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(54) **SYSTEM AND METHOD FOR CONTROLLING THE FLOW OF EXHALED BREATH DURING ANALYSIS**

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(57) **ABSTRACT**

A system and method for controlling the flow rate of a gaseous sample in an exhaled breath analysis system is disclosed. Two embodiments are described in this patent: a single pump embodiment and a dual pump embodiment. In each of these embodiments, a pump or pumps are used to control the flow rate of the breath sample as it moves through the analysis system. Also, the system includes means to conduct side stream, stopped flow analysis.

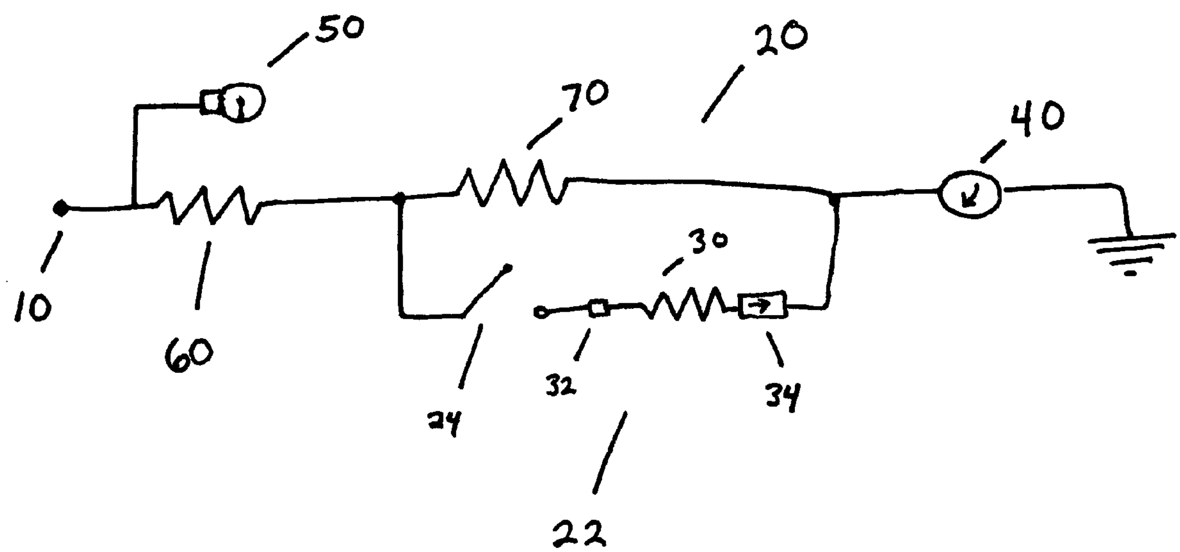


Fig. 1

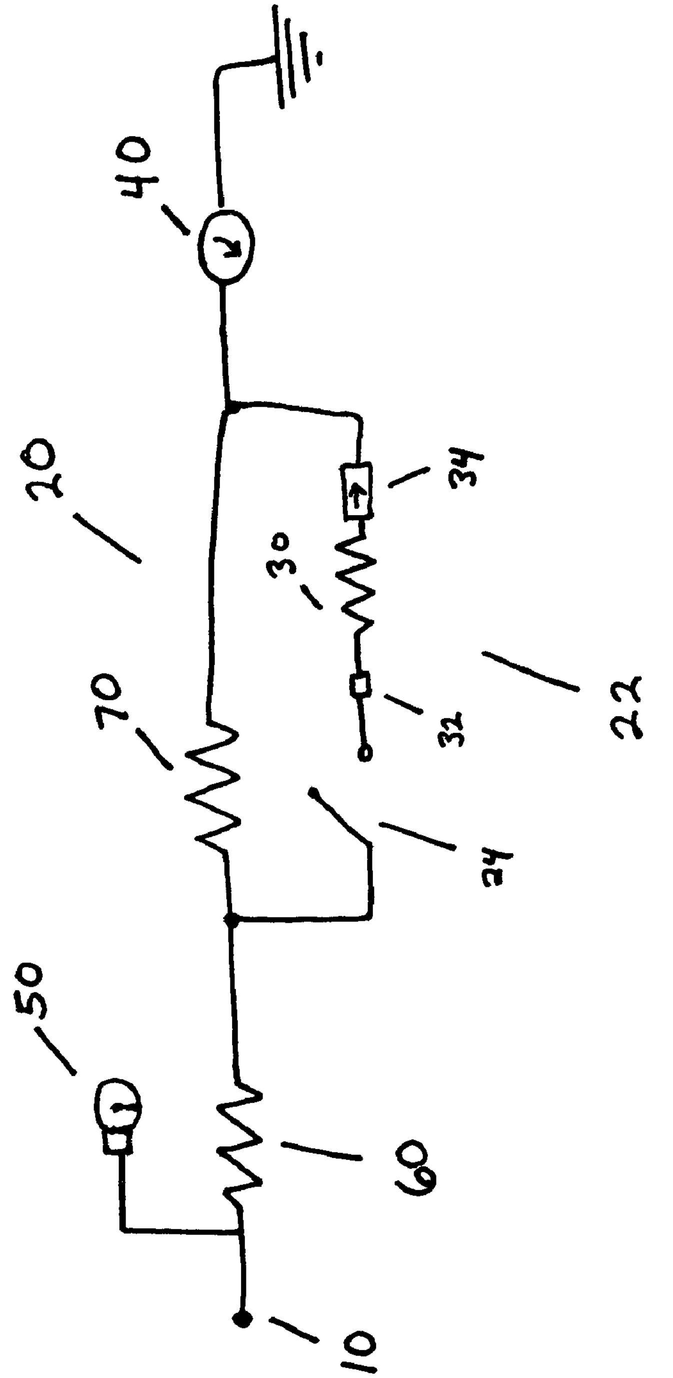


Fig. 2

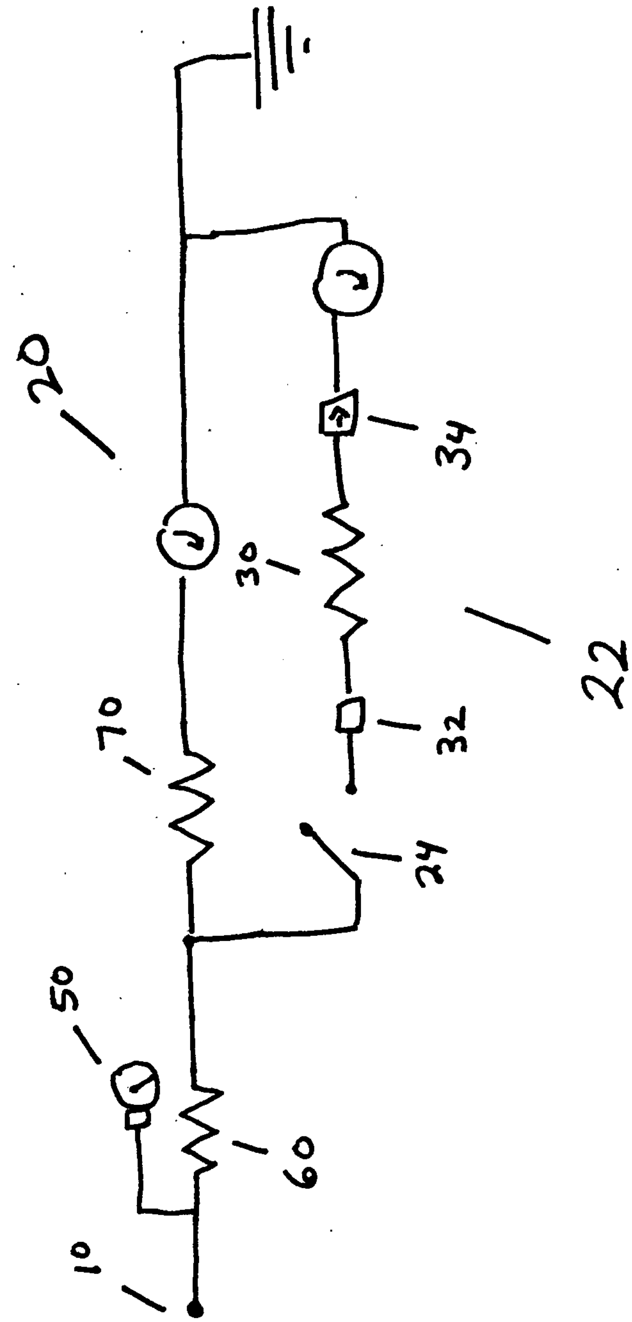
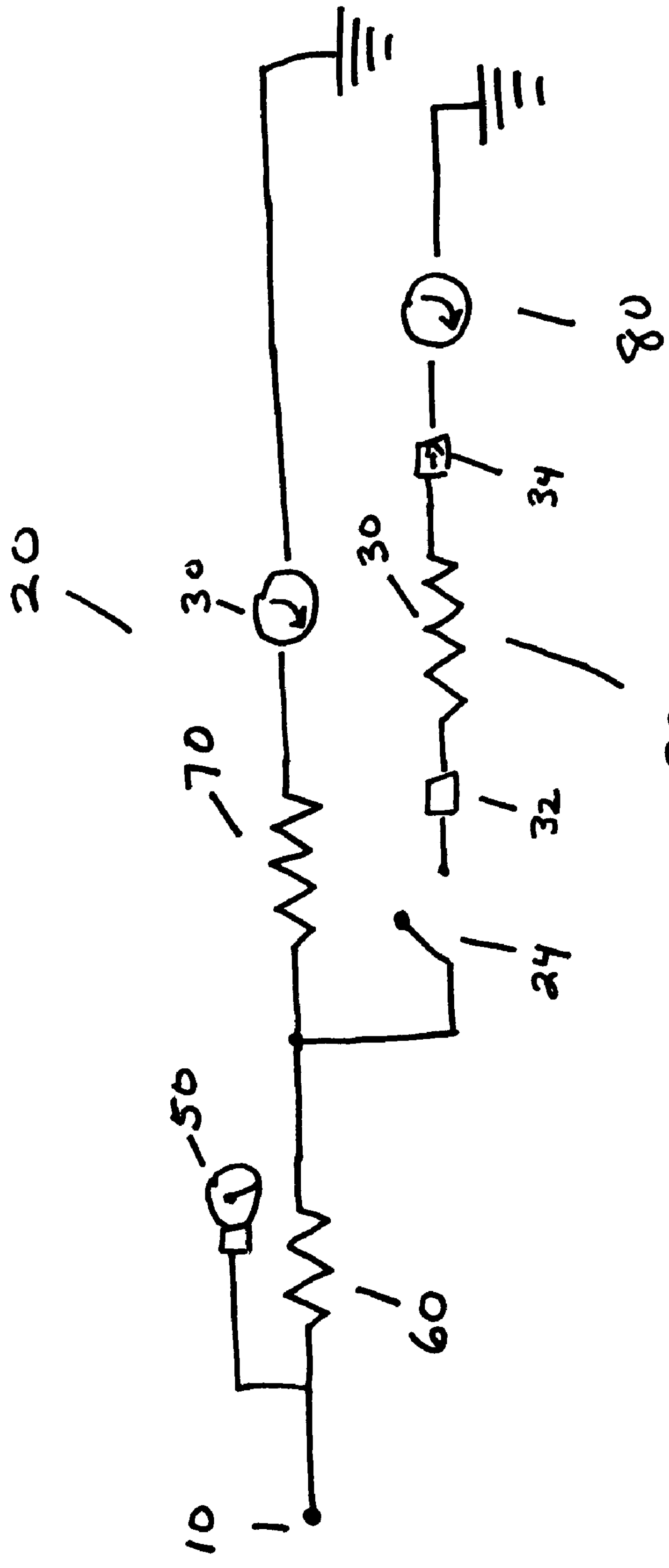


Fig. 3



SYSTEM AND METHOD FOR CONTROLLING THE FLOW OF EXHALED BREATH DURING ANALYSIS

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] This invention relates to systems and methods for the analysis of exhaled breath.

[0003] 2. General Background

[0004] Analysis of a subject's exhaled breath is a promising clinical tool, with potential application in the diagnosis and management of many conditions. For instance, changes in nitric oxide (NO) concentration in exhaled breath can indicate a change in the level of inflammation in the airway of a patient with asthma, indicating an increase in the likelihood of an asthmatic attack. Excessive carbon monoxide (CO) can indicate hemolytic jaundice, and high levels of hydrogen can indicate carbohydrate malabsorption.

[0005] It is difficult to build an exhaled breath analyzer because fluctuations in temperature, humidity, breath flow etc. complicate and interfere with the analysis. These difficulties are especially acute when the device is designed to measure trace gases, such as NO, since the sensitivity required for such analyzers also makes the devices much more sensitive to changes in testing conditions. Thus, any device that seeks to quantify trace analytes in exhaled breath must somehow minimize or account for these variables.

[0006] In particular, a trace gas breath analyzer must make some provision for changes in the flow rate of breath from the patient. In the past, the clinician or device simply provided feedback to the patient, indicating that the flow rate should be higher or lower. An alternative system alters flow resistance in response to changes in flow rate, thereby attempting to maintain a constant flow rate. See U.S. Pat. No. 6,733,463 ("Moilanen System").

[0007] But these previous systems are far from ideal. The "patient control" method is crude and imprecise, and depends on the patient's ability to adjust flow rate. Such a system would likely be impracticable for wide-scale trace-gas analysis of human breath. It is also difficult to use with children.

[0008] Likewise, the Moilanen system is somewhat complex and requires a relatively high number of components, since it depends on a relatively complicated feedback control for operation.

SUMMARY OF THE INVENTION

[0009] The present invention is a system and method for controlling the flow of a gaseous sample in an exhaled breath analysis system. This invention can be used with systems that quantify a number of analytes, including but not limited to trace gas constituents such as NO.

[0010] The present invention has a number of different embodiments, but the common element is the use of a pump or pumps to affect and control the flow rate of the exhaled breath. Two specific embodiments are described, but the scope of the present patent should be determined by its claims, and should not be limited to these two particular embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] **FIG. 1** is a circuit diagram of a "single pump" embodiment of the present invention.

[0012] **FIG. 2** is a circuit diagram of a "dual pump" embodiment of the present invention.

[0013] **FIG. 3** is a circuit diagram of a "dual pump" embodiment in the side and stream and primary stream have separate exhaust points.

DETAILED DESCRIPTION

[0014] The present invention is a system and method for controlling the flow of a sample gas in an exhaled breath analysis system. Two embodiments are described in this patent: a single pump embodiment and a dual pump embodiment. This invention may be used with sensors that have sensing elements that change in response to an analyte in a gaseous sample. Examples of sensing systems and devices that could be used with present invention are provided in U.S. patent applications Ser. Nos. 10/767,709, 10/334,625, and 10/659,408, the disclosures of which are incorporated by reference herein as if set out in full.

Single Pump Embodiment

[0015] The breath analysis begins with the user exhaling into a blow tube **10**. Other means of capturing a flow of exhaled breath can be used, such as a mask, etc. See **FIG. 1**. The breath would be captured from the mouth, and the device would typically allow an entire breath stream to flow through it, with a portion being captured for analysis.

[0016] The breath then travels to a pressure sensor **50** that monitors the pressure within the user's mouth. The pressure sensor **50** should have an operating range appropriate to breath pressure requirements, and in one embodiment this range is 5 to 20 cm H_2O. The pressure sensor **50** is used as feedback for the patient, so that the patient maintains pressure in the desired range of 5 to 20 cm H_2O. When the pressure reaches a threshold, the first pump **40** switches on. In one embodiment, this threshold is 5 cm H_2O, which represents the pressure necessary to close the velum. The upper end of the range, 20 cm H_2O, is selected because pressures above that threshold can cause discomfort in some patients.

[0017] The breath then travels through an optional first resistance means **60**. In conjunction with the second resistance means **70** (described below), the first resistance means **60** may be set to ensure a constant flow rate of 50 cc/sec from the patient. The two resistance means cause the pressure in the patient's mouth to increase, thereby causing the velum to close. The first resistance means **60** may be a fixed orifice, and in one embodiment this fixed orifice has a round aperture of approximately 0.11 cm diameter. Other conventional resistance means could be used instead of or in addition to the fixed orifice. For purposes of this patent, "resistance means" or "resistor" shall refer to a structure that creates resistance. This first resistance means **60** is not necessary, but may help to "tune" the system to the pump specifications.

[0018] After the first resistance means **60**, the circuit splits into two streams: a primary stream **20** and a side stream **22**. See **FIG. 1**.

[0019] The primary stream **20** contains a second resistance means **70** that produces a resistance R_p. In one embodiment, this resistance means **70** may be able to produce a variable resistance, as described below. The second resistance means **70** may be a motor-controlled needle valve, a solenoid controlled needle valve (as used in mass flow controllers), a manual needle valve, a fixed resistance orifice, or any other means of producing the desired resistance.

[0020] The side stream **22** contains a side stream valve **24** that controls whether this stream is open or closed. The side stream valve **24** may be a solenoid valve or other appropriate open/close valve.

[0021] After a predetermined amount of time, the side stream valve **24** opens, and while the side stream is open, the breath flow moves in parallel through the two streams. In one embodiment, the side stream **22** is open for the period of time between 7-10 seconds after exhalation into the blow tube begins. Thus, in this embodiment, for the first seven seconds, all the exhaled breath passes through the primary stream **22**, then through the pump **40**, and then is vented into the ambient atmosphere.

[0022] The side stream **22** contains a sensor **30**. The sensor **30** creates its own resistance, Rs. Other components, including a carbon dioxide scrubber, may also be placed in the side stream **22**. The inlet and outlet of the sensor **30** may have check valves **32**, **34** to prevent leakage. See **FIG. 1**. Thus, for the period of time when the breath is passing through the side stream, it is passing over the sensor **30**.

[0023] There are two different techniques to maintain a constant flow rate from the patient when the side stream **22** is opened. In the first version, the primary stream **20** has a second resistance means **70** that varies its resistance to ensure a total flow rate of 50 cc/sec (or other desired rate) from the patient throughout the entire exhalation. The resistance from the second resistance means **70** will be referred to as "Rp," where the p stands for pump. The resistance from the sensor (Rs) and the other components of the side stream **22** has a constant value, but in this embodiment, Rp has a variable value. When the side stream **22** is closed, the value of the second resistance means is Rp**1**, but when the side stream is open, the value of the second resistance means changes to Rp**2**. The values Rp**1** and Rp**2** are chosen so that the sum of the flow rates through the primary stream **20** and the side stream **22** is equal to the flow rate through the primary stream **20** when the side stream **22** is closed. In setting the values Rp**1** and Rp**2**, the resistance from the other components in the circuit (such as Rs and the first resistance means **60**) must be taken into account, and the pump voltage must also be considered.

[0024] For instance, in one embodiment, the value of Rp may change as described below:

	Side Stream Valve Closed	Side Stream Valve Open
ΔP	32 cm H2O	32 cm H2O
R1	0.4 cm H2O/mL/s	0.4 cm H2O/mL/s
Rp1	0.24 cm H2O/mL/s	Not applicable
Rp2	Not applicable	0.29 cm H2O/mL/s
Rs	infinite	1.5 cm H2O/mL/s
i	50 mL/s	50 mL/s

[0025] In this example, ΔP stands for the change in pressure across the pump, R**1** is the resistance from the first resistance means, Rp**1** and Rp**2** are the resistances from the second resistance means **70** when the side stream valve **24** is closed and open, respectively, Rs is the resistance from the sensor **30**, and i is the total flow through the system and from the patient's mouth.

[0026] As indicated above, in one embodiment, Rp**1** and Rp**2** are chosen so that a constant flow rate of 50 ml/s is maintained throughout exhalation. In this embodiment, the desired flow rate through the sensor **30** is 8 ml/s, so Rp**2**=(8/42)*Rs. Since total flow through both streams should equal the flow through the primary stream when side stream **22** is closed, Rp**1**=(42/50)*Rp**2**. When Rp is variable, as in this embodiment, the second resistance means **70** may be a solenoid needle valve (as used in mass flow controllers), or a motor-controlled needle valve, or a pinch tube valve, or any other suitable resistor that can change its resistance.

[0027] Thus, in this embodiment, when the side stream **22** is opened during the final **3** seconds of exhalation, 8 ml/s passes through the side stream **22**, with the remainder (42 ml/s) of the breath passing through the primary stream **20**. This yields a value of 0.29 for Rp**2**, according to the equation $R_p=F_s*(F_s/F_p)$, where F_s is the flow rate through the sensor in mL/min, and F_p is the pump flow rate in mL/min.

[0028] In the second technique, both Rp and Rs are fixed (Rp=8/42 Rs), and then during the period of time when the side stream **22** is open, the pump varies the pressure drop to accommodate the change in overall circuit resistance resulting from the opening of the side stream **22**.

[0029] For instance, the following table illustrates certain values in the system when the voltage of the pump is varied:

	Side Stream Valve Closed	Side Stream Valve Open
ΔP	34.3 cm H2O	32 cm H2O
R1	0.4 cm H2O/mL/s	0.4 cm H2O/mL/s
Rp	0.29 cm H2O/mL/s	0.29 cm H2O/mL/s
Rs	infinite	1.5 cm H2O/mL/s
i	50 mL/s	50 mL/s

In this example, ΔP stands for the change in pressure across the pump, R**1** is the resistance from the first resistance means, Rp**1** is the resistance from the second resistance means **70**, Rs is the resistance from the sensor **30**, and i is the total flow through the system and from the patient's mouth.

[0030] As shown in **FIGS. 1 and 2**, both the primary stream **20** and the side stream **22** terminate at the same exhaust point.

[0031] The first pump **40** is downstream from the joinder of side stream **22** and the primary stream **20**, so that it can control the overall flow of the system, and not each stream individually. See **FIG. 1**. In one embodiment, the pump **40** would be the model UNMP50 from KNF Neuberger, Inc., which has a free-flow capacity of 66.7 ml/s, a maximum vacuum of 400 mbar (407 cmH2O), and a maximum continuous pressure of 0.5 bar (510 cmH2O). The first pump **40**, which is placed downstream from the sensor **30**, draws breath at a constant flow rate. The first pump **40** is resistant enough to inlet pressure to maintain a substantially constant flow rate despite changes in the subject's mouth pressure across the range of interest for this application, namely 5-20 cmH2O. The pump model described above has the ability to maintain a flow rate within a wide pressure range that is appropriate for the chosen application. Alternatively, the pump could be closed-loop controlled using the pressure sensor **50** as feedback. In one embodiment, the acceptable range would be between 5 cm H_2O and 20 cm H_2O. The lower figure represents the minimum pressure required to close the velum, and the higher figure represents a pressure above which users may experience discomfort.

[0032] By placing the first pump **40** downstream from the sensor, the present system avoids the possibility that output from the pump **40** would contaminate the sensor **30**. When two pumps are used (as described below), both pumps would typically be placed downstream from the sensor **30**. However, it is also possible for the pump or pumps to be placed upstream from the sensor **30**.

Dual Pump Embodiment

[0033] In this embodiment, the system has two pumps: a first pump **40** (as described above), and a second pump **80**. See **FIG. 2**. The second pump **80** may be advantageous because Rs may not be constant across systems but may vary from device to device. Also, Rs may be change as part of a design change to the sensor. With the second pump **80**, independent flow rates can be established for the primary stream **20** and the side stream **22**. As shown in **FIG. 2**, the second pump **80** may be on the side stream **22**, downstream from the sensor **30**, although it could be placed in another location on the side stream **22**. It may be advantageous for the second pump to be placed downstream from sensor **30** so that materials from the pump do not interfere with the gas analysis.

[0034] Both flow rate control methods described above (variable resistance and variable pump operation) may be used in conjunction with the dual pump embodiment.

[0035] In the dual pump embodiment, it may not be necessary to employ a side stream valve **24**. Instead, the second pump **80** may be used to control flow to control flow into the side stream **22**.

[0036] Also, in the dual pump embodiment, side stream **22** and the primary stream **20** may not rejoin, but instead may vent through separate exhaust points. See **FIG. 3**.

Side Stream/Stopped Flow Analysis

[0037] As noted above, the present system uses a side stream **22** to direct breath flow through the sensor **30**. Use of a side stream **22** allows analysis of a relatively small breath sample, which in turn allows the creation of a smaller, more conveniently-sized sensing device. For instance, use of a side stream **22** allows the division of a 50 ml/s exhaled breath stream into a 8.0 ml/s side stream **22** and a 42.0 ml/s primary stream **20**. The smaller side stream **22** can be used to supply exhaled breath to a smaller sensor **30** than would be necessary if the entire breath stream were analyzed.

[0038] Also, as noted above, the side stream **22** is opened only after a period of time, such as 7 seconds after exhalation begins, to allow concentration of the exhaled analyte to stabilize. Breath will then flow into the side stream **22** and sensor **30** for a fixed period of time, such as 3 seconds.

[0039] After the expiration of this period of time, the side stream **22** can be closed to allow the sensor enough time to interact with the exhaled breath. In other words, the sensor **30** will "incubate" a sample of stopped exhaled breath for a period of time. In one embodiment, this "incubation" period or analysis period would be approximately 1 minute. After the incubation period, the sensor **30** would then be analyzed to determine concentration of the analyte. By allowing the sensor **30** to interact with the stopped exhaled breath for a relatively extended period of time, the present invention allows the use of sensors that have response times that are too slow to analyze a moving stream of breath.

[0040] Also, by opening the side stream **22** for a few seconds, the present invention allows the sensor **30** to receive multiple cycles of exhaled breath before the flow is stopped. For instance, if the sensor **30** has a volume of 5.0 ml, and if the side stream **22** provides 8.0 ml/s of exhaled breath to the sensor for 3 seconds, then approximately 24.0 ml of breath will have passed through the sensor before the final 5.0 ml is trapped. This represents three complete cycles through the sensor before analysis begins, thereby completely flushing the sensor of whatever gas was inside the sensor before capturing the breath.

[0041] The "stopped flow" aspect of the present invention provides a number of advantages. By stopping the flow of breath through the sensor during analysis, the present invention creates a stable analytical environment, with no changes in pressure or flow during the entire analysis period. Changes in pressure or flow could create artifacts that interfere with analysis.

[0042] A stopped flow system can also accommodate slow sensors that detect trace gases. By stopping the flow, the system creates a stable testing environment that can be maintained for a much longer period than is possible for a flowing system. In one embodiment, the analysis period is approximately one minute, although much longer periods are also possible.

[0043] The present system can be used for analysis of many different analytes in exhaled breath, including trace gases like NO. For purposes of this patent, "trace gas" includes gases with concentrations below 1 part per million. In one embodiment, the system can be used in a conjunction with a sensor consisting of cytochrome-c in a sol-gel to measure NO.

[0044] One skilled in the art will appreciate that the present invention can be practiced by other than the preferred embodiments, which are presented for purposes of illustration and not of limitation.

We claim:

1. A system for analysis of exhaled breath, comprising:

a. a device for capturing breath from a subject's mouth and for measuring a gaseous analyte in said breath;

b. a sensing element in said device, wherein said sensing element is responsive to trace gases in said exhaled breath; and

c. a pump associated with said device, wherein said pump maintains a substantially constant flow rate from said subject.

2. The system according to claim 1, wherein said pump is downstream from said sensing element.

3. The system according to claim 1, wherein said device captures an entire breath stream from said subject.

4. The system according to claim 1, wherein said flow rate is between 40 and 60 ml/s.

5. The system according to claim 1, wherein said device additionally comprises:

a. a primary stream;

b. a side stream, said side stream containing said sensing element;

and

c. a joinder point wherein said primary stream joins said side stream.

6. The system according to claim 5, wherein said pump is downstream from said joinder point.

7. The system according to claim 1, additionally comprising:

a. a blow tube for capturing said exhaled breath;

b. a pressure sensor downstream from said blow tube;

c. a primary stream downstream from said pressure sensor;

d. a resistor on said primary stream;

e. a side stream downstream from said pressure sensor, wherein said sensing element is on said side stream;

f. a side stream valve for opening said side stream; and

g. a joinder point wherein said primary stream joins said side stream, and wherein said pump is downstream from said joinder point.

8. The system according to claim 1, wherein said sensing element comprises a bioactive molecule.

9. The system according to claim 1, wherein said bioactive molecule comprises cytochrome-c in a sol-gel.

10. The system according to claim 1, wherein said gaseous analyte is nitric oxide.

11. A system for analysis of exhaled breath, comprising:

a. a device for measuring a gaseous analyte in exhaled breath;

b. a primary stream in said device;

c. a first pump in said primary stream for controlling a primary stream flow rate;

d. a side stream in said device; and

e. a second pump in said side stream for controlling a side stream flow rate.

12. The system according to claim 11, additionally comprising a joinder point wherein said primary stream joins said side stream, and wherein said first pump and said second pump are upstream from said joinder point.

13. The system according to claim 11, wherein said side stream and said primary stream have separate exhaust points.

14. The system according to claim 11, wherein said analyte is a trace gas.

15. The system according to claim 14, wherein said analyte is nitric oxide.

16. The system according to claim 15, additionally comprising a sensing element, and wherein said sensing element comprises cytochrome-c in a sol-gel.

17. A system for analysis of exhaled breath, comprising:

a. a primary stream for travel of said exhaled breath;

b. a side stream for travel of said exhaled breath; and

c. a variable resistor associated with said system for attaining a desired constant side stream flow rate.

18. The system according to claim 17, wherein said side stream flow rate is between 5 ml/s and 11 ml/s.

19. The system according to claim 18, wherein said side stream flow rate is between 6 ml/s and 10 ml/s.

20. The system according to claim 19, wherein said side stream flow rate is between 7 ml/s and 9 ml/s.

21. The system according to claim 17, wherein said primary stream has a flow rate of 40-45 ml/s when said side stream is open.

22. A system for analysis of exhaled breath, comprising:

a. a primary stream for travel of said exhaled breath;

b. a side stream for travel of said exhaled breath; and

c. a variable pump associated with said system for attaining a desired constant side stream flow rate.

23. The system according to claim 22, wherein said side stream flow rate is between 5 ml/s and 11 ml/s.

24. The system according to claim 22, wherein said side stream flow rate is between 6 ml/s and 10 ml/s.

25. The system according to claim 24, wherein said side stream flow rate is between 7 ml/s and 9 ml/s.

26. The system according to claim 22, wherein said primary stream has a flow rate of 40-45 ml/s when said side stream is open.

27. A system for analysis of exhaled breath, comprising:

a. a primary stream for travel of said exhaled breath;

b. a side stream for travel of said exhaled breath;

c. means for opening said side stream; and

d. a sensor in said side stream for measuring an analyte in said exhaled breath.

28. The system according to claim 27, wherein exhaled breath flows through said side stream at a rate between 5 ml/s and 11 ml/s when said side stream is open.

29. The system according to claim 27, wherein exhaled breath flows through said side stream at a rate between 6 ml/s and 10 ml/s when said side stream is open.

30. The system according to claim 27, wherein exhaled breath flows through said side stream at a rate between 7 ml/s and 9 ml/s when said side stream is open.

31. The system according to claim 30, wherein said primary stream has a flow rate of 40-45 ml/s when said side stream is open.

32. The system according to claim 27, wherein said side stream is opened between 5 and 9 seconds after exhalation begins.

33. The system according to claim 27, wherein said side stream is opened between 6 and 8 seconds after exhalation begins.

34. The system according to claim 27, wherein said side stream is opened approximately 7 seconds after exhalation begins.

35. The system according to claim 32, wherein said side stream remains open for between 1 and 10 seconds.

36. The system according to claim 35, wherein said side stream remains open for between 1 and 7 seconds.

37. The system according to claim 36, wherein said side stream remains open for between 1 and 5 seconds.

38. The system according to claim 37, wherein said side stream remains open for between 2 and 4 seconds.

39. The system according to claim 38, wherein said side stream remains open for approximately 3 seconds.

40. The system according to claim 27, wherein said sensor comprises cytochrome-c in a sol-gel.

41. The system according to claim 27, wherein said means for opening said side stream comprises a side stream valve.

42. The system according to claim 27, wherein said means for opening said side stream comprises a pump.

43. A method for analysis of exhaled breath, comprising:

a. providing a device comprising:

i. a sensor, said sensor having a sensing element;

ii. a first stream for supplying flowing exhaled breath to said sensor;

b. supplying exhaled breath to said device;

c. stopping a portion of said flowing exhaled breath in said first stream;

d. allowing said portion to interact with said sensing element for an analysis period; and

e. measuring concentration of an analyte in said portion after said analysis period.

44. The method according to claim 43, wherein said device additionally comprises a second stream.

45. The method according to claim 43, wherein said first stream is opened between 5 and 9 seconds after exhalation begins.

46. The method according to claim 45, wherein said first stream is opened between 6 and 8 seconds after exhalation begins.

47. The method according to claim 46, wherein said stopping step occurs between 7 and 13 seconds after exhalation begins.

48. The method according to claim 43, wherein said stopping step occurs between 9 and 11 seconds after exhalation begins.

49. The method according to claim 43, wherein said analysis period has a duration of between 30 and 90 seconds.

50. A system for analysis of an analyte in exhaled breath, comprising:

a. means for capturing a stream of exhaled breath from a subject;

b. means for dividing said stream into a primary stream and a side stream;

c. means for causing said side stream to flow at a substantially constant flow rate; and

d. means for stopping the flow of said side stream for an analysis period.

51. A method of analyzing exhaled breath, comprising:

a. capturing an exhaled breath sample from a subject;

b. flowing said sample through a breath analysis device;

c. ensuring a constant flow rate through said device without monitoring said flow rate.

52. A method of analyzing exhaled breath, comprising:

a. capturing an exhaled breath sample from a subject;

b. dividing said sample into a primary stream and a side stream;

and

c. analyzing said side stream to determine concentration of an analyte in said side stream.

53. A method of analyzing exhaled breath, comprising:

a. capturing an exhaled breath sample from a subject;

b. flowing said sample through a gas sensing device;

c. stopping the flow of said sample for an analysis period; and

d. analyzing said sample to determine concentration of an analyte, wherein said analyzing step occurs after said analysis period.

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