Use of a Right Ventricular Continuous Flow Pump to Validate the Distensible Model of the Pulmonary Vasculature

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Summary

In the pulmonary circulation, resistive and compliant properties overlap in the same vessels. Resistance varies nonlinearly with pressure and flow; this relationship is driven by the elastic properties of the vessels. Linehan *et al.* (1982) correlated the mean pulmonary arterial pressure and mean flow with resistance using an original equation incorporating the distensibility of the pulmonary arteries. The goal of this study was to validate this equation in an *in vivo* porcine model. *In vivo* measurements were acquired in 6 pigs. The distensibility coefficient (DC) was measured by placing piezo-electric crystals around the pulmonary artery (PA). In addition to experiments under pulsatile conditions, a right ventricular (RV) bypass system was used to induce a continuous pulmonary flow state. The Linehan's equation was then used to predict the pressure from the flow under continuous flow conditions. The diameter-derived DC was 2.4 %/mmHg (±0.4 %), whereas the surface area-based DC was 4.1 %/mmHg (±0.1 %). An increase in continuous flow was associated with a constant decrease in resistance, which correlated with the diameter-based DC (r=-0.8407, p=0.044) and the surface area-based DC (r=-0.8986, p=0.028). In contrast to the Linehan's equation, our results showed constant or even decreasing pressure as flow increased. Using a model of continuous pulmonary flow induced by an RV assist system, pulmonary pressure could not be predicted based on the flow using the Linehan's equation. Measurements of distensibility based on the diameter of the PA were inversely correlated with the resistance.

Key words

Pulmonary circulation • Distensibility • Assist device • Vascular resistence

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Introduction

In the pulmonary circulation, resistance is usually considered to be the ratio of the driving pressure (mean pulmonary arterial pressure [MPAP] minus the left atrial pressure [LAP]) to the flow. However, the observed measurements are not consistent with the predicted values (Naeije 2003). Indeed, the relationship is curvilinear instead of linear, and the intercept is higher than the outflow pressure. One explanation is that there is a critical opening pressure for the vessels and that some vessels may be recruited according to the need (i.e. a so-called Starling resistor) (Permutt and Riley 1963). However the mean pressure/mean flow relationship is not optimally predicted by sequential vessel opening (Mitzner 1983); thus, other hypotheses have been proposed to explain the observed relationships.

One hypothesis is based on the distensibility properties of the resistive vessels. In the pulmonary circulation, there is an overlap of compliance and resistive features within the same vessels, and these compliance properties have been observed to extend down to the capillary level (al-Tinawi *et al.* 1991, Presson *et al.* 1998). Such a design has been shown to be optimal for the homogenous distribution of flow in the lung

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vasculature (Dawson *et al.* 1999*a*).

In practice, if resistance vessels exhibit distensibility properties, as pressure increases, vascular resistance is expected to decrease.

Krenz and Dawson (2002) and Linehan *et al.* (1992) have thoroughly investigated this question and developed an equation linking the pulmonary arterial pressure (P) to the flow (Q) through unrelated variables:

$$P = \frac{\left[(1+\alpha.LAP)^5+5.\alpha.R_0.Q\right]^{\frac{1}{5}}-1}{\alpha} \qquad (1)$$

where R_0 is the resistance at zero flow, a mathematical abstraction translating the maximal resistance of the vascular tree based on its morphology, LAP is the left atrial pressure; and alpha (α) is the distensibility coefficient (DC_α), which reflects the elastic properties of the vessels. This mathematical expression describes a weakly nonlinear relationship between pressure and flow, with higher distensibility leading to a lower increase in pressure for any given flow.

A potential use for this equation could be to compare patients based on the value of their resistance at zero flow (R_0), thereby reflecting the true resistivity of the pulmonary circulation that is unrelated to the distension pressure. However, determination of R_0 requires knowing the value of the distensibility coefficient, which has not been determined under pathological conditions.

One way to derive the distensibility coefficient is to make some assumptions about R_0, which is sometimes reported as the resistance at rest (Malhotra *et al.* 2016) rather than the resistance at zero pressure. Several studies have used dobutamine and exercise to obtain pressure and flow relationships that could be fitted with the Linehan's equation to obtain the DC_α (Reeves 2005)**.**

Although the Linehan's equation is used in the clinical setting (Wauters *et al.* 2015), its reliability has been poorly explored. The initial equation was designed in the lower lobe of the lung, exclusively in zone 3 of West, and whether the equation applies to the whole lung has never been validated.

The goal of this study was to validate the Linehan's equation in an *in vivo* experimental model wherein the pulmonary system functions in its physiological environment, but the pulmonary flow is tightly controlled by a continuous flow system bypassing the right ventricle. We also compared the DC_α as defined by Linehan *et al.* (1992) which requires measurements at zero pressure, with the DC derived using diastolic-systolic cross-sectional area variation (DC_A), which can be determined non-invasively.

Materials and Methods

The study protocol was performed according to the standards of "The Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (publication 85-23, revised 1996) and approved by the ethical committee for animal research of the Ghent University Hospital (ECD 18/30).

Experimental preparation

Six landrace pigs (weight: 50.6±4.2 kg) were included in the study. Following premedication with intramuscular tiletamine and zolazepam in a combined solution with 2 % xylazine (0.2 ml/kg), anesthesia was induced with intravenous propofol (3 mg/kg), sufentanil (0.005 mg/kg) and rocuronium bromide (1 mg/kg). After endotracheal intubation, the animals were mechanically ventilated with FiO_2 (40 %) and tidal volumes of 0.1–0.15 l/kg. Anesthesia was maintained with continuous sevoflurane (2.5 %) administered through the AnaConda® system (Sedana Medical, Sundbyberg, Sweden), additional boluses of sufentanil (0.005 mg/kg) were administered as needed. Basic monitoring included electrocardiography, body temperature measurement and capnography. Intermittent arterial blood gas sampling was performed to control the ventilatory settings.

A central venous line was inserted via the external jugular vein for saline infusion at a constant rate of 3-5 ml/kg/h. A single-lumen fluid-filled catheter was placed in the left carotid artery for continuous monitoring of systemic arterial pressure.

The heart was exposed through a midline sternotomy and longitudinal opening of the pericardium. A pressure transducer-tipped catheter (Millar SPR-524, Millar Instruments, Houston, TX) was inserted into the pulmonary artery (PA).

Four 2-mm piezo-electric crystals (Sonometrics, London, Ontario, Canada) were secured with 6/0 prolene stitches to the base of the PA in a two-by-two diametrically opposed pattern to measure the instantaneous PA diameter under pulsatile flow conditions. The diameter of the PA at zero pressure was measured after sacrificing the animals.

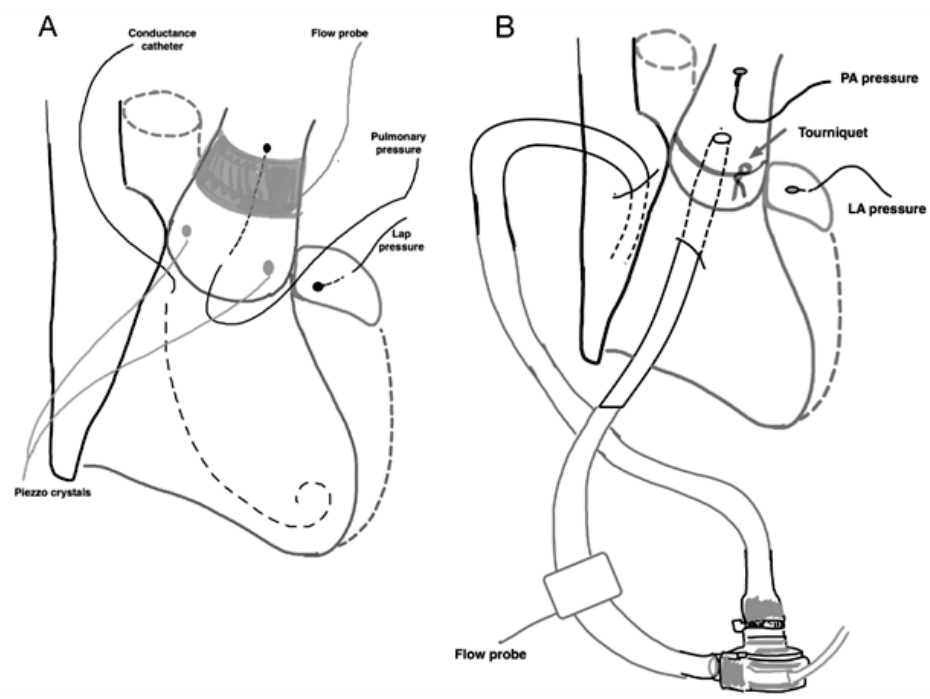

Fig. 1. Experimental settings. **A**: Pulsatile setting. **B**: Right ventricular bypass with continuous flow pump.

A 16-mm perivascular flow probe (Transonic Systems, Ithaca, NY, USA) was placed around the PA for continuous measurement of the PA flow. A second pressure transducer-tipped catheter (Millar SPR-524; Millar Instruments, Houston, TX, USA) was inserted into the left atrium to monitor LAP, while a 7F dual-field pressure-volume catheter (Millar, Millar Instruments, Houston, TX) was inserted by direct puncture into the right ventricle to monitor intraventricular pressure. The pressure and flow in the PA, LAP and right ventricular (RV) pressure were recorded at the basal level under pulsatile conditions (Fig. 1A).

In the second phase, the PA perivascular flow probe and the piezo-electric crystals were removed. The PA was encircled with umbilical tape as a tourniquet for PA constriction. A 29Fr multiperforated cannula (Stöckert Instruments, München, Germany) was inserted into the right atrium. Simultaneously, a straight 22Fr cannula (Medtronic Inc., Minneapolis, USA) was inserted into the PA through the RV outflow tract and secured with a 5/0 prolene purse-string suture. The cannulas were connected to a continuous flow pump (Heartware Inc., Miami Lakes, FL, USA) via two silicon tubes (size 31Fr at the inflow side and size 27Fr at the outflow side, Fig. 1). The pump was initiated at 2000 RPM, and the tourniquet was tied around the PA cannula to limit the PA flow that was delivered by the continuous flow pump. The exact pump flow was recorded via a flow probe Transonic Systems, Ithaca, NY, USA) connected to the arterial tubing. The pump flow was progressively increased by increments of 100 RPM until the flow doubled (Fig. 1B).

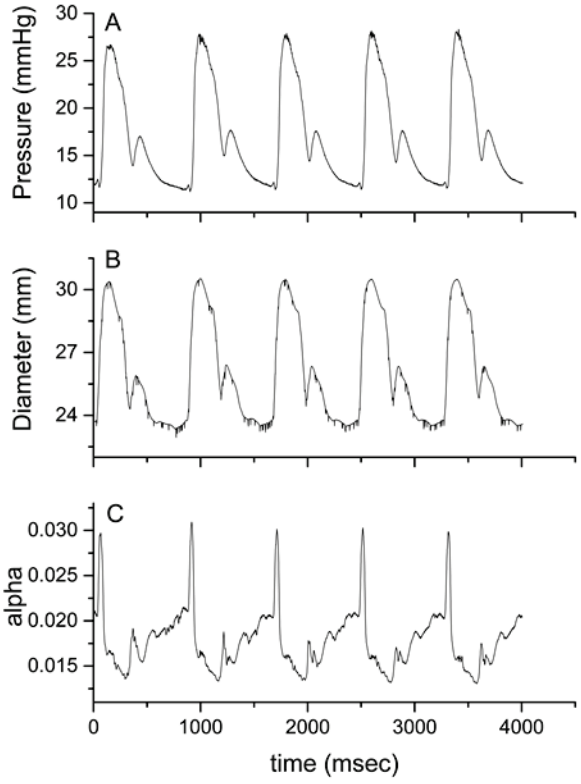

Fig. 2. Pig 1 instantaneous measurements. **A**: Pulmonary artery pressure. **B**: Instantaneous diameter. **C**: instantaneous distensibility coefficient α.

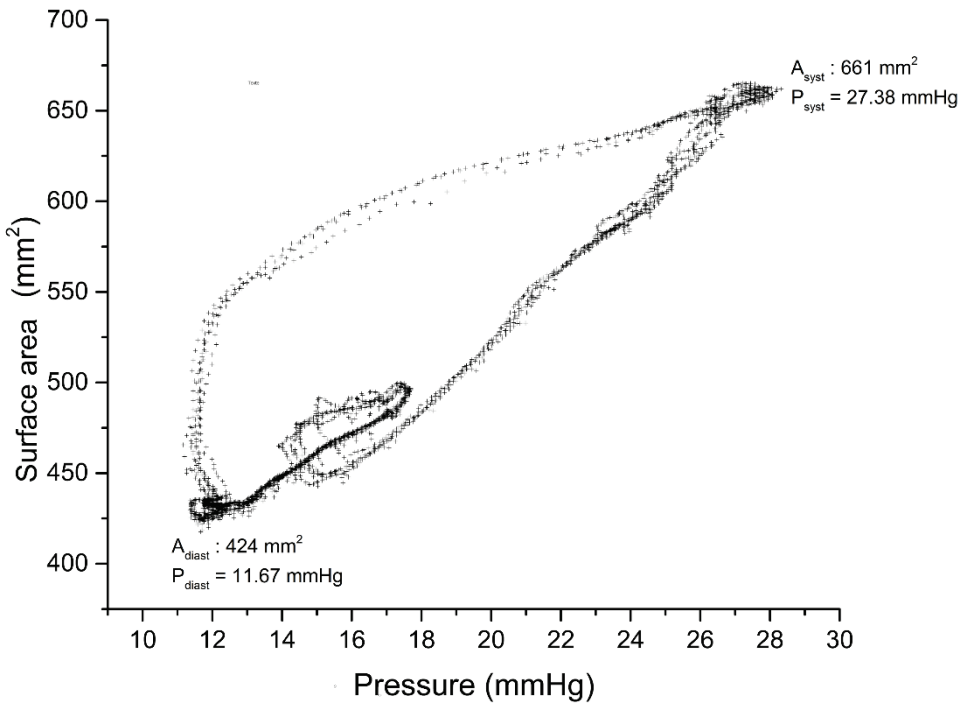

Fig. 3. Pulmonary artery pressure and surface relationship. The surface area distensibility coefficient was measured based on the systolic area (A_{syst}), diastolic area (A_{disat}) and the pulse pressure (P_{syst}-P_{diast}).

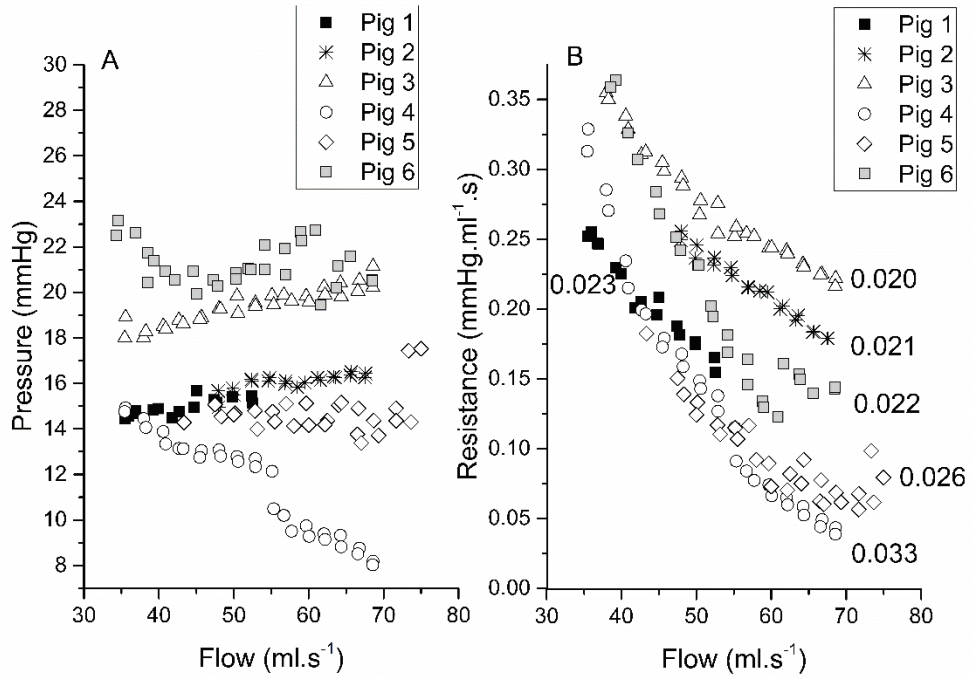

Fig. 4. A: Flow and pressure relationship with increasing pump flow. **B**: Flow and resistance relationship with increasing pump flow. Distensibility coefficient alpha is indicated for every animal.

Data acquisition and processing

Pressure, flow, intraventricular volume and PA diameter data were recorded and digitized at 1000 Hz with a data acquisition system (Powerlab 16/9, Ad Instrument, Dunedin, New Zealand) and software (Labchart 7, Ad Instrument, Dunedin, New Zealand). Data analysis was performed using embedded or custom-made functions in a MATLAB environment (MATLAB, Mathworks, Natick, MA).

Validation of the Linehan paradigm

i) Distensibility

According to Linehan *et al.* (1982), the diameter of the PA (D) is linearly related to the pressure (P) when normalized to its diameter at zero pressure (D_0):

$$\frac{D}{D_0} = 1 + \alpha P \qquad (2)$$

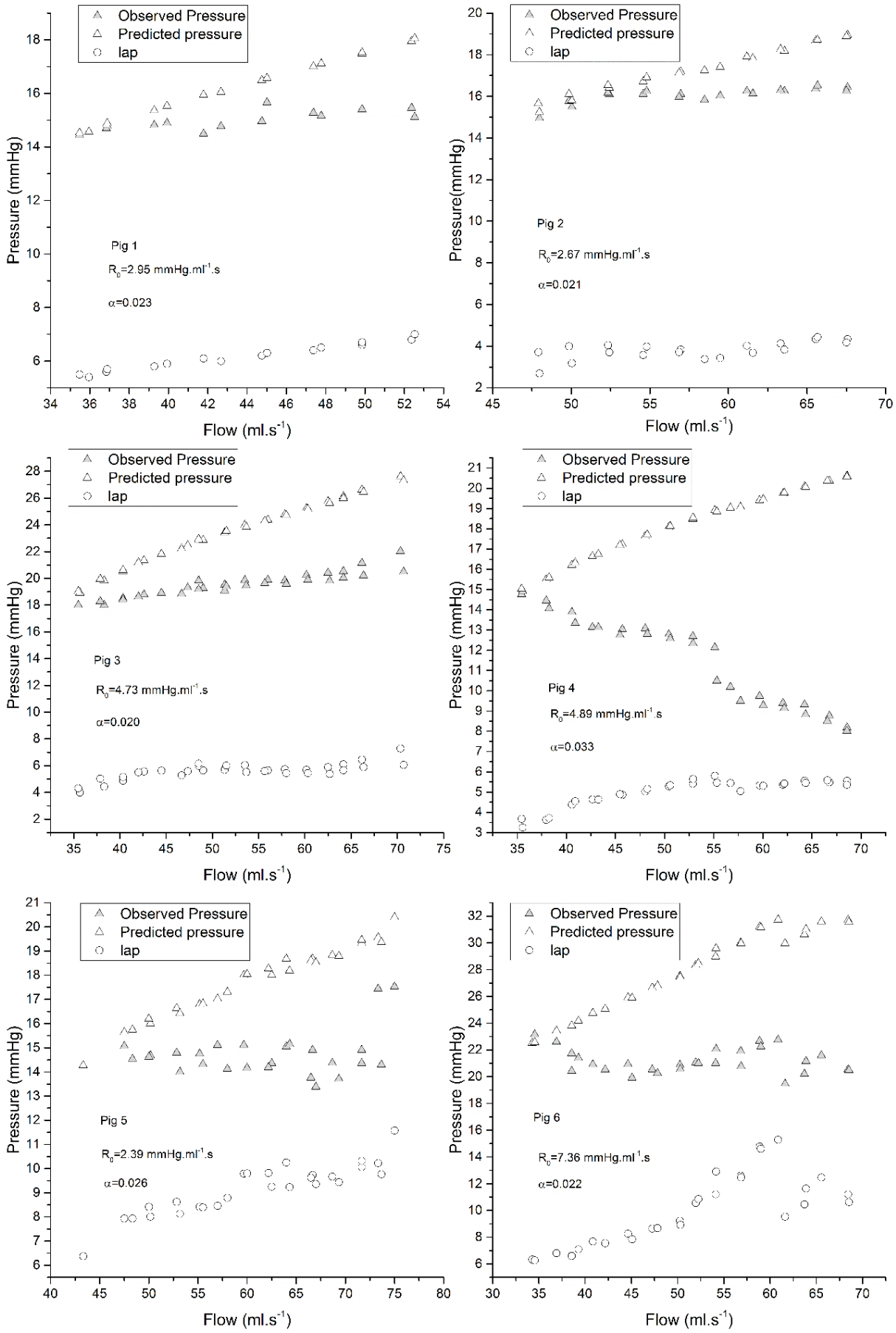

Fig. 5. Measured pressure under continuous flow conditions and the predicted values for pressure according to Linehan's equation.

Table 1. Distensibility coefficients

	MPAP	Mean α	min α	max α	DC_A
Pig 1	13.4	0.023	0.009	0.027	0.041
Pig 2	21.1	0.021	0.016	0.037	0.042
Pig 3	14.9	0.020	0.010	0.023	0.040
Pig 4	11.8	0.033	0.023	0.060	0.042
Pig 5	15.1	0.026	0.018	0.033	0.044
Pig 6	14.1	0.022	0.018	0.031	0.040

Distensibility coefficients (DC); MPAP: Mean pulmonary artery pressure in mmHg; DC_α presented with mean, minimum and maximum value in %/mmHg. Area based distensibility coefficient.

The coefficient α was calculated for five coupled pressure-diameter cycles under pulsatile flow conditions (Fig. 2) while the animal was disconnected from the ventilator.

Two perpendicular diameters at zero pressure were measured after the animals were sacrificed, and the PA was harvested to obtain D_0. A ring of a height of 0.5 to 1 cm was cut at approximately 1 cm from the pulmonary valve, and the diameter was immediately measured *ex vivo*.

Another distensibility coefficient was measured: the area-based DC (DC_A), which is defined as

$$DC_A = \frac{\frac{(Asyst - Adiast)}{Adiast}}{pulse\ pressure} \qquad (3)$$

where A_{syst} and A_{diast} are the cross-sectional areas of the PA in systole and diastole, respectively, and the pulse pressure is the systolic-diastolic pressure difference. Areas were calculated from both orthogonal diameters using the equation of an ellipse (π*vertical diameter/2*horizontal diameter/2). Pressure-surface area curves were plotted to identify the highest and lowest pressures and their corresponding diameters (Fig. 3), and the DC_A was calculated for each animal concomitant with DC_α.

ii) Pressure-flow relationship

Pressure was measured for different flows under the continuous flow condition. Flow was controlled by changing the RPM of the pump, starting at 1800 RPM; the concomitant resistance was measured (pressure-LAP/mean flow) and compared to the distensibility coefficient.

iii) Validation of the Linehan equation

After determining DC_α, we could further assess the validity of equation (1). The values obtained *in vivo* for the pressure, LAP, hematocrit and flow were used to obtain R_0 under continuous flow conditions at the lowest value of flow achievable with the pump (1800 RPM). This value was used to predict the pressure-flow relationship and was compared to the measured pressure.

Statistics

Correlation analysis was performed using Spearman's correlation. The test results were considered statistically significant at $p<0.05$.

Results

Pulmonary arterial compliance in pulsatile flow

Table 1 reports the values of DC_α under pulsatile flow conditions according to the Linehan *et al.* (1992) definition as well as the values of DC_A.

The correlation between the two DC values was poor (rho=0.4816, p=0.334).

Pressure-flow relationship

Figure 4A shows the pump rate-to-pressure relationship. In 2 out of 6 animals, the pressure remained constant (the slope of the linear fit was zero for pigs 5 and 6). The pressure slightly rose in 3 pigs as the pump rate increased (pigs 1, 2 and 3: maximum slope under 0.002). One animal exhibited a clear pressure decrease as the pump rate increased (pig 4: slope of -0.004).

Figure 4B shows the relationship between flow and resistance, indicating that resistance decreases with increasing flow. The different curves are related to DC_α. Furthermore, the resistance at 52 ml/sec (the highest common flow achieved) correlated with DC_α. Correlation

analysis revealed a statistically significant inverse relationship with a Spearman's rho coefficient of -0.8407 (p=0.044). The same analysis was performed with DC_A, yielding a Spearman's rho coefficient of -0.8986 (p=0.028).

The Linehan's equation

Figure 5 presents the pressure-flow relationship determined in the different animals. R_0 was calculated based on the lowest flow, and this value was used to predict the pressure-flow relationship as flow increased. This semi-quantitative method illustrated the discrepancies between the predicted values and observed values in the animal with the lowest DC_α (pig 3) and the animal with the highest DC_α (pig 4).

Discussion

The Linehan's equation relates flow and pressure in the pulmonary arterial system through independent variables, including the $DC_\alpha$of the pulmonary vessel, the resistance at zero flow and the outflow pressure. In this experimental study, we attempted to validate this equation by more precisely measuring the DC_α and by comparing the theoretical pressure-flow relationship with the observed pressure-flow relationship. The novelty of our methodology was that the flow was completely controlled by inducing a continuous flow state using an RV bypass system injecting blood in both lungs with an independently functioning left heart. The result showed that the observed and predicted pressures were different.

The Linehan's equation

Linehan *et al.* (1982) aimed to establish an equation linking flow to pressure while reflecting the non-linearity of the relationship and its dependence on the hematocrit.

This Linehan's equation was developed as an alternative model of the pressure-flow relationship that is neither an ohmic relationship nor a Starling resistor relationship reflecting sequential opening of the vessels (waterfall model), as these models failed to predict the exact pressure-flow relationship. The model proposed by Linehan *et al.* (1982) was based on a property of the pulmonary vessels in which both compliant and resistive features are present down to the capillary vessels. Such a system implies that resistance decreases with increased flow proportionally to the distensibility of the vessel, which has been shown to be optimal for homogenous distribution of the flow (Dawson *et al.* 1999*b*, Krenz and Dawson 2002).

Linehan *et al.* (1982) used a tightly controlled model to obtain their equation. Rigid cannulas permitted the control of the inflow and outflow of an isolated left lower lobe of a dog's lung, and measurements were taken at end-expiration, ensuring that outflow pressure was tightly controlled and fixed at 2 mmHg. While such a model was optimal to explore the effect of hematocrit changes on the pressure-flow relationship, which was the initial purpose of the original study, the model poorly reflects the physiological conditions in the lung vasculature. As Linehan *et al.* (1992), his model will reveal the robustness of the parameters under various experimental conditions. To the best of our knowledge, testing the different parameters has not been done, but the equation was nonetheless used in the clinical setting.

To validate the equation, we used a model of whole lung perfusion in an *in vivo* setting. The exact values of DC_α, the hematocrit, pressure, flow and LAP were measured in every animal, and the equation described by Linehan *et al*. (1992) was reduced to an equation with only one remaining unknown value: the resistance at zero flow (R_0).

Using our experimental setup with a continuous pump flow, R_0 was calculated for the lowest flow, and then, the pressure change per flow increment was computed, with adjustment for the measured LAP while assuming that both the DC_α and hematocrit remained constant. No overlap between the measured values and the predicted values was observed. In all animals, the equation predicted an increase in pressure, whereas the observed pressure was constant.

Discrepancies between the observed and predicted measurements were not surprising since Linehan *et al.* (1982) specifically developed their equation in zone 3 of West and recognized that in zone 2 of West, the outflow pressure would be the closing pressure (West 1977), which is commonly discussed in a Starling resistor and accounts for recruitability (Mélot *et al.* 1995). Hence, the actual situation is probably an overlap between distensible vessels and opening pressures, thus explaining the absence of an observed pressure increase with flow increase.

Another significant difference among Linehan's group experiment, our experiment and the physiological condition is that continuous flow equalizes pressure among all the compartments of the vascular tree,

exploiting the distensible properties of arteries, capillaries and veins, whereas under pulsatile conditions, inertia induces a heterogeneous distribution of the stroke volume with arterial loading that is redistributed during diastole, thus preventing the exposure of capillaries to excessive pressure. Under artificial continuous flow conditions, pressure and flow are uniformly distributed, which may explain our observation of a constant pressure value despite flow increase. The pressure-flow relationship should be further explored, as assist devices that are used to support the right ventricle are constant flow devices and may have an effect on capillary structure when they are used long term (Sezai *et al.* 1999).

Our inability to reproduce Linehan's group prediction in our observed pressure-flow model leads to questions regarding the premise and formulation of the Linehan's equation. The first question is regarding the nature of the pulmonary circulation, which should not be viewed as either an exclusively distensible system or an exclusively recruitable system but possesses both properties. The other question refers to the formulation of the equation; while the equation may be pertinent to the lower lobe in zone 3 of West, the coefficients may be different in other zones.

One should be aware of the limitations of Linehan's group equation before applying it in the clinical setting. Studies have used the equation to report differences in distensibility between men and women (Argiento *et al.* 2012), loss of distensibility as an early marker of pulmonary vascular disease (Lau *et al.* 2016) and lower distensibility in patients with heart failure (Malhotra *et al.* 2016). To draw their conclusions, these studies have made questionable assumptions: they have used either dobutamine or exertion to increase cardiac output and used the resting cardiac output as R_0. The distensibility coefficient was obtained using an iterative approach with the least-squares method (Reeves 2005). One important feature of the equation that is eluded by the assumption made on R_0 in these studies is that all the variables are independent of each other and that there is no scale effect. Avoiding scale influence is possible by computing R_0 at zero flow, when resistance is normalized. However, when the R_0 is approximated by the resistance at resting cardiac output, it is not normalized, and the body surface area (BSA, that takes into account height and weight) may influence the results and the conclusions. For example, women have a lower BSA than men on average; therefore, R_0 will be higher in women since pressure at rest is the same despite a lower cardiac output and distensibility will be biased toward higher values.

Distensibility coefficient

The DC_α, which relates the diameter to pressure, is physiologically remarkable because the value of 0.02 %/mmHg appears to be constant among species (Krenz and Dawson 2003).

Moreover, this coefficient is clinically appealing because it is presumably constant down to the arterioles in a normal pulmonary circulatory system (Presson *et al.* 1998), at least under normal physiological conditions in healthy specimens.

Linehan *et al.* (1982) used DC_α to reflect the "lumped distensibility of those vessels that contribute substantially to the vascular resistance". Although some values of DC_α in the major trunk of the pulmonary arteries have been reported in the literature (Hervé *et al.* 1989) (with some reserve on the pressure measurement at zero flow), most of the values were measured in more distal arteries (Greenwald *et al.* 1982). While more proximal arteries are larger, less resistive and less affected by the relationship of resistance to distensibility (increasing the diameter will not significantly decrease the resistance, which is already low), they are more accessible for non-invasive assessment; hence, it would be valuable to confirm that the constant distensibility observed from arterioles to capillaries extends to more proximal arteries, including the pulmonary trunk. To the best of our knowledge, this study was the first to include an instantaneous measurement of the DC_α. The mean value of DC_α was approximately 0.02/mmHg. The coefficient exceeded 0.03/mmHg in only one animal, and that animal showed even higher fluctuations, with a maximum coefficient of 0.06/mmHg.

The value of 0.02/mmHg is also the value reported for the distal arteries (Greenwald *et al.* 1982) and we could advance that our measurement is a good argument in favor ofa homogeneous distribution of distensibility, from the pulmonary trunk to capillaries. But to prove the concept, a simultaneous measurement in proximal and more distal vessels should be done which, our best knowledge, has never been done. Moreover, we made the assumption that the relation between the distensibility that we measured and the distensibility in the vessels for which the Linehan's group equation was designed, are linearly related. This has not been proved and it is a main limitation of our study. If the compliant properties of the proximal

vessels and intermediate vessels are different, it could explain the discrepancies with the predicted model that we observed.

Beyond the context of the Linehan's equation, a proper measure of pulmonary vascular distensibility is interesting because the elastic properties of the lung vasculature may exert a strong clinical impact on diseases involving pulmonary arterial hypertension (Tan *et al.* 2014, Schäfer *et al.* 2016).

However, measuring the DC_α is controversial, as it requires measuring the vessel diameter at zero pressure, which is nearly impossible in the clinical setting. The methodological requirements to obtain exact DC_α values explain why DC_α values are not reported in the literature for pathological states. Additionally, we have stressed the limitation of DC_α obtained with assumptions regarding R_0 in the setting of the Linehan's equation.

The aforementioned disadvantages underlie the need to use other vascular stiffness indices. One of these indices, the DC_A, which we measured in our study, is based on the area change between systole and diastole and has gained widespread acceptance, at least for evaluation of the systemic circulation (Cavalcante *et al.* 2011).

In the pulmonary circulation, DC_A has been measured in patients without pulmonary hypertension and has been reported to have a value of 3.1 %/mmHg (range 2 to 4.1 %) (Sanz *et al.* 2009). DC_A decreases in patients with pulmonary hypertension and this decrease has a negative impact on ventricular function (Stevens *et al.* 2012). In our study, the DC_A was fairly constant for all animals (mean: 4.15±0.16 %), and a correlation was observed between the DC_α and the decrease in resistance with increased flow.

We compared the two DCs and observed a poor correlation, but the study used a limited number of animals and is underpowered to compare the two indices.

Use of the DC_α is appealing because it appears to remain constant across many species and throughout the lung independent of pressure, but our observations suggest that DC_A may share the same properties as DC_α in terms of its consistency among species (at least in pigs and humans) and that it has the advantage of being measurable in clinical settings. Therefore, measuring the DC_A may be more appropriate, as it can be achieved non-invasively.

Conclusions

This experiment, which used a continuous pulmonary flow model, was designed to verify Linehan's equation, which links pressure to resistance and flow via a distensibility coefficient based on diameter and pressure variations relative to the diameter at zero pressure. The Linehan's equation is valuable for the calculation of resistance at zero flow, which reflects geometrical properties of the vascular tree and could help in the diagnosis of pulmonary vascular diseases, but we did not observe the predicted values. Other formulas of the pressure-flow relationship should thus be developed using distensibility coefficients based on surface variation and pulse pressure, which can be measured in the clinic with modern imaging techniques.

Conflict of Interest

The authors report that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Competing interests

All authors declare that they have no competing interests.

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Compliance with ethical standards

This work was supported by a grant from "Le fond pour la chirurgie cardiaque". This work does not contain any studies with human participants performed by any of the authors. The study protocol was performed according to the standards of "The Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (publication 85-23, revised 1996) and approved by the ethical committee for animal research of the Ghent University Hospital (ECD 18/30).

Abbreviations

DC, Distensibility coefficient; DPAP, Diastolic pulmonary artery pressure; MPAP, Mean pulmonary artery pressure; LAP, Left atrial pressure; PA, Pulmonary artery; R, Resistance; SPAP, Systolic pulmonary artery pressure.

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