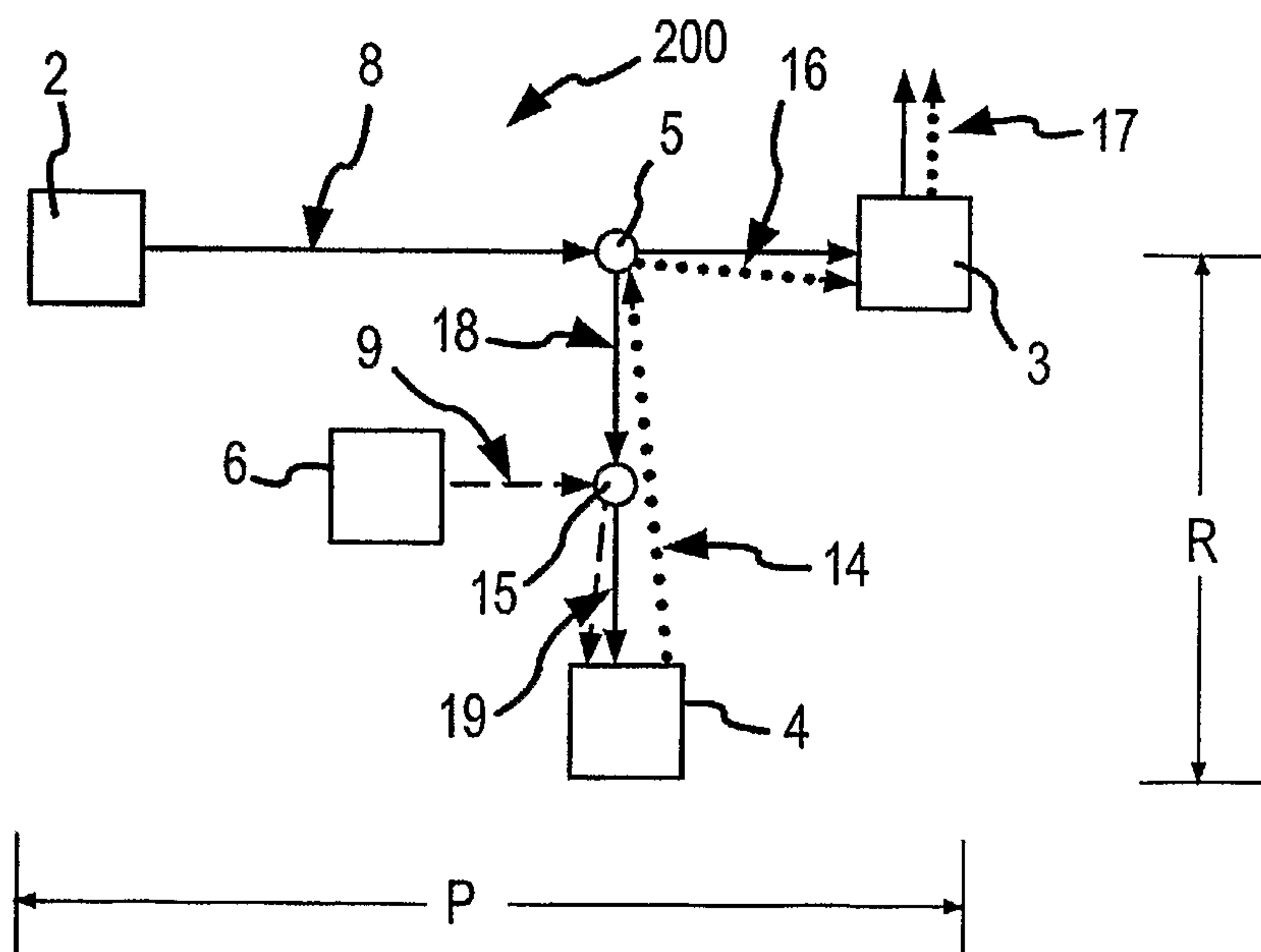


FIG.2

2/21

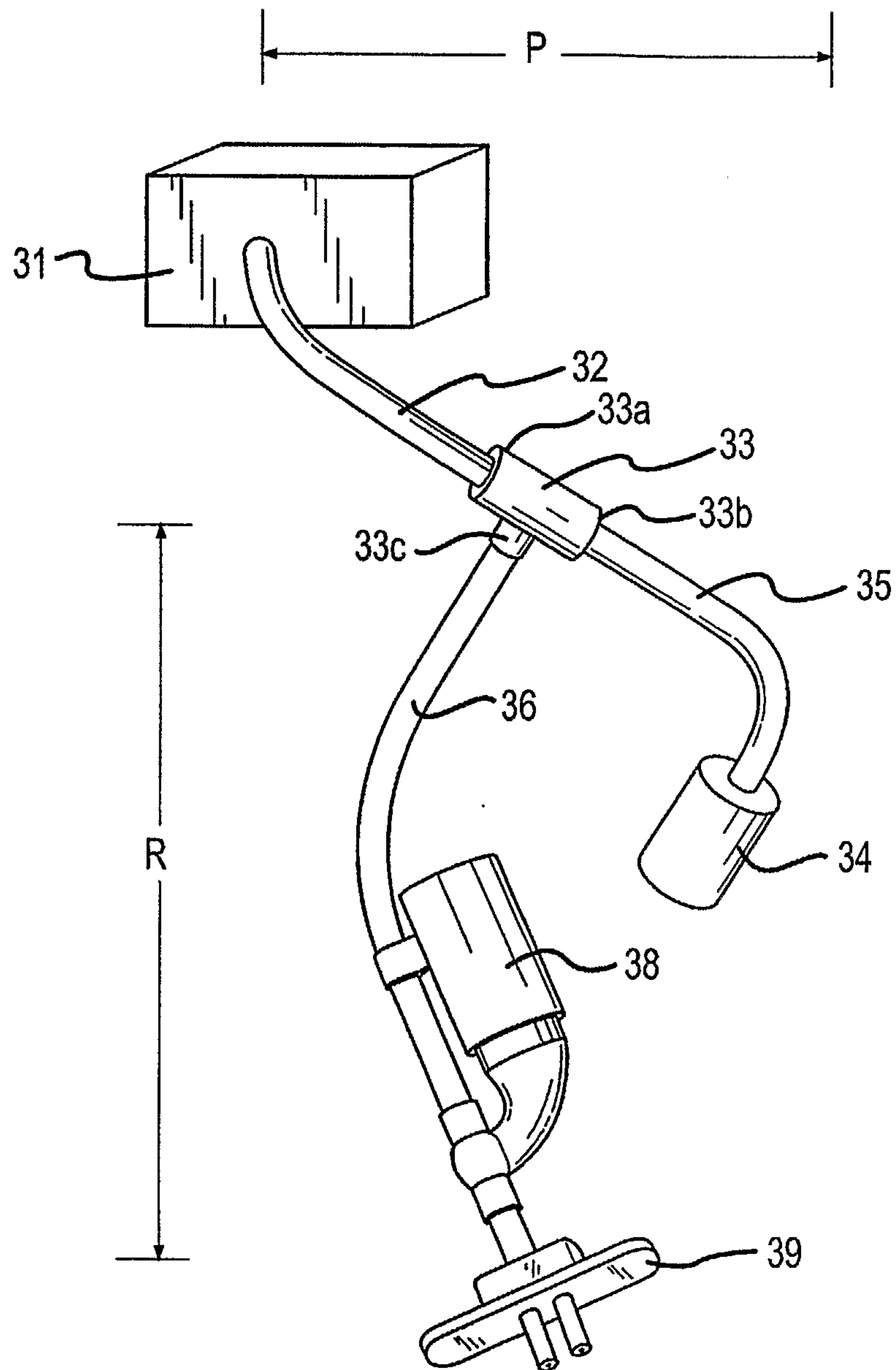


FIG.3

3/21

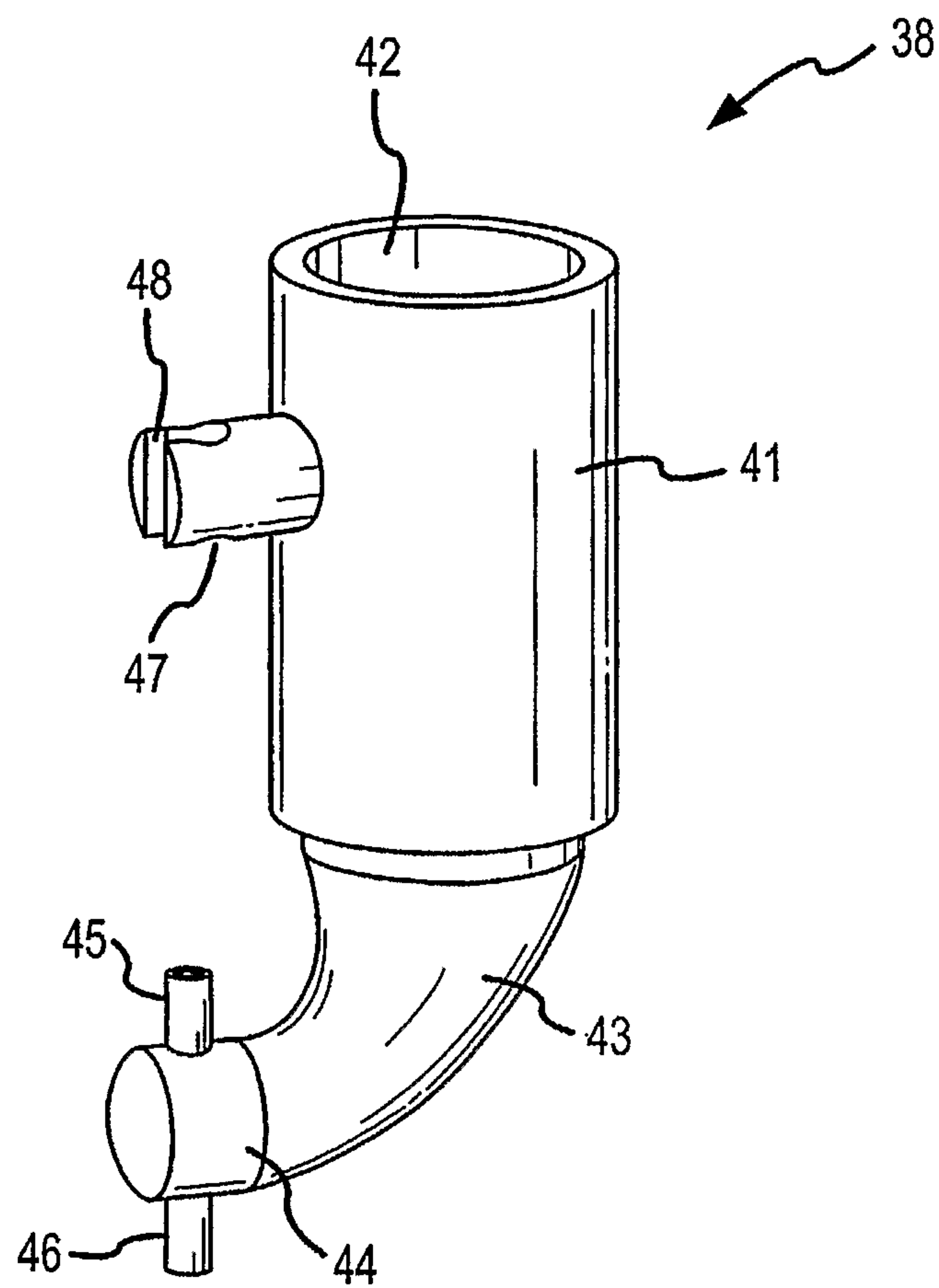


FIG.4

4/21

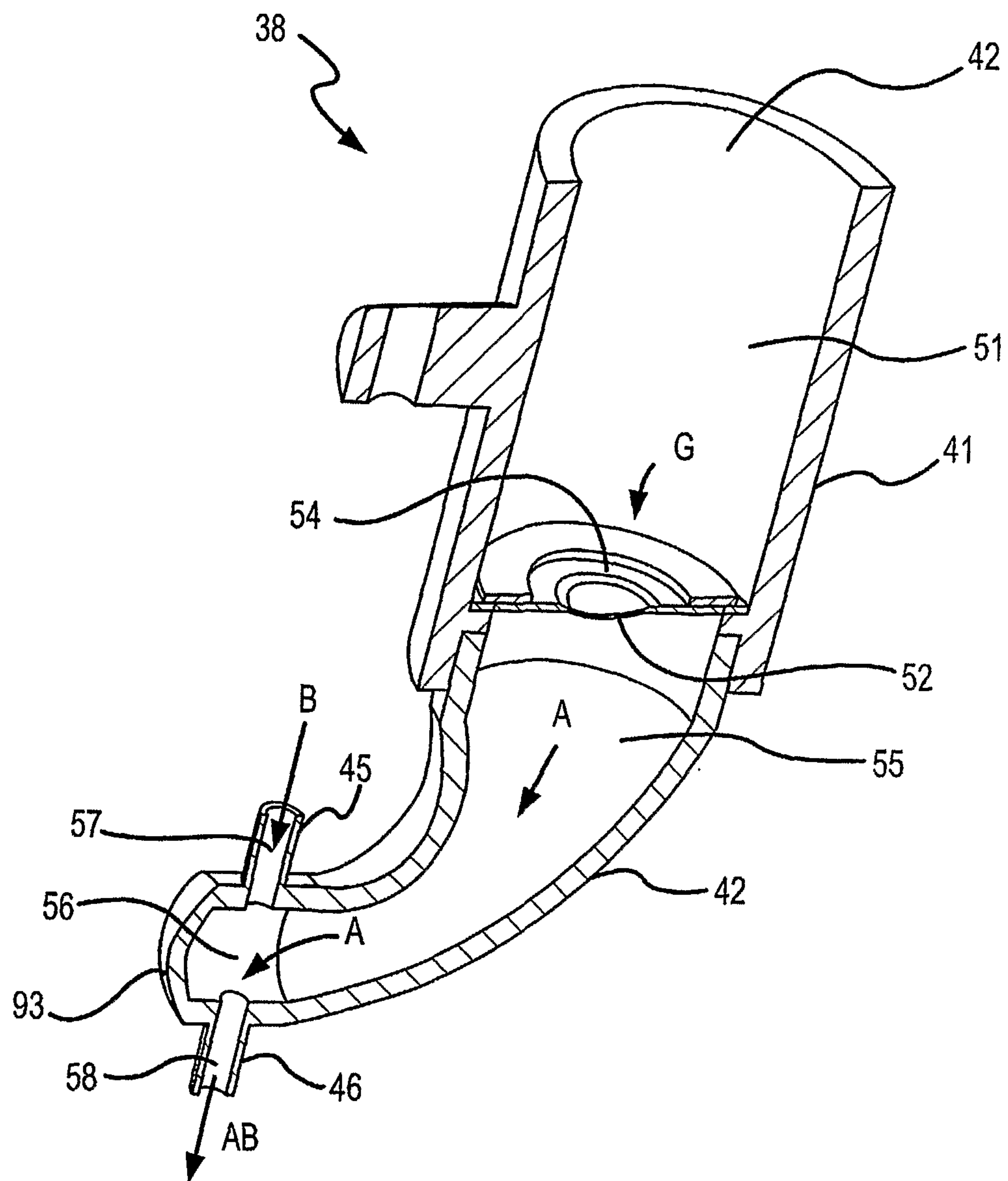


FIG.5

5/21

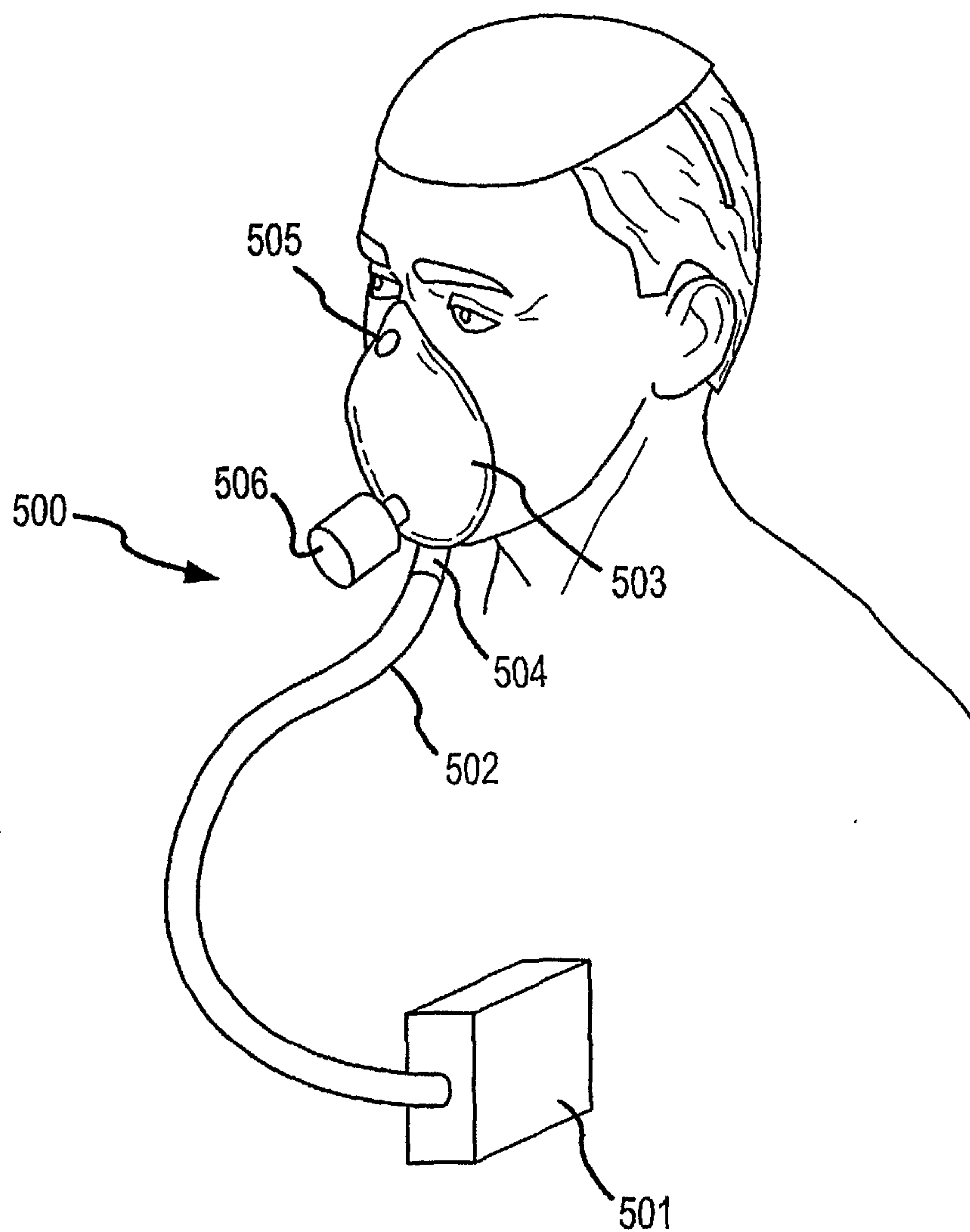


FIG.6

6/21

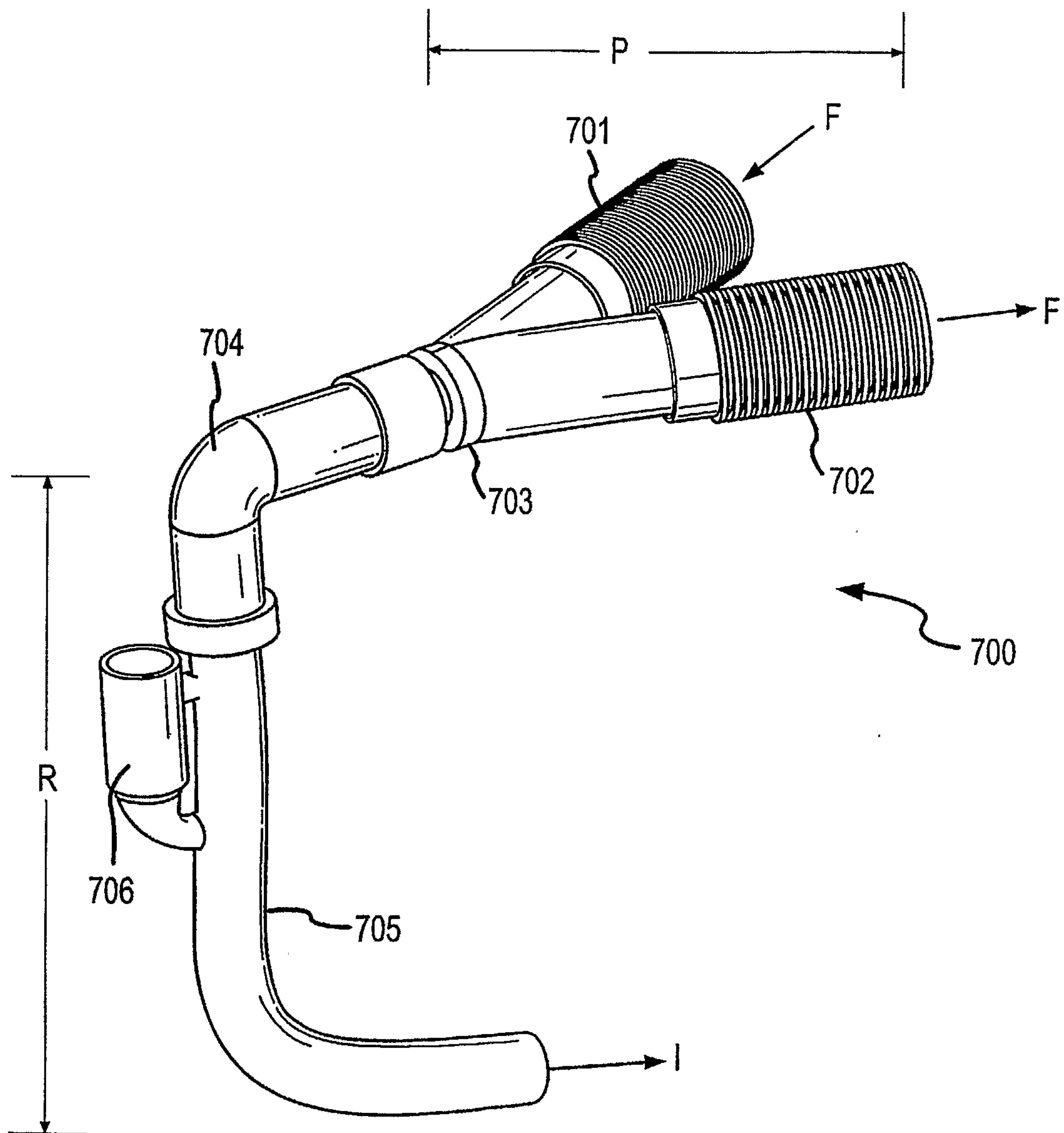


FIG. 7

7/21

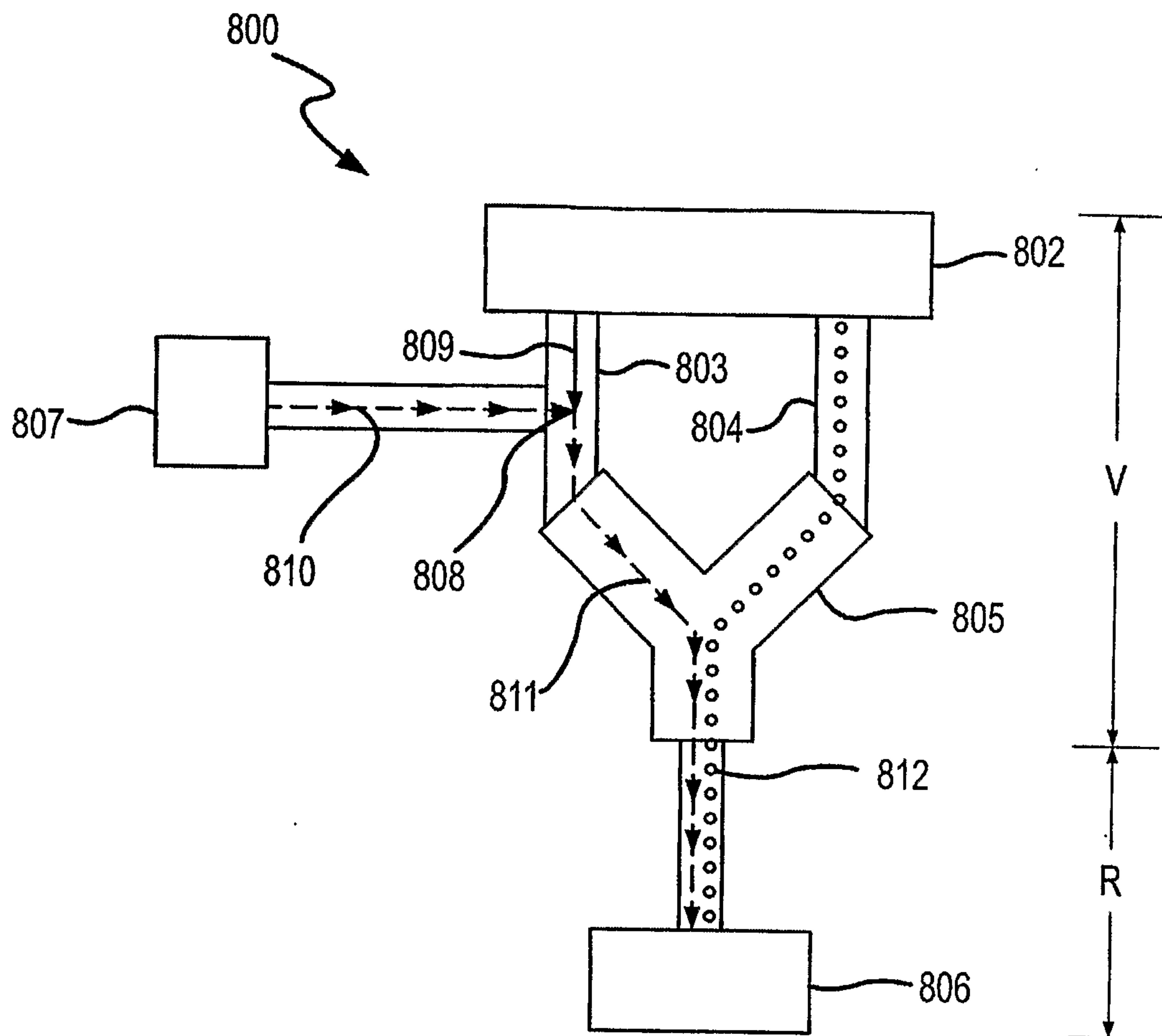


FIG.8

8/21

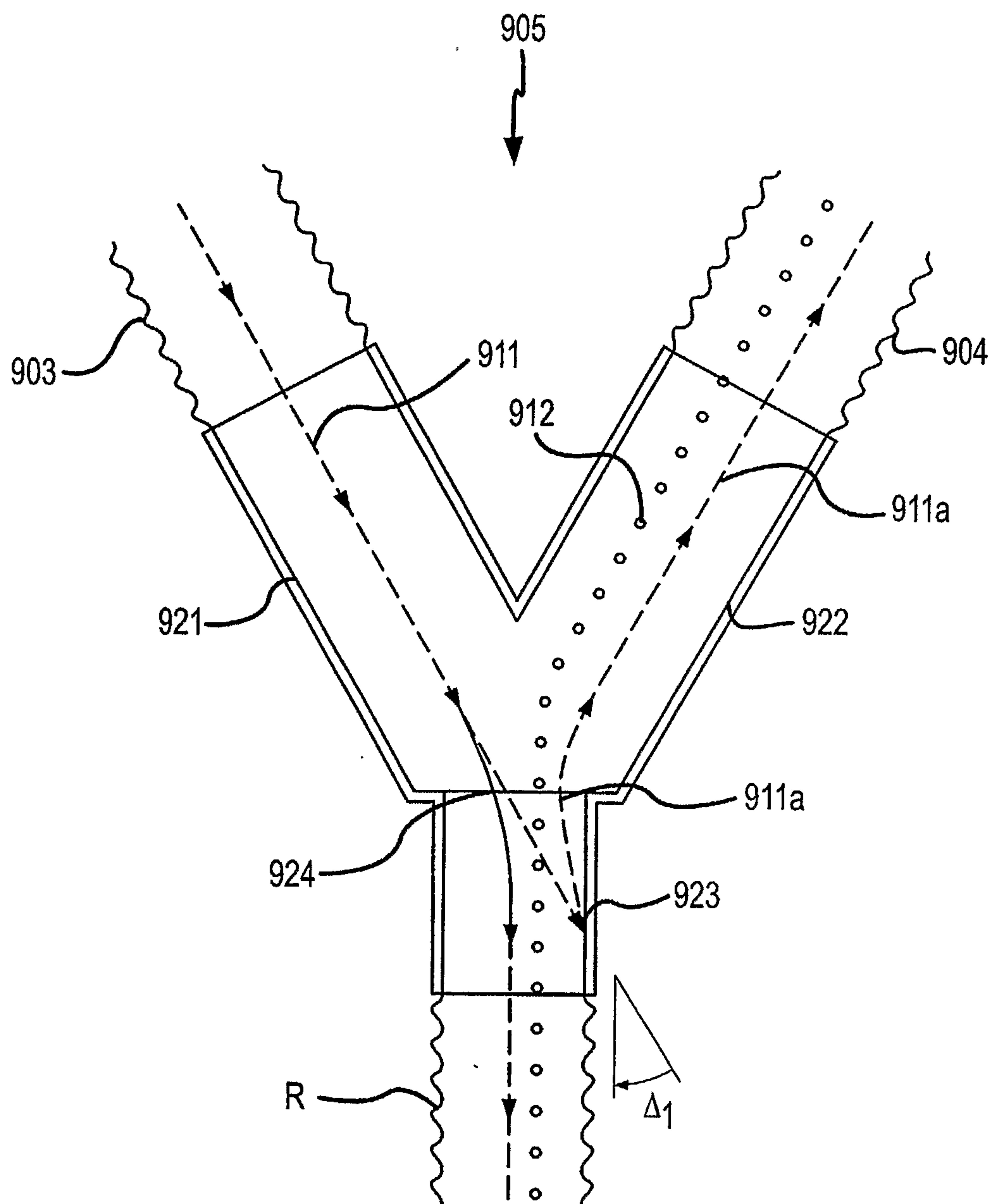


FIG.9

9/21

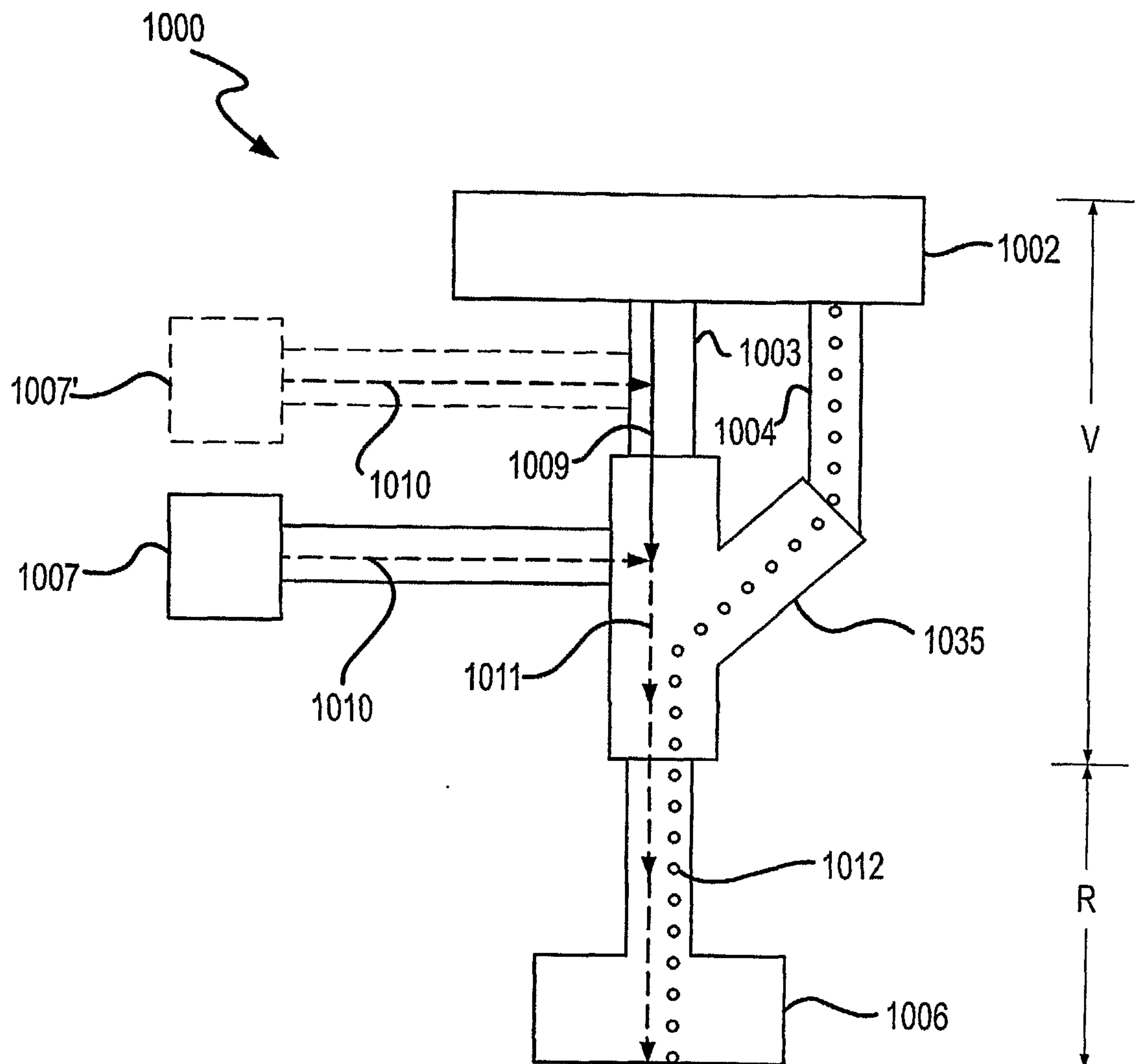


FIG. 10

10/21

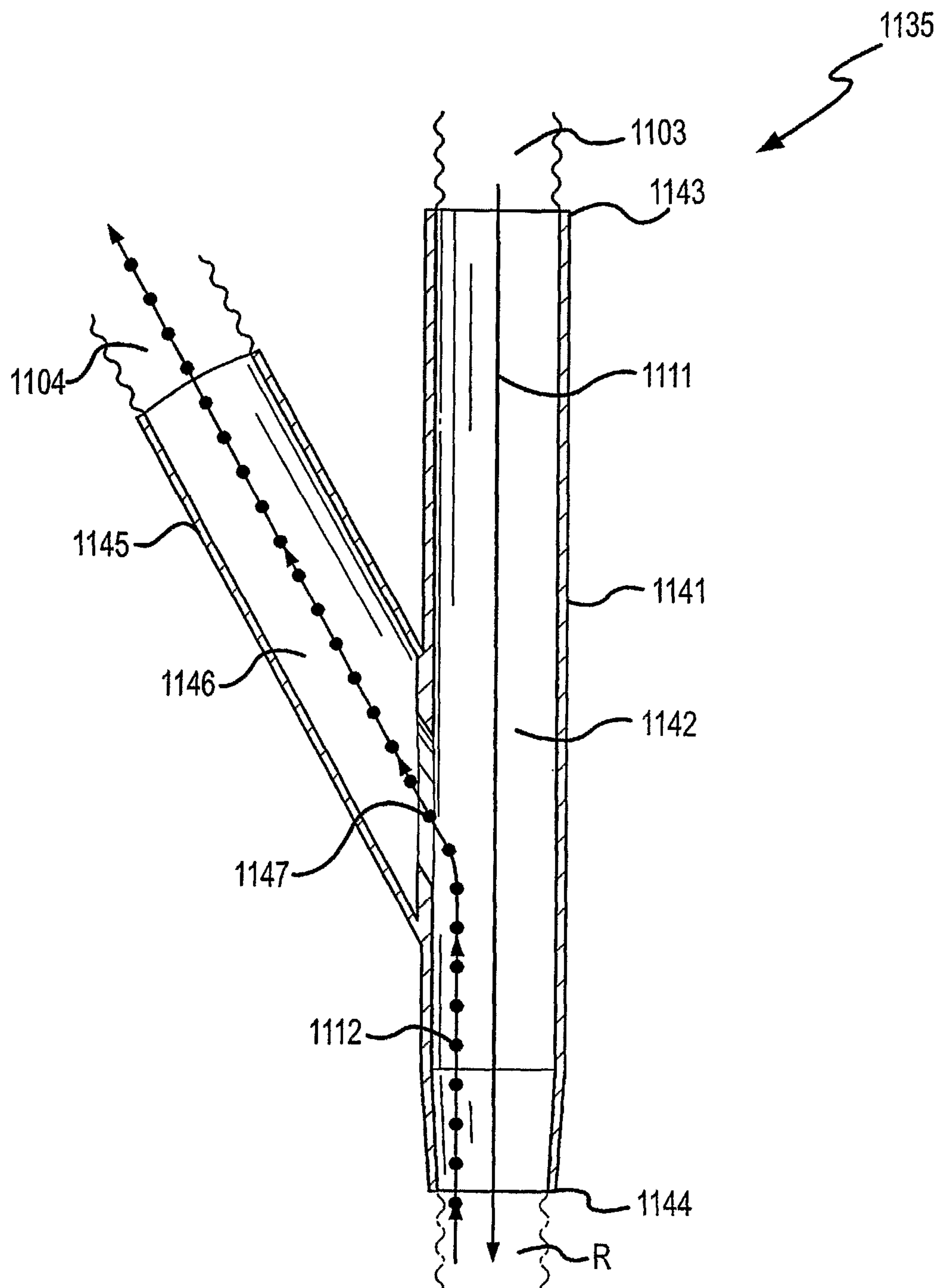


FIG. 11

11/21

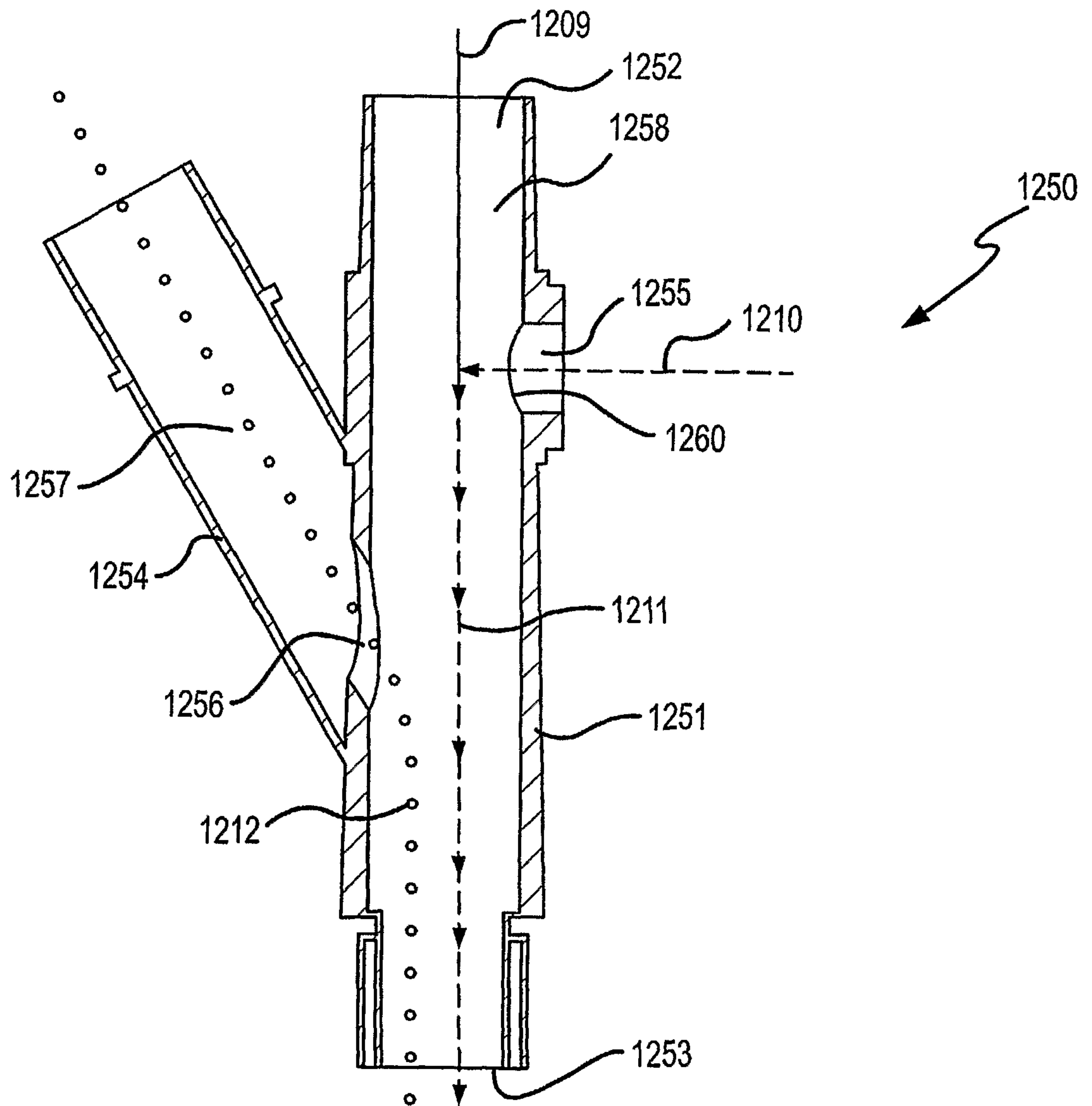


FIG. 12

12/21

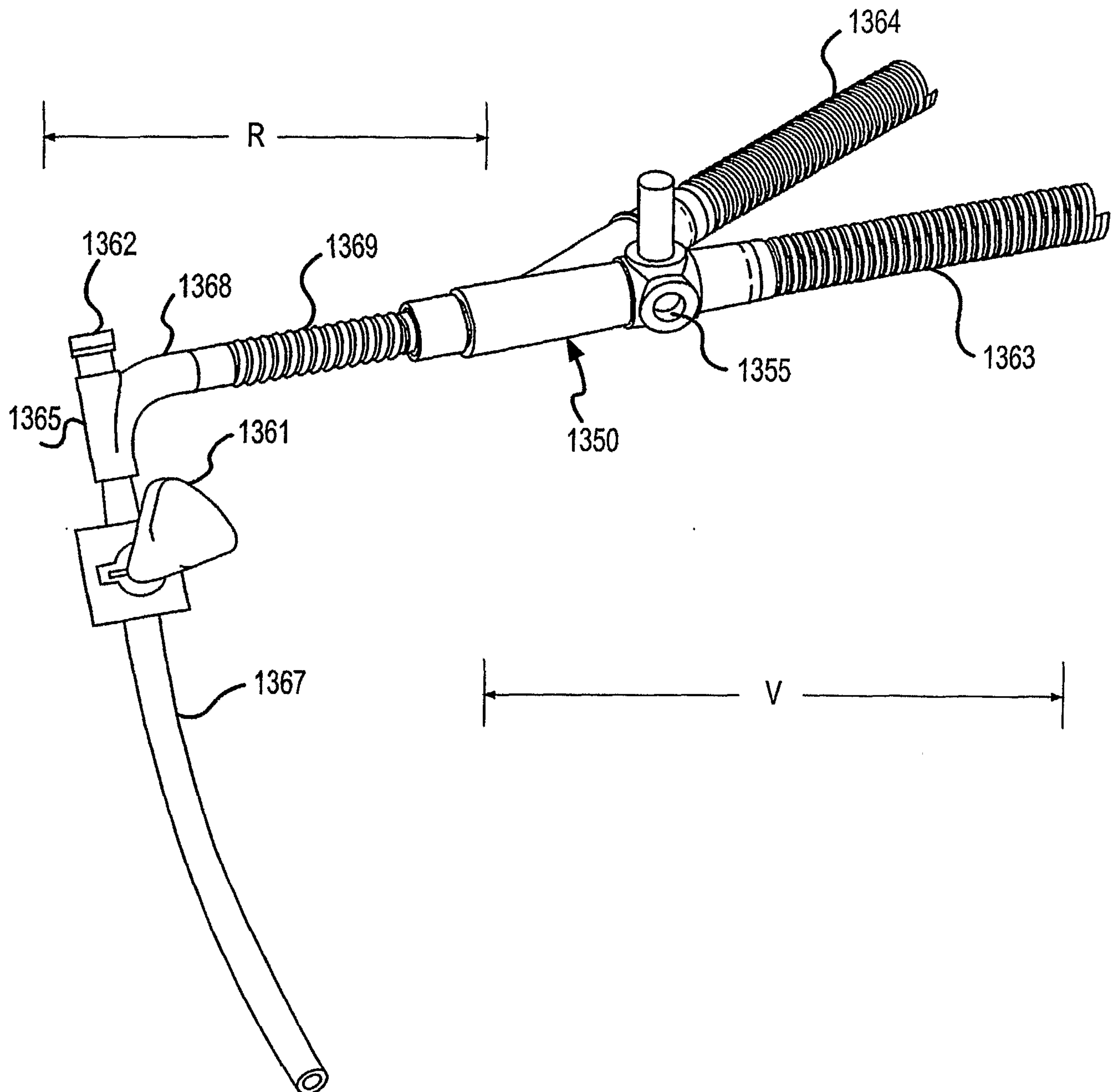


FIG.13

13/21

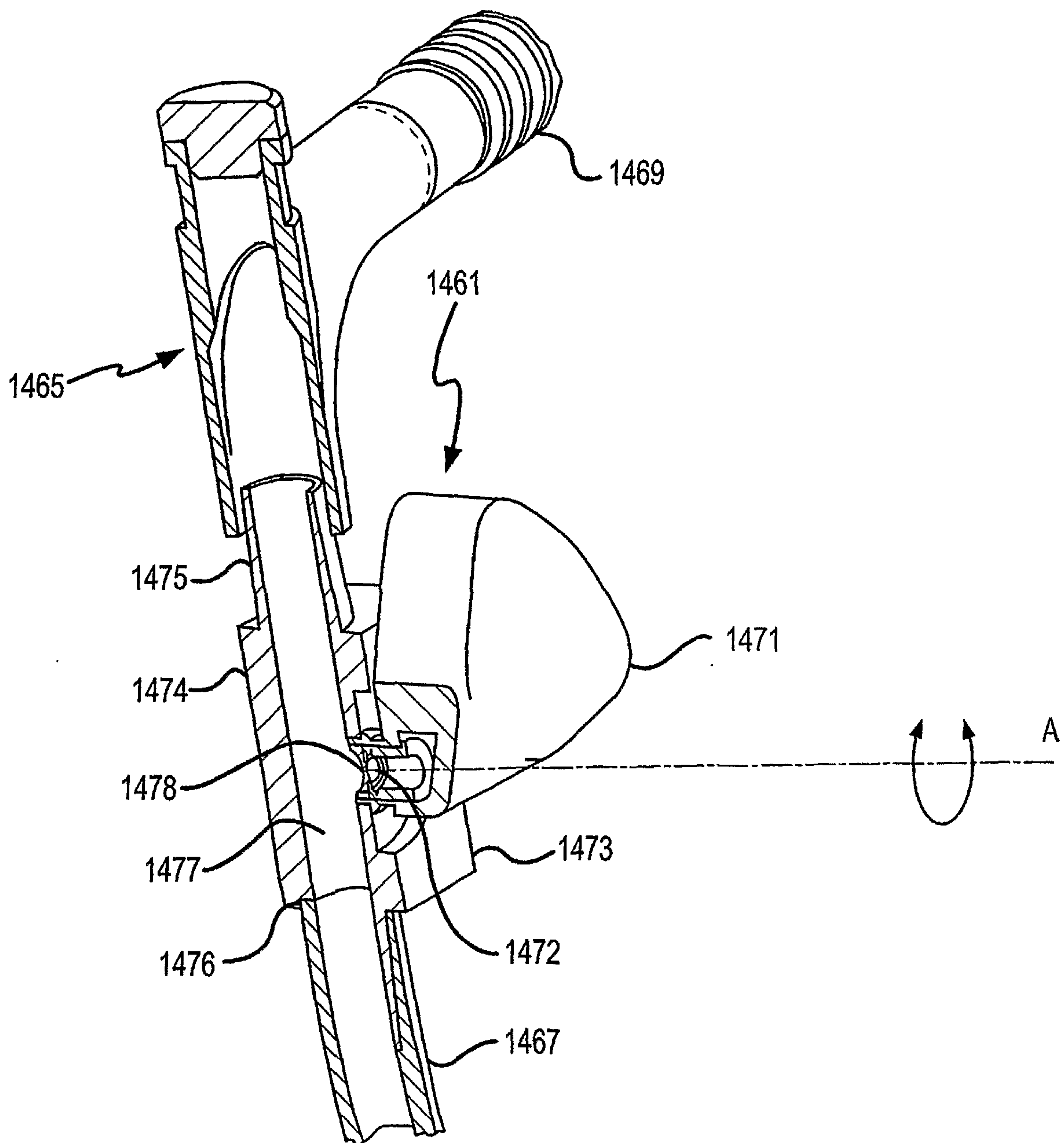


FIG.14

14/21

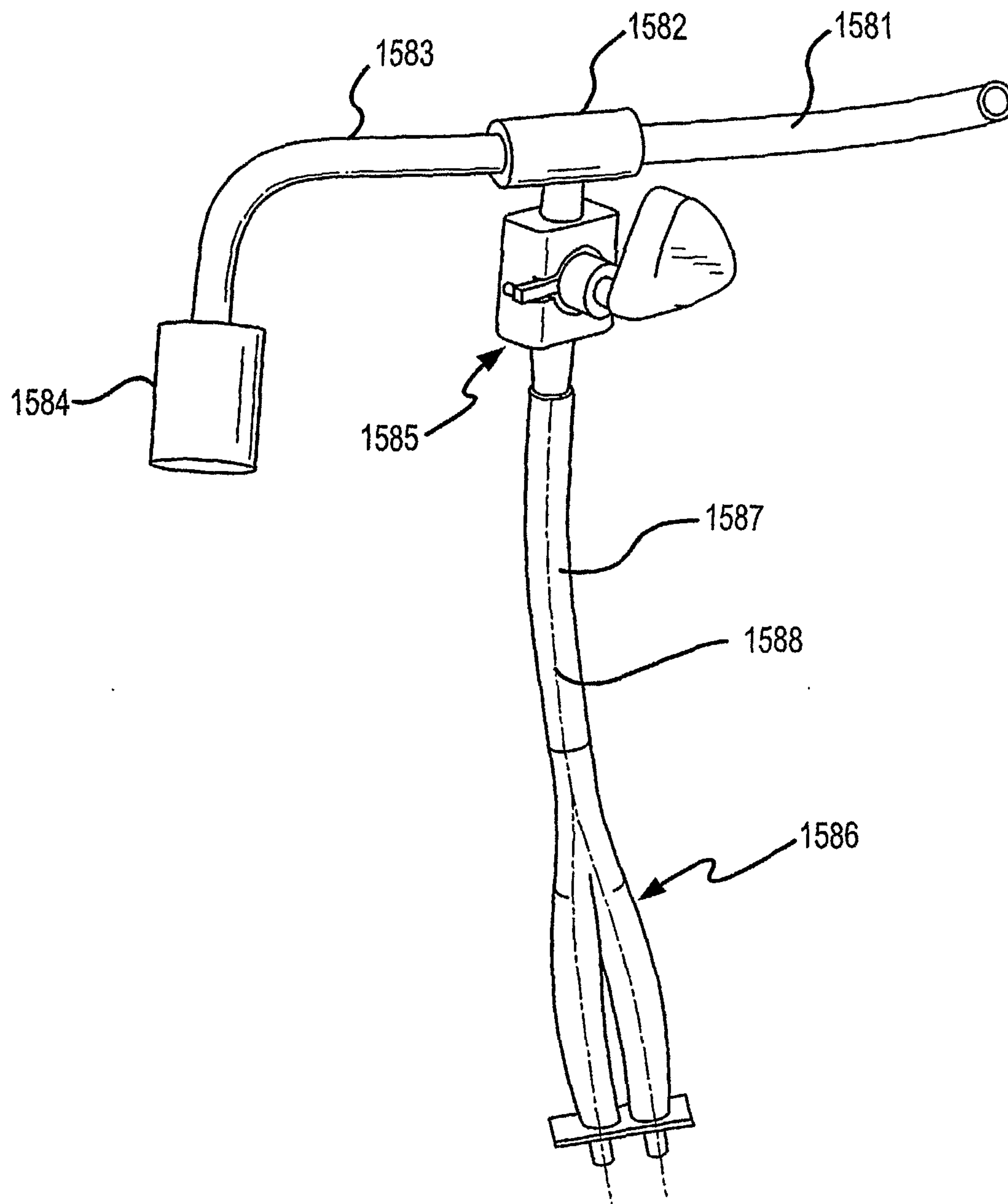


FIG.15

15/21

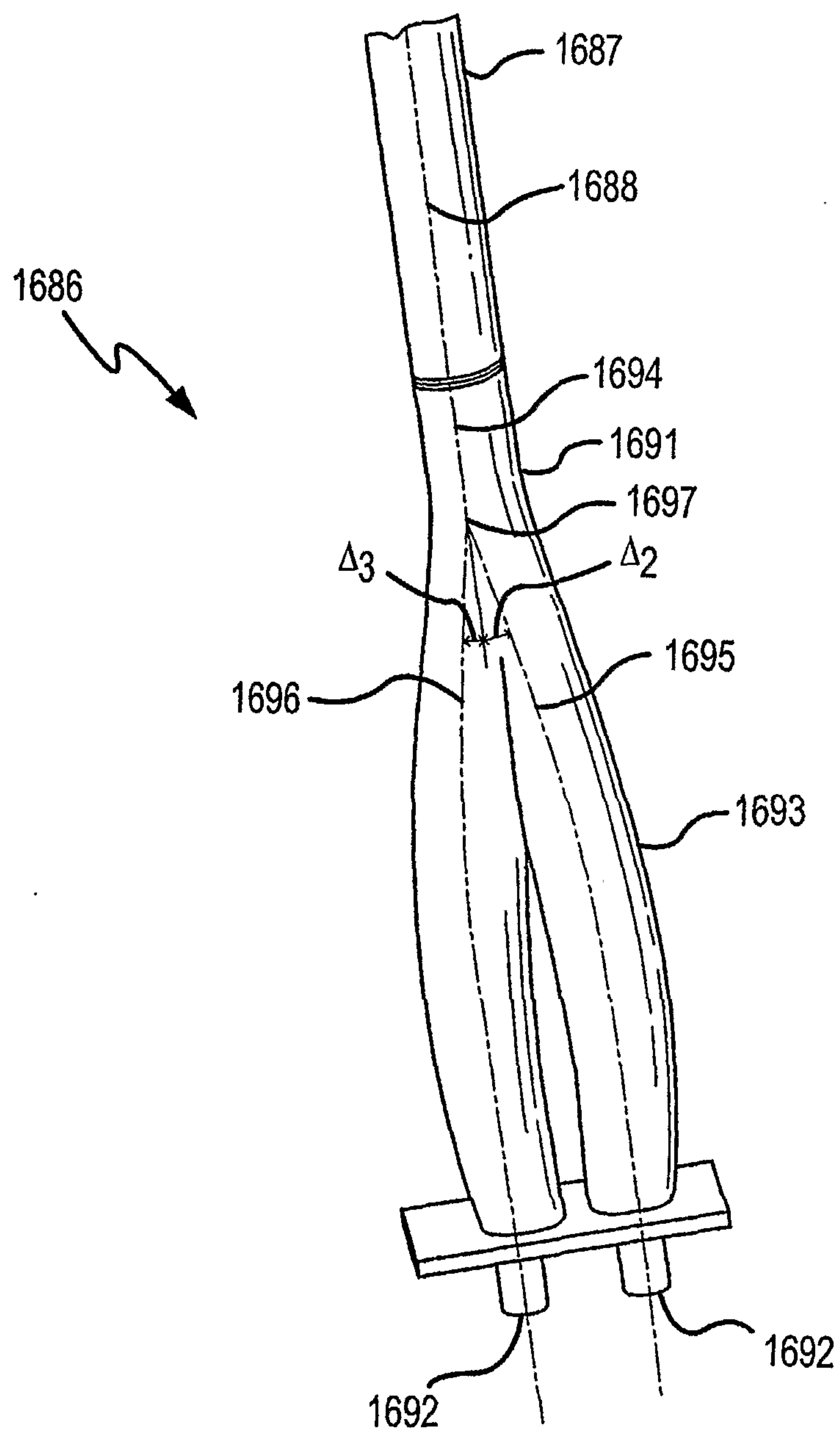


FIG. 16

16/21

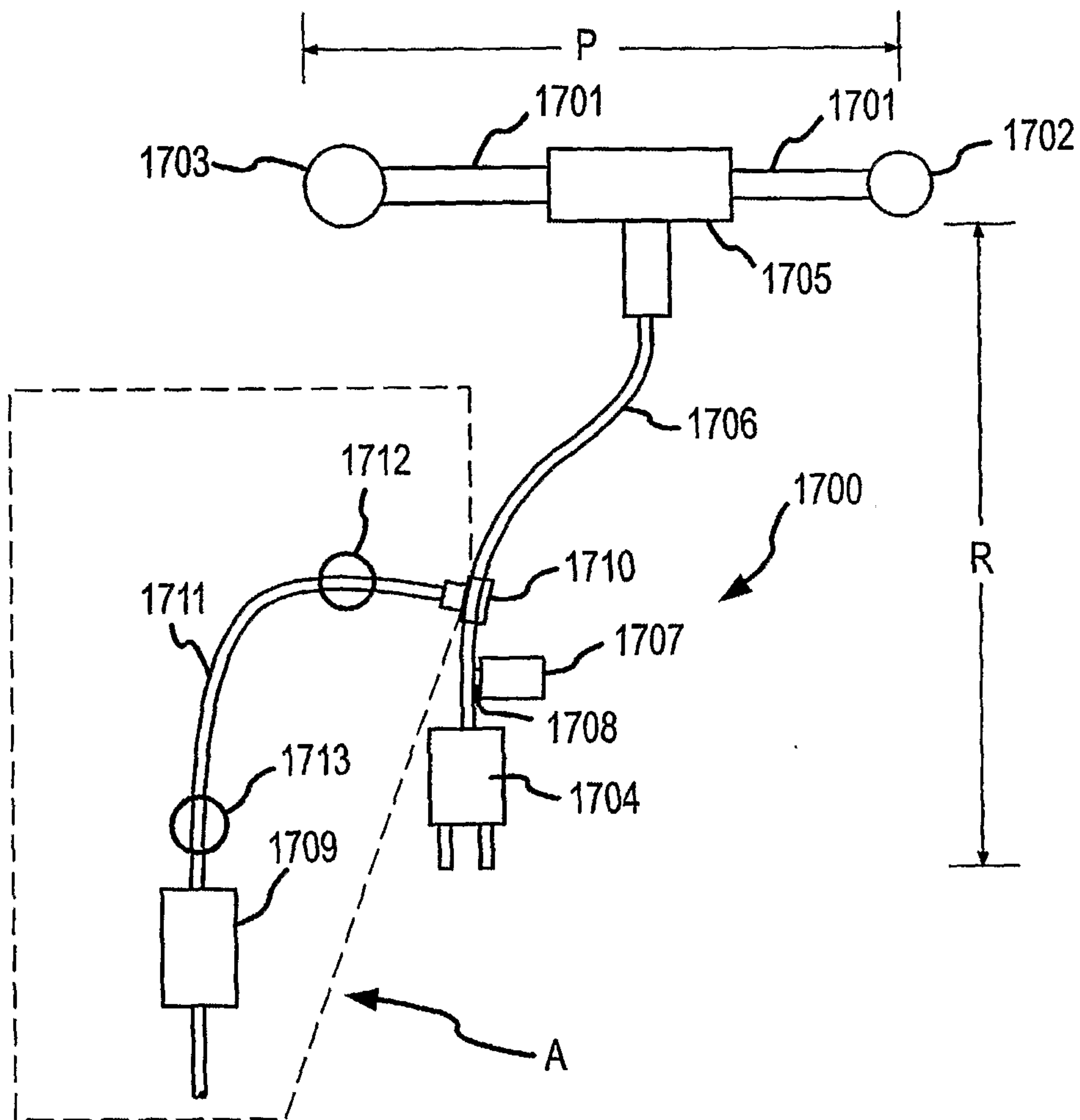


FIG.17

17/21

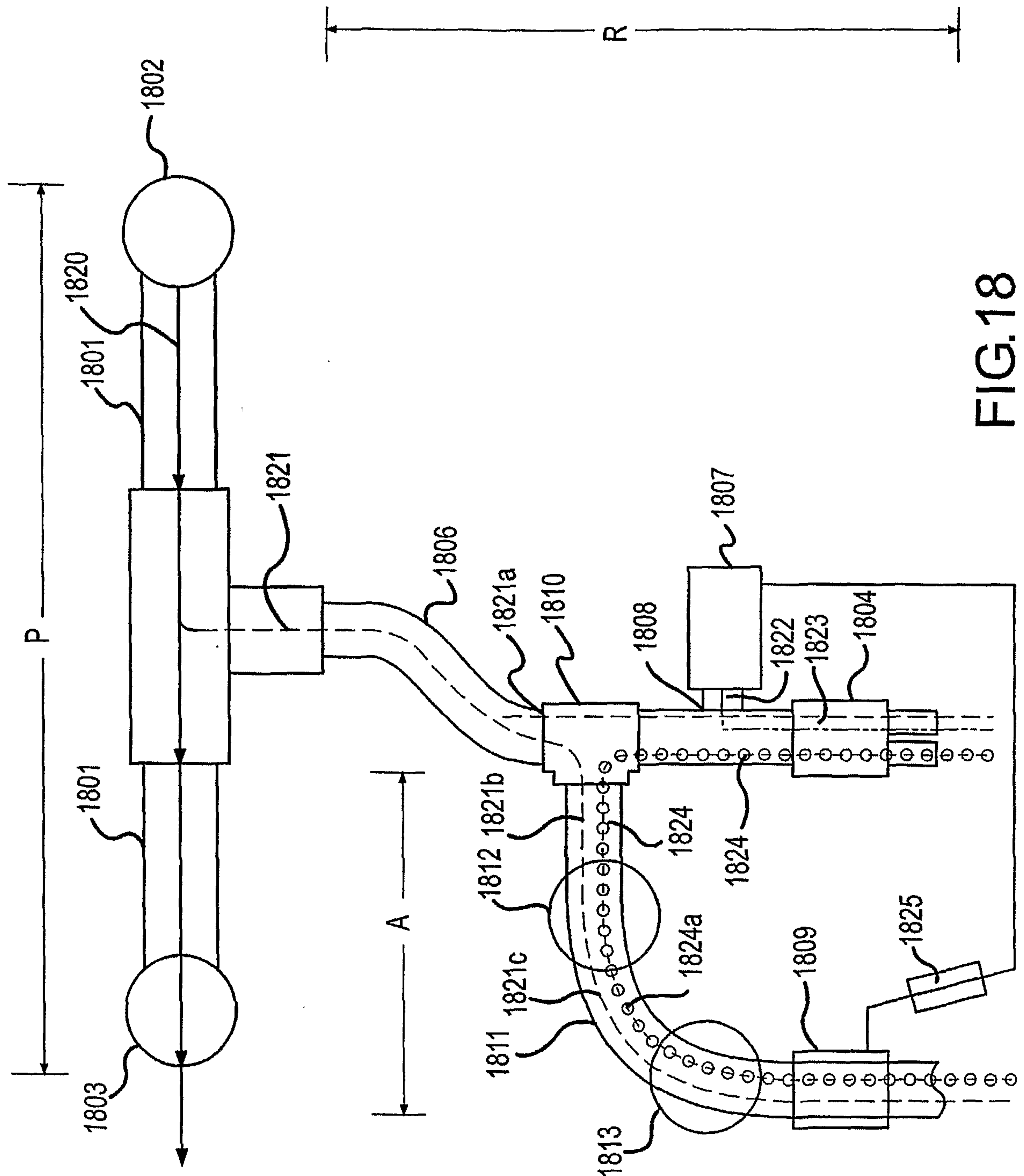


FIG. 18

18/21

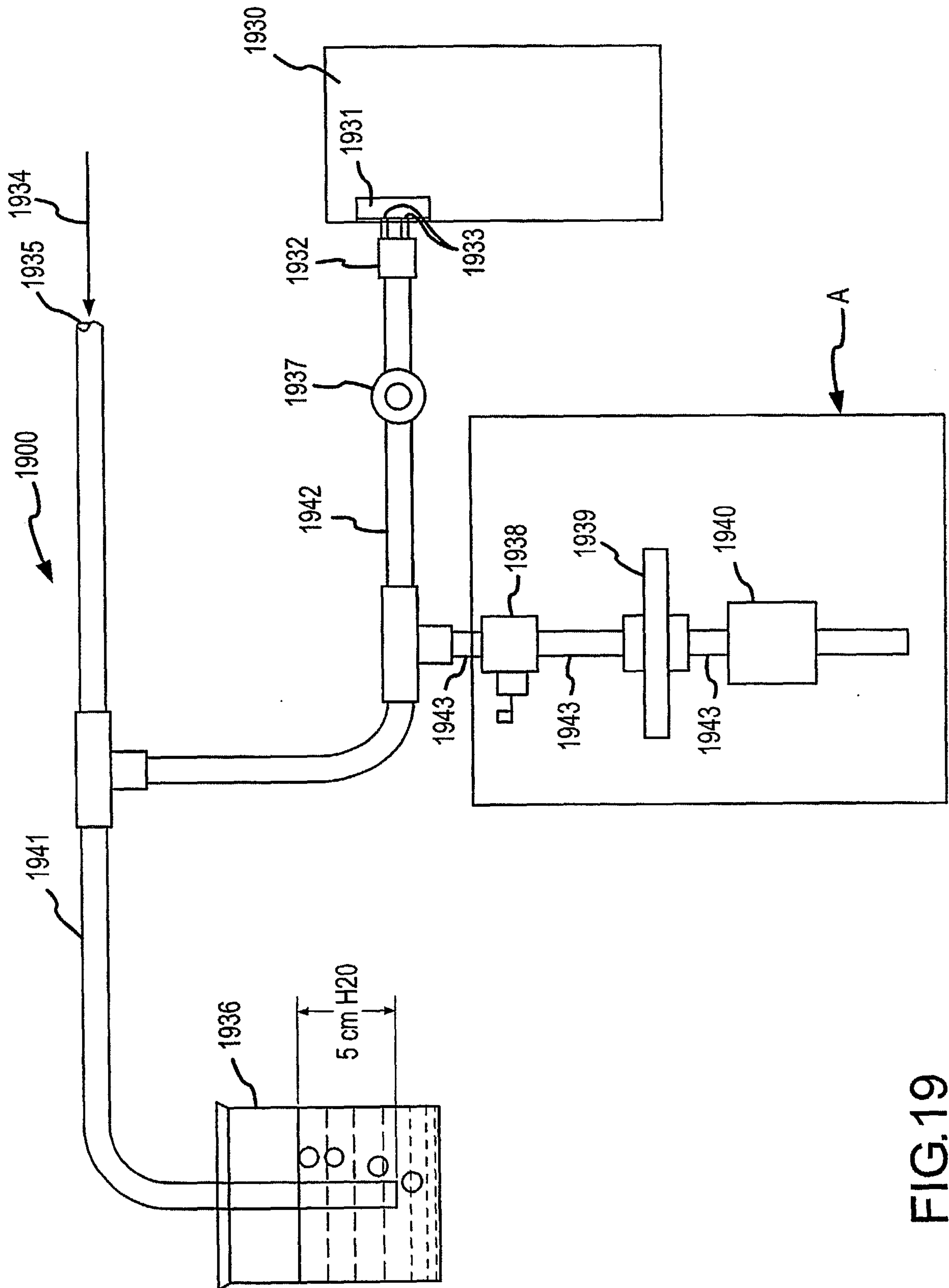


FIG. 19

19/21

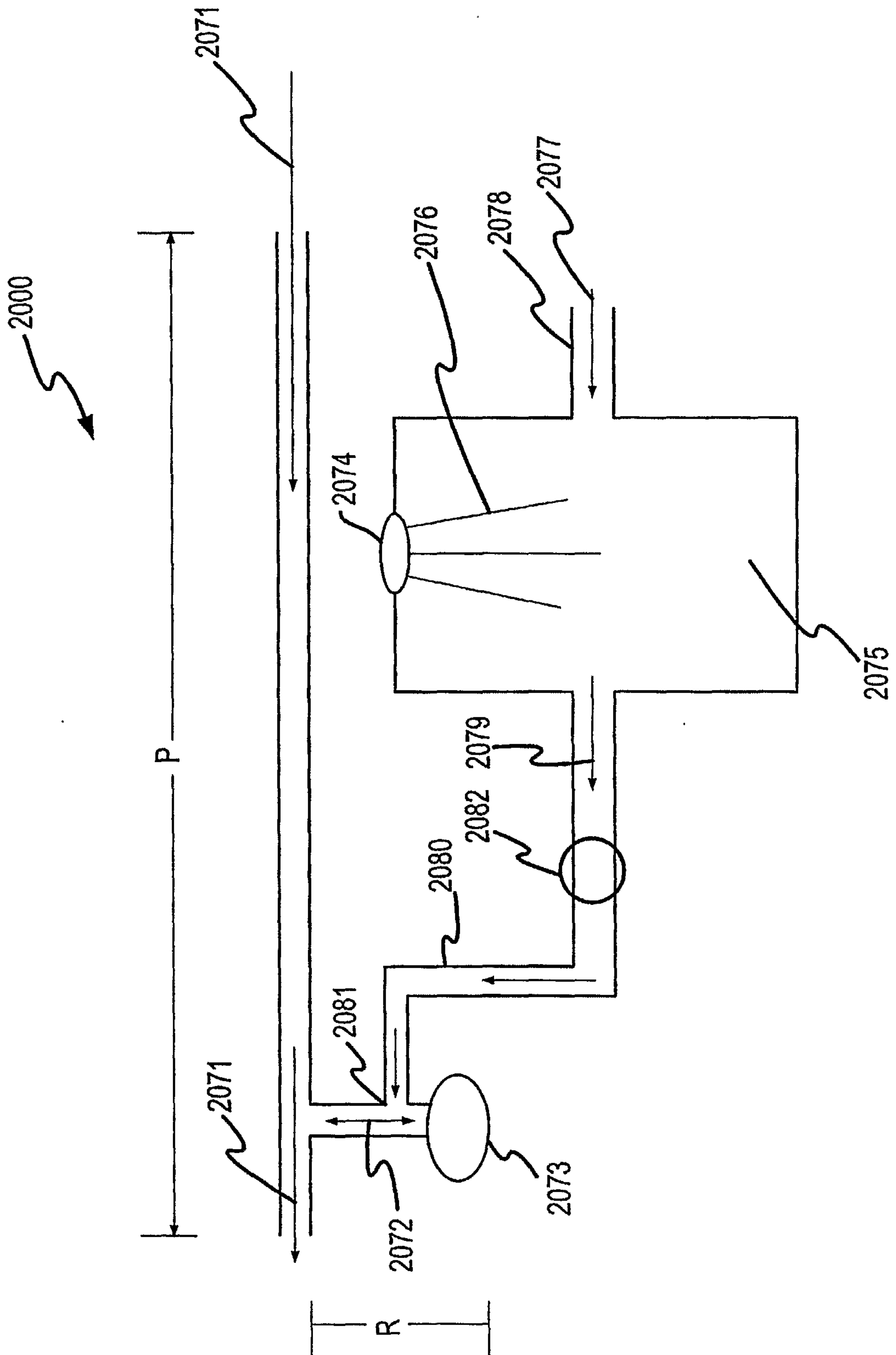


FIG.20

20/21

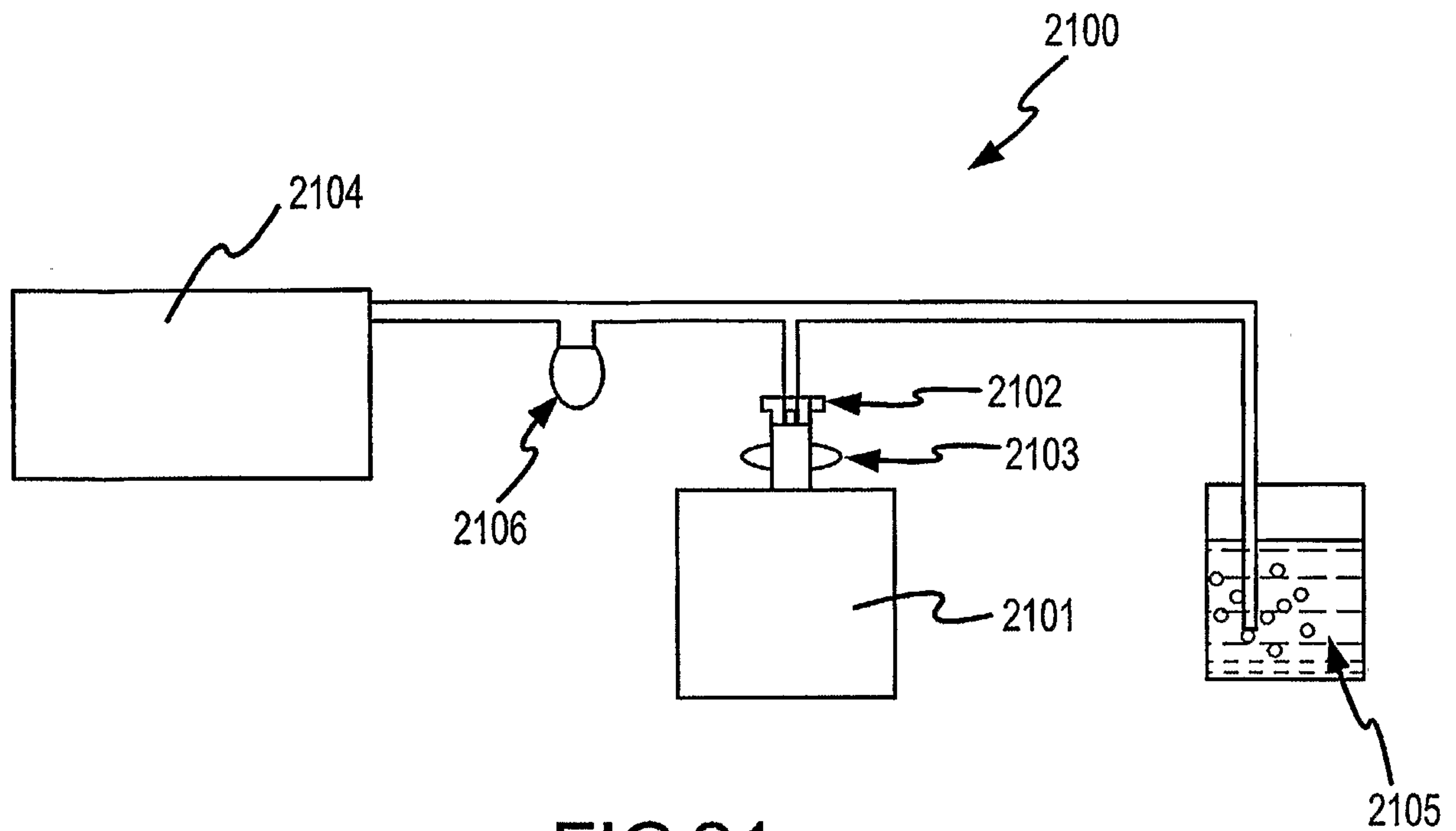


FIG.21a

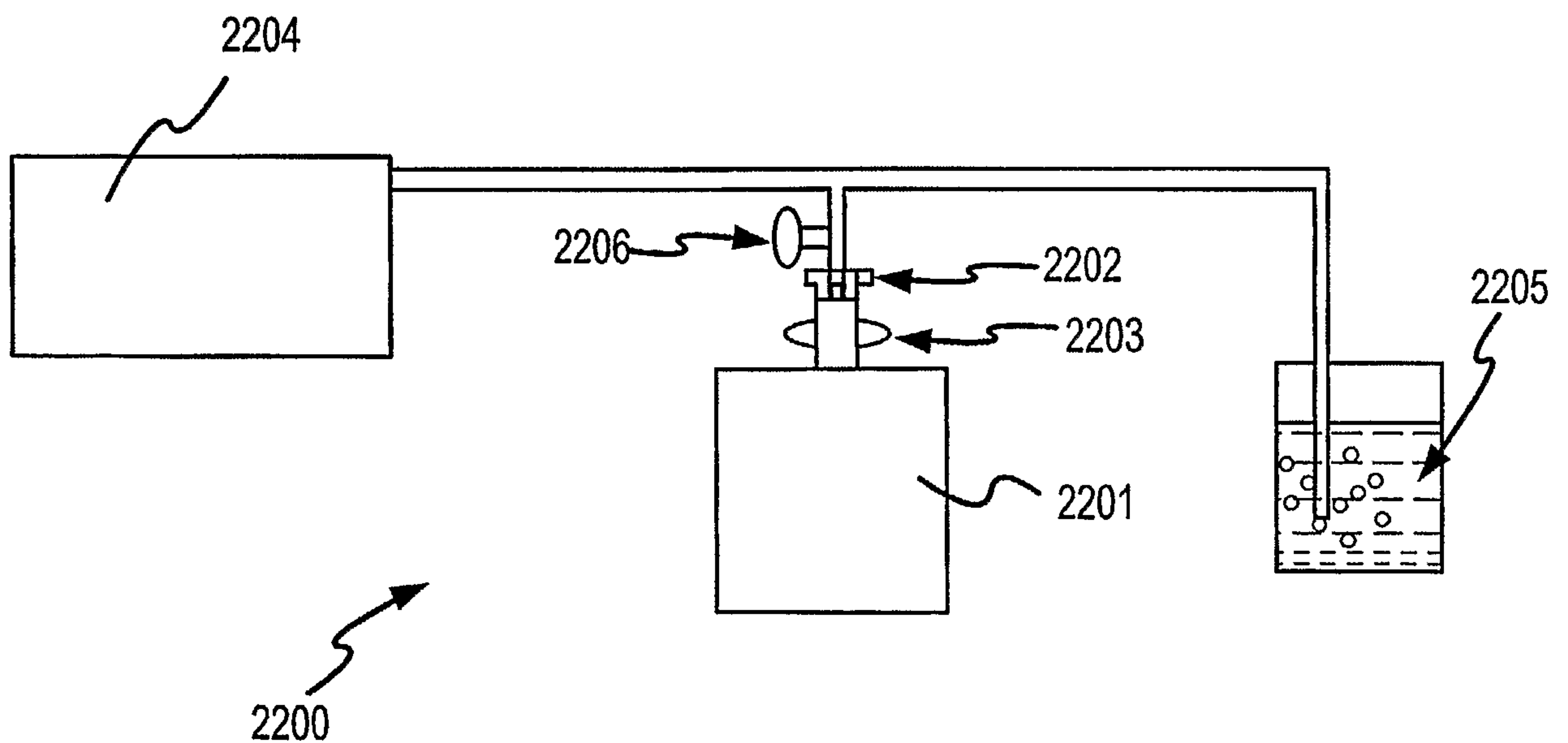


FIG.21b

21/21

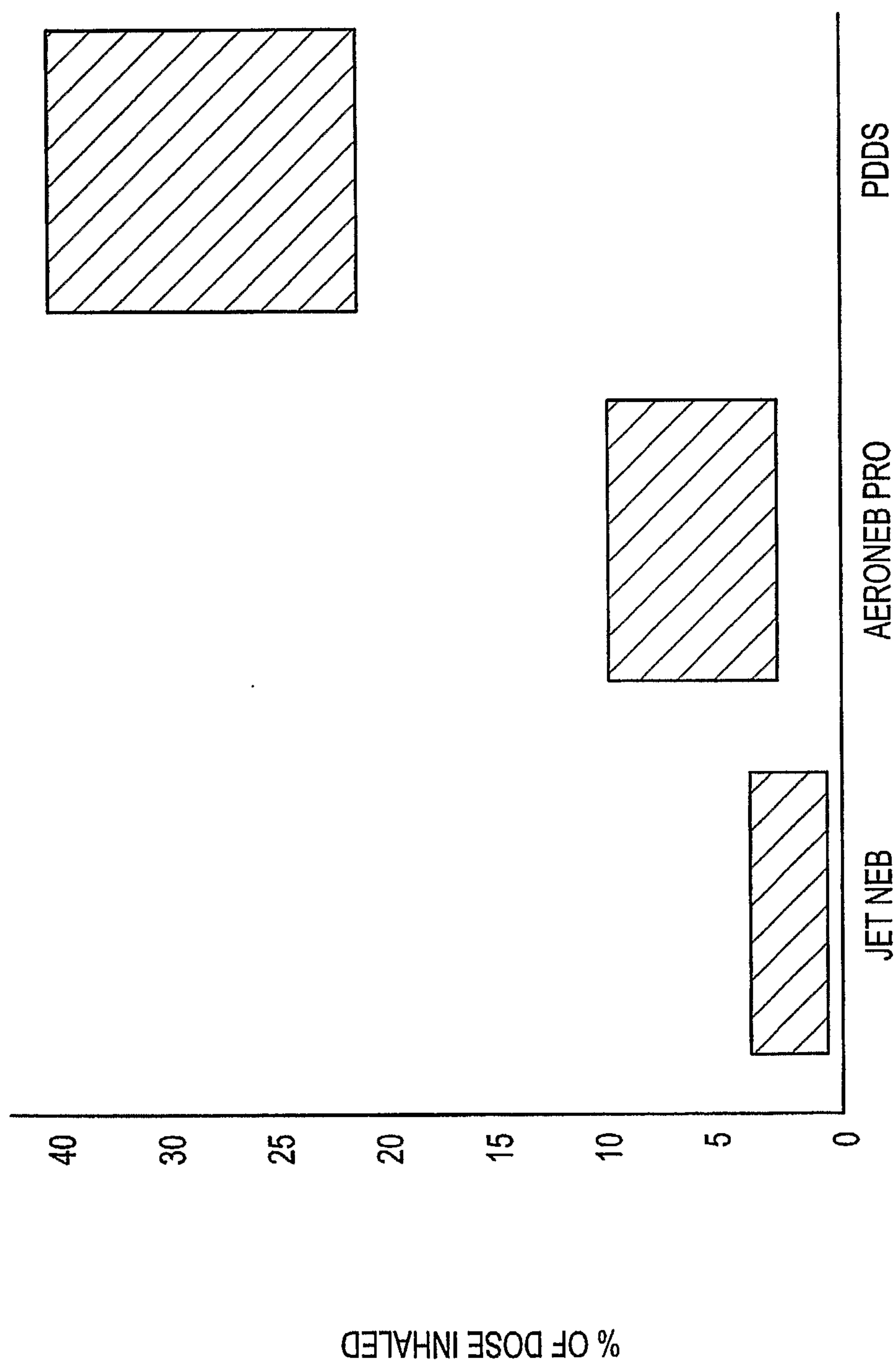


FIG.22

$P$

