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Flow measurement in mechanical ventilation: a review

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Abstract

Accurate monitoring of flow-rate and volume exchanges are essential to minimize ventilator-induced lung injury. Mechanical ventilators employ flowmeters to estimate the amount of gases delivered to patients and use the flow signal as a feedback to adjust the desired amount of gas to be delivered. Since flowmeters play a crucial role in this field, they are required to fulfill strict criteria in terms of dynamic and static characteristics. Therefore, mechanical ventilators are equipped with only the following kinds of flowmeters: linear pneumotachographs, fixed and variable orifice meters, hot wire anemometers, and ultrasonic flowmeters. This paper provides an overview of these sensors. Their working principles are described together with their relevant advantages and disadvantages. Furthermore, the most promising emerging approaches for flowmeters design (i.e., fiber optic technology and three dimensional micro-fabrication) are briefly reviewed showing their potential for this application.

Keywords: Flowmeter, artificial ventilation, Fleisch pneumotachograph, hot wire anemometry, orifice meter, ultrasonic flowmeter, fiber optic sensor, micromachined sensor.

1 Introduction

Accurate and continuous monitoring of gas exchanges during artificial ventilation is pivotal, to avoid common side effects related to uncorrected ventilation, such as volutrauma or barotrauma (too high amount of gas delivered to patients). In this scenario flowmeters play a crucial role, being used to accurately measure the right amount of gas. Moreover, the volumes of gases exchanged by patients (e.g., minute volume and tidal volume) are estimated by passing the flow signal through an electronic integrator [1]. As a consequence, flowmeters must fulfill strict requirements in terms of both dynamic (i.e., adequate frequency response and short response time) and static (i.e., good accuracy and resolution, high sensitivity, and adequate turndown ratio) characteristics. The use of these sensors with critically ill patients does not allow frequent calibration, therefore zero and sensitivity drifts should be reduced as much as possible. Furthermore, the pneumatic resistance and the volume added to the breathing circuit should be minimized. Lastly, the sensors must be able to reject the influence of gas temperature and composition. This concern is important because both gas composition and gas temperature can experience large changes in mechanical ventilation. Therefore, the influence of gas temperature and composition and the influence of water vapour content on sensors' output must be negligible or well predictable.

In the early 1975, Hayward estimated more than one hundred different types of commercially available flowmeters [2] with a mode of operation based on almost any physical domain. Furthermore, other approaches have been developed due to the advances of three dimensional techniques of micro-fabrication [3] and fiber optics technology [4]. On the other hand, the mentioned strict requirements limit the number of flowmeters suitable in mechanical ventilation. In fact, the commercial mechanical ventilators are equipped with few kinds of flowmeters: orifice meters, ultrasonic flowmeters, hot wire or hot film anemometers, Fleisch and screen (or Lilly) pneumotachographs.

Linear resistance pneumotachographs (both Fleisch and Lilly), which transduce flow-rate in pressure drop across a linear resistance, have been largely employed in mechanical ventilation for years [1]. Good accuracy, compactness, mostly linear response and short response time are the main advantages; but their output suffers from the dependence on gas mixture composition and temperature, and the shift from linearity at high flow-rate [5]. Orifice flowmeters show the same advantages and drawbacks with respect to linear pneumotachographs. The main difference is their quadratic response, however it could be linearized (variable area orifice meter). Hot wire anemometers are based on convective heat exchange. Their main advantages are: good accuracy, high sensitivity at low flow-rate and short response time, the main drawback is their fragility [6]. The most popular ultrasonic flowmeters are based on time of flight, where the change in transit time through a streaming medium is related to the flow-rate. The main advantages are: absence of mechanical parts, negligible pneumatic resistance, good dynamic response, and the possibility to make negligible the output dependence on gas composition and temperature [7, 8, 9]; on the other hand they seem to be less accurate than the above cited flowmeters.

In addition to the already well-established techniques, many research groups are working on the development of micromachined and fiber optic-based flowmeters. Micromachined sensors hold immense potential thanks to low energy consumption, good accuracy, and small size; moreover the continuous development of three dimensional technologies of micro-fabrication is improving their design [3]. Fiber optic technology allows developing sensors with good sensitivity, good accuracy, low pneumatic resistance, and large bandwidth [10,11]; moreover, their immunity from electromagnetic interferences enables the use of these sensors during magnetic resonance procedures.

This paper aims to provide a detailed description of the flowmeters employed in commercial mechanical ventilation, and an overview of the most promising emerging technologies. Sensors' working principle is described in detail, then sensor advantages and weaknesses, considering the main critical issues due to the particular application field, are discussed (i.e., wide range of flow-rates, dynamic performances, changes in gas concentrations, vapour condensation).

2 Traditional Flow Metering in Mechanical Ventilators

In this section flowmeters traditionally used in mechanical ventilation are described. As shown in Table 1, commercial mechanical ventilators mainly use: linear resistance pneumotachographs, described in section 2.1; ultrasonic flowmeter, described in section 2.2, hot wire anemometers, described in section 2.3; and orifice meter described in section 2.4.

Table 1. Type of flowmeters used on several commercial mechanical ventilators

Manufacturer	**Mechanical ventilator**	**Working principle**
Drager	Babylog® VN500; Evita	Hot wire anemometry
CareFusion	AVEA© Ventilator System 200, 300; BEAR 1000	Hot wire anemometry
Covidien	Newport™ e360 Ventilator	Hot wire anemometry
Philips	Respironics V200	Hot wire anemometry
SLE	SLE5000	Hot wire anemometry
Life Medical Equipment Inc.	BEAR CUB™ 750vs Infant Ventilator	Hot wire anemometry
CareFusion	Bird 8400ST; Vela©	Variable orifice
Hamilton Medical	HAMILTON-C1; HAMILTON-C2; HAMITON-C3; HAMILTON-T1; HAMILTON-S1; HAMILTON-G5; GALILEO	Variable orifice
eVent Medical	Inspiration Series Ventilator F7300000, F7200000, F7100000	Screen pneumotacograph
Maquet	Servo Ventilator 900 C/D/E	Screen pneumotacograph
Maquet	Servo-i Ventilator Siemens; Servo-n; Servo-U	Ultrasonic flowmeter and Hot wire anemometer

2.1 Linear resistance pneumotachographs

As well known, the working principle of pneumotachographs is based on the placement of a resistance into a pipeline, in which the fluid is running full: the pressure drop (ΔP) across the resistance (i.e., the primary device) is linearly related to the flow-rate (Q), according to the Hagen-Poiseuille law, under laminar regime. Therefore, the measurement chain needs a differential pressure sensor (i.e., the secondary device) to measure the ΔP.

Two configurations of pneumotachographs, which differ each other in the design of the resistance, are largely used: Fleisch pneumotachographs, FPs, (Fig.1A), proposed by Fleisch in the early nineties [12], are constituted by a number of parallel capillary tubes; after few decades, Lilly introduced a different solution with a linear resistance based on a fine wire mesh (Fig.1B) [13]. Fig.1C schematically shows the entire measurement chain: ΔP, which is proportional to Q, can be generated by the fine wire-mesh screen or by the capillaries (primary device); then, this pressure is transduced by the secondary device (i.e., a differential pressure sensor) into a voltage output.

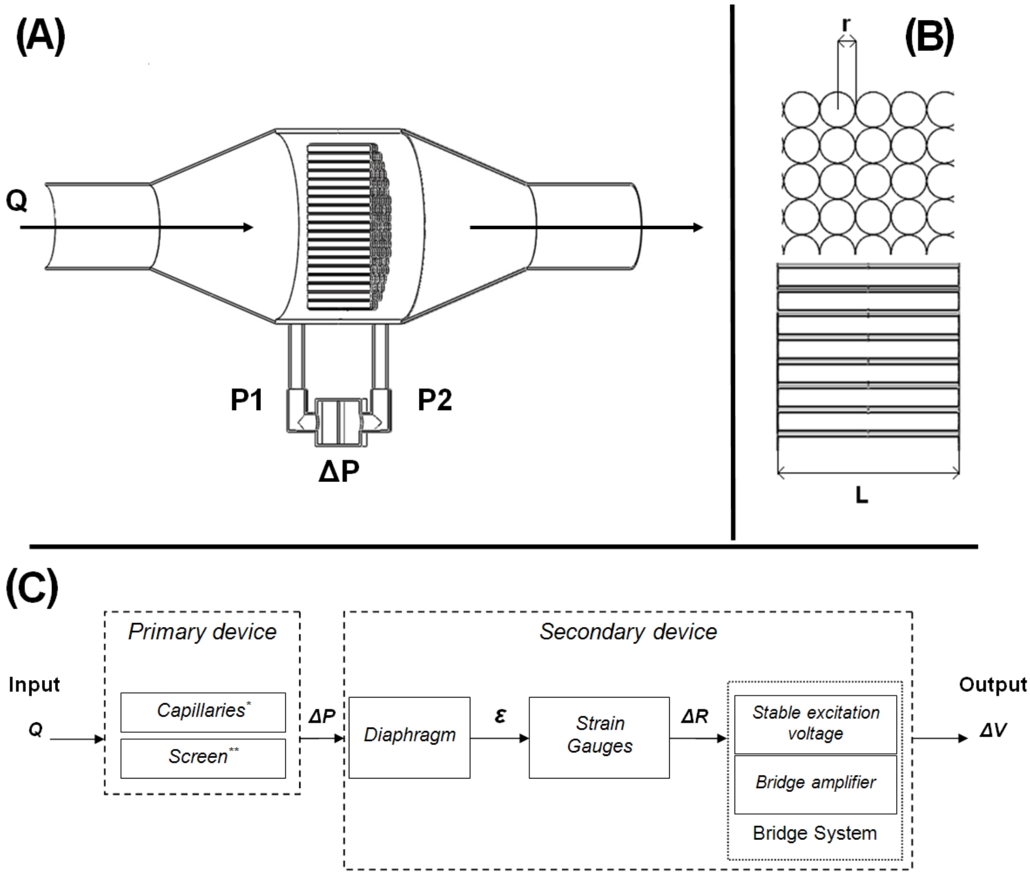

Figure 1. (A) Design of a Fleisch pneumotachograph, (B) Capillary tubes geometry, (C) Working principle block diagram of a pneumotachograph (*Fleisch, **Lilly).

The linear relationship between Q and ΔP depends on the geometry of the resistance (capillary length L, capillary radius r, and number of capillaries n) and on the physical characteristics of the gas:

$$\Delta P = \frac{8 \cdot \mu \cdot L}{n \cdot \pi \cdot r^4} Q \tag{1}$$

where μ is the dynamic viscosity of the fluid. This linear model is the most popularly accepted relationship to describe FP behavior, although some authors have investigated a second order polynomial model [14,15], called Rohrer equation [16].

Considering valid the linear model, the sensitivity (S) of the FP can be expressed as:

$$S = \frac{\partial \Delta P}{\partial Q} = \frac{8 \cdot \mu \cdot L}{n \cdot \pi \cdot r^4} \tag{2}$$

Equation 2 provides useful information to drive the design of FPs and to adjust the sensitivity by modifying the geometry of the resistance: S can be increased by extending the capillaries or by making smaller r. Moreover, Eq.2 shows that the influence of r on S is higher than the one of L: for instance an increase of 50 % of L causes an increase of 50 % of S; an increase of 50 % of r causes a marked sensitivity decrease which becomes 6% of the initial one. Therefore, the geometry can be adapted by considering the particular range of measurement, which strongly changes from adult to pediatric ventilation, and the sensitivity. It is crucial to consider that S is equal to the pneumatic resistance added to the respiratory resistance of the patient, therefore it cannot reach values too high and it is usually defined as a fraction of the respiratory resistance [17].

FPs have to fulfill other requirements as clearly described by Giannella-Nieto and coworkers [17]. First of all the linear relationship between ΔP and Q needs laminar regime within the capillaries (Reynolds number lower than 2000):

$$n \cdot r \geq \frac{Q_{\max} \cdot \rho}{1000 \cdot \pi \cdot \eta} \quad (3)$$

where Q_{max} is the maximum value of flow-rate measured by the FP, ρ and η the density and the viscosity of the gas, respectively. Further requirements are introduced by the need to keep the volume added to the breathing circuit as low as possible, especially in neonatal ventilation. At this purpose several authors developed low volume FP (e.g., 1.8 mL [18] or slightly bigger [15]) for neonatal ventilation.

Equation 1 shows the influence of gas composition and temperature on FP response. In fact, the calibration curve of FP is a function of μ, that depends on gas temperature and composition. This issue is important because patients are ventilated with a gas mixture of O_2 and air, whose composition varies between inspiration and expiration or during therapy (O_2 concentration can range from 21% up to 100%). The gas temperature varies from environmental temperature, when patients need short term ventilation, up to about 310 K, when a breathing circuit equipped with an active humidifier and a heating wire is employed in long term ventilation; temperature of expired gas decreases, from the lungs to the endotracheal tube, from 310 K to about 306 K [19]. Several studies have been performed to assess the influence of oxygen concentration and gas temperature [20,21,22,23]. Some authors proposed correction coefficients to minimize this influence [5,24]. This solution is relevant since frequent calibrations are unfeasible during mechanical ventilation; therefore, the introduction of correction factors allows avoiding excessive errors.

Since the FP requires a secondary sensing device to measure ΔP, its static characteristics such as accuracy, discrimination threshold (i.e., largest change in a value of a quantity being measured that causes no detectable change in the corresponding indication) and range of measurement, are strongly influenced by the choice of an adequate differential pressure sensor.

The dynamic response of FP is largely determined by the sum of two contributions: the first one is mainly due to gas physical properties, and takes into account the conversion of the flow rate into a pressure difference; the second one is related to the response of the secondary device, and takes into account the conversion of the pressure difference into a voltage. Many authors estimated the time constant of FPs [5, 14, 25], and they found values close to 2 ms.

2.2 Ultrasonic flowmeters

Three different types of ultrasonic flowmeters are known. The first type, based on the transmission of ultrasonic signal between a pair of transducers, analyses changes in transit time caused by the velocity of the intervening medium. The second type uses ultrasonic sensing of gas vortices that are generated by a body placed in the gas flow. This "vortex principle" is valid only for unidirectional gas flow and is not very accurate [2]. The third type is based on the Doppler effect: the ultrasound pressure waveform is reflected by particles (i.e., bubbles) flowing in the medium stream. The difference between the frequency of the emitted waveform and the received one is related to the medium velocity. In this kind of flowmeters a sufficient quantity of particles should be spread in the medium.

In this review we focus our attention on the description of the first type, since it is the most used on commercial mechanical ventilators (e.g., Servo-i by Maquet) and on commercial analyzers for pulmonary function testing (e.g., Analyzer CLD 88sp by Eco Medics AG). Such ultrasonic flowmeters are based on the principle that the velocity of sound travelling through a medium is increased or decreased by movement of the medium. For a fixed distance, this decreases the transit time going downstream and increases the transit time going upstream [8]. The properties of ultrasonic transducers, made of piezoelectric material and able to act as both transmitters and receivers, are fundamental for these flowmeters.

Figure 2 shows a schematic representation of an ultrasonic flowmeter: if we represent the duct with a horizontal tube, a pair of piezoelectric transducers (C_1 and C_2) are located at the extremities of a crosstube, whose axis lies at an angle α respect on the axis of flow. The transducers generate ultrasonic signals alternately upstream and downstream and each of them behaves alternately as transmitter or receiver. They must be in close contact with the medium to achieve an adequate acoustic transmission and they have to operate in the range from about 40 kHz to 200 kHz: indeed, frequencies lower than 40 kHz are audible and frequencies higher than 200 kHz will make the absorption losses in the gas drastically large [8].

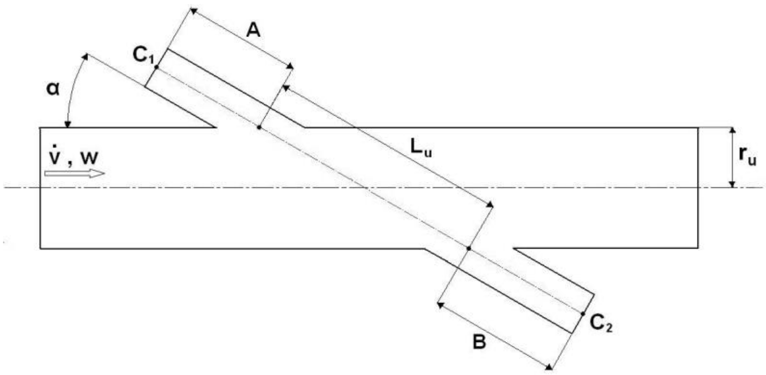

Figure 2. Schematic representation of an ultrasonic flowmeter.

If w is the fluid velocity, the component of w ($w \cos \alpha$) parallel to the C_1-C_2 axis is additive to the velocity of sound propagation; the transit time decreases with gas flow-rate. Difference in transit time provides an indirect measure of the gas velocity, and hence of flow [26], therefore this working principle is called "Time-of-Flight".

Considering Figure 2, each ultrasonic pulse travels the distances A and B at the speed of sound c, and the distance L_u at a speed $c + w \cos \alpha$ (in case sound waves and gas flow propagate in the same direction) or $c - w \cos \alpha$ (in case sound waves and gas flow have opposite sense of propagation). A and B can be neglected respect on L_u if the transducers are placed as close as possible to the duct.

Aiming to describe the basic operation of such flowmeters we may consider that C_1 generates a pulse train at a certain frequency, which is received by C_2 after a transit time T_1. Another pulse train is subsequently emitted from C_2 and the same principle is applied, with the only difference that the medium velocity contrasts the propagation of sound, increasing the transit time T_2.

The electronic of ultrasound flowmeters measures the difference between transit times:

$$D(c,w) = T_2 - T_1 = \frac{L_u}{c - w\cos\alpha} - \frac{L_u}{c + w\cos\alpha} = \frac{2L_u w\cos\alpha}{c^2 - w^2\cos^2\alpha} \tag{4}$$

If α is equal to 45° and c>>w, equation 4 becomes:

$$D(c,w) = \frac{4r_u w}{c^2 - w^2/2} \cong \frac{4r_u w}{c^2} \tag{5}$$

Such approximation for the range of flow encountered in mechanical ventilation is reasonable, since the maximum flow velocity is about 10% of the minimum value of *c*. This leads to a maximum error of 1% [8].

Equation 5 allows estimating the volumetric flow-rate:

$$V(w,c) = \pi \cdot r_u{}^2 \cdot w = \frac{\pi \cdot r_u \cdot c^2}{4} D \tag{6}$$

and consequently, the sensitivity S of the ultrasound flowmeter results:

$$S = \frac{\partial V}{\partial D} = \frac{\pi \cdot r_u \cdot c^2}{4} \tag{7}$$

According to equation 7, S is linearly dependent on the radius of the duct: an increase of the radius corresponds to a proportional increase of S, on the other hand, it causes an increase of the sensor's volume.

Although the mathematical relationships are clear, the potential variability of *c* can introduce considerable complexity. The value of *c* is strictly dependent from composition and density of the gas, its temperature, pressure, and moisture content [27].

For example, a maximal mean error of 3.0 % for measurements in pure oxygen was estimated after calibration performed with air [28].

In essence, composition, temperature, and water vapour dependence require careful control to implement corrections and to obtain accurate flow measurements; therefore, it results indispensable to integrate an algorithm correcting the raw data obtained by such systems. For example, as pointed out by Blumenfeld *et al.* [26], flowmeter calibrated with dry air at 30 °C has a bias of 5.3% of the reading value if the measurement is performed on air having 44 mmHg water vapour pressure at 40 °C. Such bias is even higher when gas composition changes.

Alternatively, other solutions aim at removing the dependency of *w* from *c*.

A first method considers the sum between the two times of flight and the linear approximation explained above:

$$w = \frac{DL_u^{\,2}}{r_u(T_1 + T_2)^2} \tag{8}$$

A second method is based on the product between the two times of flight:

$$w = \frac{L_u}{2\cos\alpha}\frac{D}{T_1 \cdot T_2} \tag{9}$$

A further method is based on the use of a temperature sensor which allows correcting the flow measurement changes due to c dependence on temperature. The use of this additional temperature sensor is implemented on a commercial mechanical ventilator (Servo-i, Maquet).

Ultrasonic flowmeters based on other measurement principles are also manufactured, but they are not described in this paper. They are classified considering the operation in time or in frequency domain, and whether the ultrasounds are continuous or pulsed [8]: 1) Pulsed, time domain - “direct time-of-flight” described above, 2) Pulsed, frequency domain – “sing around”, based on the measurement of pulse frequency difference (as reciprocal of the transit time); 3) Continuous Wave, time domain – “phase shift”, based on the generation of a continuous ultrasonic signal and the measurement of the phase angle between the sinusoidal signal at the transmitter and the receiver to detect change in transit time due to flow; 4) Continuous Wave, frequency domain – “phase-locked frequency-shift” that keeps constant the phase shift between transmitted and received signal, but, when transmit time changes due to flow, the frequency is varied to maintain the phase lock; 5) Beam deflection flowmeters, based on the estimation of flow velocity by measuring the spatial deflection of an ultrasonic beam caused by a moving medium (this method has been successfully applied to liquid flow measurements, but never to measurement of ventilatory gas flow).

2.3 Hot wire anemometers

Hot wire anemometers (HWAs) are based on the heat transfer phenomenon. The heat exchange takes place between the fluid flow and the hot body, which consists of one or more platinum wires. The wires are heated by Joule effect using two fundamental modalities of operation [6]: 1) constant current mode. This approach is based on maintaining the current in the hot body at a constant value, thus, the wire temperature depends on the flow; 2) constant temperature mode. In this design rapid variations in the current heating the hot body are used to keep the sensing element temperature constant. Thereby the hot resistance is constant with flow speed: the higher the speed, the higher the current value to establish the thermal equilibrium. This modality is usually used for velocity measurements in isothermal flows due to the good frequency response [6].

Considering negligible the conductive heat losses, in steady-state conditions, the hot element, placed in a fluid stream at temperature T_f, reaches an equilibrium temperature -T_W-, depending on the heat flow exchanged with the fluid and can be obtained by the following equation:

$$I^2 \cdot R_f = h_W \cdot S_e \cdot (T_W - T_f) \tag{10}$$

where I is the current which flows on the heated wire, h_W is the heat transfer coefficient, and S_e is the heat exchange surface.

The heat transfer coefficient depends on the system geometry, the physical properties of the fluid, and the fluid velocity. It can be expressed as:

$$h_W = A + B \cdot (\rho \cdot v)^n \tag{11}$$

where A and B are two calibration constants, ρ is the fluid density, v is the mean fluid speed, and n is usually considered equal to 1/2, following the pioneering study by King [29]. Since the use of King's law can cause large measurement errors, the HWA input-output relationship is often modelled by a fourth order polynomial relationship [30], or different n values in particular at low gas speed [31].

When operating in constant temperature mode, the relationship between fluid velocity and I is not linear (see equations 10 and 11).

The working principle does not allow discriminating the fluid flow direction. Different solutions have been proposed to fulfill the requirement of bi-directionality, thereby to discriminate inspiratory and expiratory flows.

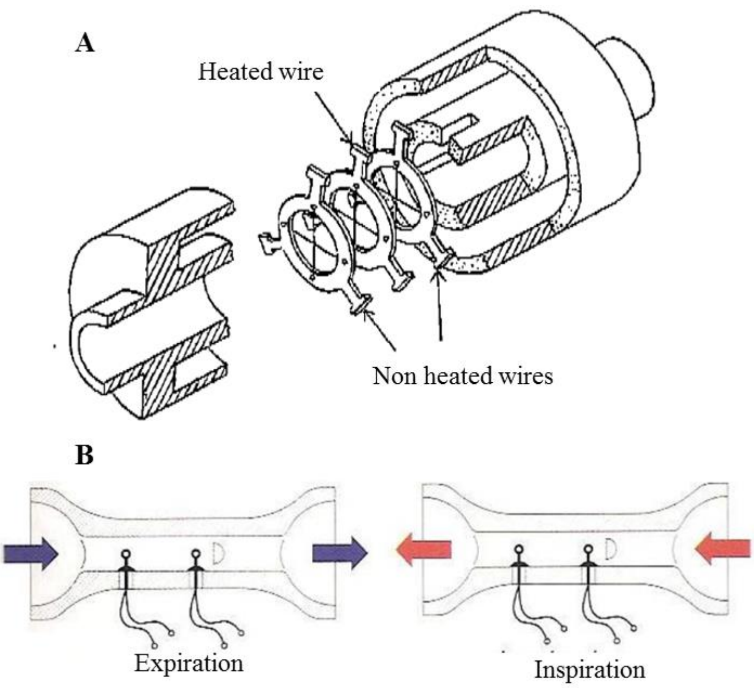

Figure 3. Two solutions to discriminate flow direction: A) the HWA consists of three wires [32]; B) the solution is based on the presence of two heated wires and a screen.

They can be split in two main approaches: 1) two wires are placed on each side of a heated wire. When the hot wire is hit by the fluid flow, the upstream wire is cooled, whereas the downstream one is heated (Figure 3.A). At different flow direction, the sign of the difference between the resistances of the two wires changes, allowing the discrimination of the flow direction [32]. In this solution the heated wire operates at constant temperature and both the upstream and downstream wires operated at constant current. A simplified version employs only two heated wires: the temperature of the fluid hitting the downstream wire is higher than the temperature hitting the upstream one. As a consequence, the electrical output of the sensor changes polarity with flow direction [33]; 2) the second configuration is based on two heated wires and a screen, placed close to a wire (Figure 3.B). In steady state condition the heat exchanged by the two hot bodies is nominally identical during expiration phase; in inspiratory phase the wire close to the screen exchange a negligible amount of heat with the fluid flow.

As previously described the input-output relationship of HWAs is non-linear; in particular, the lower is the fluid velocity, the higher is the sensitivity.

Concerning the dynamic response of HWAs, it is not instantaneous due to the thermal inertia of the hot body. When employed in constant current mode, HWAs' response is modelled with a first order equation, therefore the step response can be described with the time constant (τ). Time constant value of HWAs depends on the geometrical properties of the wire; for typical value (e.g., wire diameter of some µm and wire length of about 1 mm), the time constant is a fraction of ms. The frequency response can be considered flat up to hundreds of Hz. The dynamic performances in controlled temperature mode are deeply investigated [34]. In this configuration, the HWAs improve the frequency response (flat up to 10^4 Hz). The good dynamic response allows using the HWA to monitor gas exchanges during high frequency oscillatory ventilation (HFOV) with good accuracy [35].

The influence of gas temperature changes and gas composition can be minimized by some techniques, as shown during HFOV [36,37]. A further possible source of error is related to the non-uniform gas velocity distribution along the length of the wire; however, the short length of the HWAs and the not excessive velocity of the gas during mechanical ventilation minimize this concern.

Commercially available mechanical ventilators (see Table 1) are equipped with HWAs manufactured with platinum wires, but some research groups have investigated the chance to develop HWAs by employing other hot bodies based on silicon technology [38] or transistors [39].

2.4 Orifice flowmeters

Orifice meters (OMs) are constituted by an orifice plate placed inline a pipeline where gas is supposed running full. The gas flowing through the orifice generates a pressure drop (ΔP) between the upstream and downstream sides of the plate. A differential pressure sensor is employed to pick up the ΔP. A root square function, based on the Bernoulli equation, relates the flow rate with the ΔP [40].

The relationship between Q and ΔP is usually achieved by simplifying hypotheses (e.g., hypotheses of one-dimensional flows and incompressible, non-viscous and isothermal fluid conditions), and then modified by correction factors based on empirical evidence [2]:

$$Q = N_{v\rho} \frac{Cd^2Y}{\sqrt{1-\beta^4}} \frac{\sqrt{\rho_{f1}}}{\rho_b} \sqrt{\Delta P} \tag{12}$$

where β is the diameter ratio expressed by the relation β=d/D, d is the orifice diameter and D the pipe internal diameter, C is the discharge coefficient; Y is the expansion factor of the gas; ρ_{f1} is the upstream gas density at flowing conditions [kg/m^3]; ρ_b is the gas density at base conditions (T=288.15 K, P=101325 Pa) [kg/m^3]; N_{vp} is the factor for flowing volume with density determination (N_{vp}≅169.4 for volumetric flow-rate expressed in L/min) [41].

An important concern is related to the influence of gas temperature and gas composition on OM output because they influence the physical characteristics of gas reported in equation 12 [42] (e.g., a temperature increase determines an increase of the ΔP, considering same Q).

Variable orifice flow sensors have become popular in the long-term critical care monitoring environment in order to overcome the biggest limitation of the fixed OM (i.e., the effect of water condensation, caused by the difference between body and ambient temperature, and the presence of secretions). This is allowed by new configurations, for example including a flap made of flexible sheet materials like plastic or stainless steel. The flap, cut in the middle and placed into the gas stream, creates an opening that widens with the increase of Q. As a consequence, variable OMs effect an automatic mechanical linearization between ΔP and Q by changing flow resistance. By appropriately choosing elasticity and shape of the flap the orifice will enlarge with Q, avoiding the increase in resistance [42]; in this way the resistance of the orifice remains almost constant over a wide range of Q; it allows obtaining a linearization of the calibration curve, hence a larger range of measurement than in fixed OM [43]. Different designs have been proposed and patented in the previous years from J.J. Osborn [44], Guillaume D.W. *et al.* [45], Stupecky J. [46], and Ciobanu C.I. *et al.* [47].

3 Flow Metering in Mechanical Ventilators: emerging technology

During last decade different research groups are focusing their scientific interest in developing fiber optic-based flowmeters. Many of these sensors cannot be applied in mechanical ventilation due to their encumbrance or because able to only monitor flow of liquids [48, 49, 50, 51]. On the other hand some authors focused their attention on the application of fiber optic-based flowmeter in mechanical ventilation. The research groups of Schena and Battista proposed different designs of target flowmeters based on fiber optics for application in neonatal ventilation [10, 52, 53, 54]. All these sensors can be considered intensity-modulated fiber optic sensors. Although these sensors are not ready to be embedded in commercial ventilators, they showed some valuable characteristics, such as good sensitivity (up to 72 mV·min L^{-1}), higher sensitivity at low flow-rates, low pneumatic resistance (up to 0.48 Pa·min·L^{-1}), and in some cases they were able to perform bidirectional measurements. The mentioned studies did not focus on the dynamic response of the sensors, but the working principle and the sensors' design allow supposing good dynamic characteristics. Moreover, the fiber optic immunity from electromagnetic interferences and their small size, make this technology attractive for several applications occurring inside, or close to, the magnetic resonance scanner [55]. The need for "MR-compatible" sensor is growing considerably because of the impact of MRI in biomedical research and practice, and the continuous increasing request for high field devices (7 Tesla or even more) MRI.

The micromachining technology is developing very rapidly during the last decades. A valuable work describing the research and development of micromachined flowmeters in the first 20 years of their history was published by Nguyen [56]. After the first applications for industrial and consumer applications, micromachined sensors have been applied in different fields of medicine [3]. This technology has been also proposed to develop flowmeter for mechanical application. Van Putten *et al.* designed a flowmeter for respiratory applications with very interesting performances, such as a measuring range from -60 L/min to +60 L/min, a short rise-time (i.e., 40 ms), and bidirectionality [57]. This technology has also been employed to develop different kinds of flowmeters for other applications related to respiratory monitoring: Shikida *et al.* developed a novel flow sensor based on King's law for measuring the aspirated- and inspired-air characteristics trans-bronchially [58] and to prevent the insertion of the tube into the esophagus [59]; Svedin *et al.* developed a flowmeter consisting of a turbine fixed to a torque sensor, which converts the volume flow into a torque [60]; Zhe Cao developed a low cost respiratory monitor based on a micro- hot film flowmeter [61].

4 Discussion

Mechanical ventilation is indispensable in support of patients with respiratory failure who are critically ill. The mechanical ventilators have to accurately deliver the required amount of gases in order to avoid the increase of incidence of ventilator-induced lung injury. The flowmeters embedded into the ventilators provide a real time feedback useful to adjust flows and volumes of gases delivered to patients; therefore, these flowmeters have to perform accurate and rapid measurements. This requirement is particular challenging because of some critical issues, such as a wide range of measurement, changes in gas composition, sometimes the vapour condensation, adequate dynamic response, and low pneumatic resistance, among others. Due to these strict requirements only few kinds of flowmeters are employed.

FP shows short response time, low volume, good sensitivity and accuracy; on the other hand, the influence of gas composition and temperature on the output, and the increase of resistance with sensitivity are the main concerns. A further influencing factor is the flow distribution within the pipe; as a consequence the geometry of the connectors between the FP and the pipe interferes with the FP's output. For this reason the FP should be calibrated with the same connection as used during the measurements. Moreover, they have to be equipped with an electric heater resistance around the capillaries or the screen to avoid condensation of vapour. When condensation happens, a partial occlusion of capillaries or fine mesh of the screen results in an increase of FP response.

The ultrasonic flowmeters show fast response time and good accuracy (the mean error in the estimation of tidal volume is lower than 6.5% [8, 28]), adequate dynamic range (estimated frequency response of an ultrasonic flowmeter is flat and unaffected by the presence of an endotracheal tube until 4.5 Hz), good stability (repeated measurements over 5.5 h have a mean error of 0.4% [28]), absence of moving parts, negligible flow obstruction and low volume, inherent bidirectionality, ease of sterilization and cleaning. One of the main drawback is that changes in flow velocity, gas composition, and temperature alter the shape of the received pulse making accurate detection more difficult. This must be added to the poor acoustic efficiency of ultrasonic transmission through gases. Another major drawback, when the ultrasonic flowmeters are used in bidirectional applications, is the considerable difference between inspiratory and expiratory tidal volume estimations: this might be due to the fact that T_1 and T_2 should be equal when airflow is zero [62], but practically it is impossible to build a perfectly precise and symmetrical device. To overcome this problem, the manufacturer recommends modifying the inspiratory and expiratory gains [28].

The HWAs show a non-linear input-output relationship; in particular, the lower is the fluid velocity the higher is the sensitivity. This characteristic can be considered an advantage when employed to monitor low flow (e.g., in neonatal ventilation). The dynamic response is not instantaneous, because of the thermal inertia of the hot body. Time constant values of HWAs depend on the geometry of the wire, typical values are fractions of ms. The frequency response can be considered flat up to hundreds of Hz. This good dynamic response allows using the HWA to monitor gas exchanges during high frequency oscillatory ventilation (HFOV) with good accuracy [63].The influence of gas temperature changes and gas composition can be minimized by some techniques, as shown during HFOV [64]. A further possible source of error is related to the non-uniform gas velocity distribution along the length of the wire. Further advantages of HWAs are the almost null pneumatic resistance and the low volume.

Among others, the advantages of OMs are: ease of manufacturing and robustness, no maintenance required, ability to distinguish the flow direction. A further valuable characteristic is the good accuracy (can be better than 2% [65]). As noted by Heulitt *et al.* [66] in neonatal ventilation, OMs are more accurate than HWAs and allow a better estimation of the tidal volume. On the other hand, the OM response is influenced by gas temperature and composition, which can weaken the sensor's accuracy, and by presence of moisture and secretions [67] or additional liquid compounds in the breathing circuit: in case of partial liquid ventilation a fixed OM can overestimate the tidal volume (up to 16%), after addition of perfluorocarbon [68]. Variable OMs are immune to measurement errors caused by moisture and mucous in the breathing circuit: in fact probability of obstruction or resistance variation caused by deposition of material (i.e., water, mucous) is lower when compared to fixed OMs. On the other hand the accuracy and the sensor response depend on the stress-strain characteristics of the variable orifice flap, which can be degraded by inter-device variations or intra-device changes due to fatigue during long-term use. In order to solve this problem, some manufacturers offer sensors with specific pre-calibration parameters stored within a memory chip attached within the flowmeter connector. Moreover, variable OMs are susceptible to changes in flow patterns generated by different breathing circuit adapters placed in the upstream side of the flowmeter, and can suffer from resonant vibration or flutter of the leaves which comprise the flow obstruction at low flow rates.

The main advantages and drawbacks of the flowmeters are reported in table 2.

Table 2. Advantages and drawbacks of the traditional flowmeters for mechanical ventilators.

	Advantages	**Drawbacks**
FP	linear response; bidirectionality; good accuracy; constant sensitivity; short response time; low volume; robustness; not particularly expensive.	pneumatic resistance increases with sensitivity; influence of gas composition and gas temperature on response; presence of condensation influences the response; connectors geometry between the pneumotachograph and the pipe influences pneumotacograph’s output.
OM	linear response (variable orifice meter); bidirectionality;	pneumatic resistance increases with sensitivity; influence of gas composition and gas

	good accuracy; short response time; low volume; robustness; not particularly expensive.	temperature on response; presence of condensation influences the response; quadratic response, hence low sensitivity at low flow-rate (fixed orifice meter).
HWA	short response time; good accuracy; low volume; negligible pneumatic resistance; high sensitivity at low flow-rate (crucial in neonatal ventilation).	fragility; high cost; not intrinsic bidirectionality.
US	short response time; negligible pneumatic resistance; low volume.	not accurate as the other flowmeters; considerable difference between inspiratory and expiratory tidal volume estimation.

In addition to the already well-established techniques described in the present review, there is a growing interest in research activities related to micromachined and fiber optics-based flowmeters. Some studies have shown the possibility to design FOSs with high sensitivity, low pneumatic resistance, small size, bidirectional characteristics, and immunity from electromagnetic interferences; some research groups developed micromachined flowmeters for mechanical applications, with very interesting performances in terms of wide measuring range, short rise-time, and bidirectionality. Considering these characteristics, although both FOSs and micromachined sensors are not yet embedded in commercial ventilators, they seem promising to be employed in this field.

A recent valuable article written by Jewitt and Thomas [69] reviewed the physical principles that underpin some techniques used in the clinical setting for measuring flow and volume of gases (e.g., FP, HWA and ultrasonic flowmeter). They reported a clear description of the working principles, on the other hand they did not focus on the main advantages and drawbacks of traditional flowmeters and on the description of emerging technologies. The present work focuses on the most common principles used to design flowmeters employed on mechanical ventilators, on their static and dynamic characteristics, and on their advantages and drawbacks considering the particular requirements and critical issues of the application fields.

Definitively, the flowmeters used in mechanical ventilation show several features which motivate their employment in this field. The chance to introduce flowmeters based on other technologies (i.e., fiber optics or micromachining) is just at the beginning, but some valuable characteristics make their exploitation attractive and motivate the growing scientific interest in these technologies.

Conflict of interest statement

No conflict of interest.

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