Pulmonary arterial hypertension is a frequent and serious complication of several cardiovascular or respiratory diseases that is difficult to assess non-invasively. As the options for treatment of pulmonary hypertension have expanded, the requirement for accurate and non-invasive methods to allow regular and safe estimation of pulmonary arterial pressure (PAP) has increased. Measurement of PAP by Doppler echocardiography provides a high degree of correlation (0.89 < r < 0.97) in comparison with pulmonary artery catheterisation. However, PAP cannot be estimated by Doppler echocardiography in approximately 50% of patients with normal PAP, 10–20% of patients with increased PAP, and 34–76% of patients with chronic obstructive pulmonary disease because of the absence of tricuspid regurgitation, a weak Doppler signal, or a poor signal to noise ratio (SNR). Moreover, Doppler echocardiography cannot be used to monitor PAP continuously. Consequently, it would be useful to develop other non-invasive methods to allow frequent and accurate measurement of PAP.

It is well known that the time interval between the aortic (A2) and the pulmonary (P2) components of the second heart sound (S2), as well as the dominant frequency of P2, are increased in the presence of pulmonary hypertension. It has therefore been suggested that the A2-P2 splitting interval (SI) may be useful to estimate the PAP. However, the basic relation between the SI and the PAP is not well known. Moreover, the applicability of this acoustic approach is limited because the SI is relatively short (generally 100 ms) and is difficult to measure, especially in patients for whom A2 and P2 are overlapping.

Recently, we have proposed a new approach based on advanced signal processing that can successfully identify and extract overlapping A2 and P2 components from S2 recordings and that can be used to measure the A2-P2 SI accurately. The objective of this work was to study the relation between the SI measured using this new acoustic method and the PAP measured by catheterisation. This relation was first studied in an animal model designed to vary the PAP over a wide range and then in patients undergoing pulmonary artery catheterisation.

### METHODS

#### Animal study

**Animal model**

Animal care and experiments were conducted in accordance with the guidelines of the Canadian Council for Animal Care. The protocol was approved by the institutional animal care committee of Laval University, Ste-Foy, Canada. Sixteen pigs weighing between 27–35 kg were anaesthetised and ventilated with ketamine, anaesthesia was induced by intravenous injection of fentanyl (5 µg/kg) and pentobarbital (6.5 mg/kg). After orotracheal intubation, intermittent positive pressure ventilation was initiated and adjusted to maintain the arterial partial pressure of carbon dioxide between 35–45 mm Hg. Anaesthesia was maintained with a continuous infusion of fentanyl (4 µg/kg/h) and pentobarbital (10 mg/kg/h). Muscle relaxation was achieved by administration of pancuronium 0.30 mg/kg/h. The animal was positioned in the right lateral recumbency position and immobilised.

The PAP was measured using a 7 French gauge Swan-Ganz Millar catheter (Model Mikro-tip, MPA-372 T, Millar, Houston, Texas, USA) inserted into the left jugular vein and then directed into the main pulmonary artery. The systemic arterial pressure was measured using a fluid filled catheter inserted...

### Abbreviations:

- A2: aortic component of the second heart sound
- HR: heart rate
- NSI, normalised splitting interval
- PAP: pulmonary arterial pressure
- P2: pulmonary component of the second heart sound
- S2: second heart sound
- SEE: standard error of the estimate
- SI, splitting interval
- SNR, signal to noise ratio
into the carotid artery. Figure 1 shows a schematic representation of the acoustic system used in this study. A microphone with characteristics similar to those of the electronic stethoscope previously developed by our group was positioned and fixed on the thorax of the pigs in the pulmonary area (third to fourth left intercostal space) to record the heart sounds. A first order Butterworth filter with a cut off frequency of 100 Hz was used to de-emphasise the high intensity, low frequency components of the heart sound signal and to provide better accuracy in the estimation of SI.

After the initial instrumentation of the animal, the study was delayed until a stable and normal physiological state was obtained. The PAP was modulated using the following experimental protocol divided into four stages of 15 minutes each. (1) Baseline measurements were made while the systolic PAP was within the normal range (15–20 mm Hg). (2) Moderate pulmonary hypertension was induced by a continuous intravenous infusion of a thromboxane analogue (U44069, Sigma, St Louis, Missouri, USA). (3) Severe pulmonary hypertension (systolic PAP > 45 mm Hg) was then obtained by increasing the infusion rate (range 10–60 µg/min) to maintain a stable systolic PAP of approximately 35–45 mm Hg for 15 minutes. (3) Severe pulmonary hypertension (systolic PAP > 45 mm Hg) was then obtained by increasing the infusion rate (range 10–60 µg/min). (4) “Back to baseline” measurements were made after stopping the infusion and allowing sufficient time to ensure that the animal’s PAP had returned to normal. For each stage, the PAP, the ECG, and heart sounds were recorded and digitised at 1 kHz with 12 bit resolution on a personal computer (fig 1). The recordings were made at the end of the inspiratory phase after stopping (20 seconds) the ventilator and digitised at 1 kHz with 12 bit resolution on a personal computer (fig 1). The recordings were made at the end of the inspiratory phase after stopping (20 seconds) the ventilator temporarily to minimise mechanical ventilation noise on the heart sound recordings. This animal experimentation provided 64 recordings (16 animals × 4 stages) in total.

### Signal processing and data analysis

The ECG was used to detect the S2s on the heart sound recordings that contained 20–30 cardiac cycles. In each of the detected S2s, the A2 and P2 components were identified by using a spectral dechirping method that has been previously described in detail. This method is based on the time–frequency representation of transient non-linear chirp signals for modelling A2 and P2. When S2 is analysed in the time domain, the measurement of SI is feasible only if A2 and P2 are partially or totally overlapped (fig 2A). This dechirping method allows the detection and separation of A2 and P2 in the time–frequency domain and thus makes possible the measurement of SI even when A2 and P2 overlap in the time domain. Once A2 and P2 are reconstructed in the time domain from the non-linear chirplet parameters (fig 2B), the cross correlation function between the reconstructed A2 and P2 is calculated (see equation in appendix). The A2–P2 SI is then determined by measuring the time delay between the beginning and the maximal positive amplitude on the cross correlation function (fig 2C). This method is more robust than measuring the time delay between the onset of A2 and the onset of P2 (as shown in fig 2B) because the exact onset of the reconstructed A2 and P2 is dependent on the presence of background noise on the S2 signal recording. Since the SI is indirectly related to heart rate (HR), it was normalised with respect to the duration of the cardiac cycle, as previously proposed by Leung and colleagues, as follows:  

$$\text{NSI} = \frac{\text{SI} \times \text{HR}}{600}$$  

where NSI is the normalised SI expressed as a percentage of the cardiac cycle duration. The NSI was measured in each S2 detected within a given recording and then averaged.

### Clinical study

Twenty three consecutive patients (eight women, 15 men, mean (SD) age 67 (10) years) undergoing pulmonary artery catheterisation were recruited for the study. The research protocol was approved by the ethics committee of the Quebec Heart Institute/Laval Hospital and informed consent has been obtained from each patient. The predominant disease was severe aortic stenosis in seven patients, severe aortic insufficiency in two, severe mitral stenosis in two, severe mitral insufficiency in three, moderate mitral and aortic regurgitation in one, coronary artery disease in three, acute myocardial infarction in one, unstable angina in one, congestive heart failure in one, cardiogenic shock in one, and cardiomyopathy in one patient. The PAP was measured using fluid filled Zucker (19 patients) or Swan-Ganz (four patients) 7 French gauge catheters.

Heart sounds were recorded and the PAP was measured by catheter simultaneously in four patients who were hospitalised at the critical care unit and had a Swan-Ganz catheter for PAP monitoring. In the other (19) patients, heart sounds were recorded within three hours following measurement of PAP at the catheterisation laboratory. The heart sounds were recorded at the pulmonary area (second left intercostal space...
along the sternal border) during approximately 30 seconds while the patient was breathing spontaneously. The microphone, the acquisition system, and the signal processing method were identical to those used for the animal study. The SNR of S2 was estimated by computing, for each patient, the energy ratio of a 100 ms window containing S2 (E(S2)) and a 100 ms diastolic window containing the noise (E(noise)). Ten cardiac cycles were analysed and the average energy ratio was computed. The SNR was computed and expressed in dB by using the following formula:

$$\text{SNR} = 10 \log \left( \frac{E(S2)}{E(\text{noise})} \right)$$  \hspace{1cm} \text{Equation (2)}$$

### Statistical analysis
The association between PAP and NSI was statistically analysed using the determination coefficient adjusted for degrees of freedom (Table Curve 4.0, SPSS, Chicago, Illinois, USA). Multivariate analysis of variables was performed using a stepwise forward regression analysis. Probability values of $p < 0.05$ were considered significant.

### RESULTS

#### Animal study
Analysis of the data of the 64 pressure and heart sound recordings showed that the systolic PAP varied between 14–73 mm Hg and the NSI between 1.6–12.0%. NSI was measurable in 97% of the recordings. Indeed, it could not be measured in one recording with normal PAP and one recording with high PAP because P2 could not be detected because of a higher background noise than usual. There was a strong relation between the NSI and systolic PAP ($r = 0.94$, standard error of the estimate (SEE) = 5.3 mm Hg; fig 3A), mean PAP ($r = 0.94$, SEE = 4.1 mm Hg; fig 3B), or diastolic PAP ($r = 0.93$, SEE = 4.3 mm Hg). This relation can be described by the following equation:

$$\text{PAP} = a + b \times \sqrt{\text{NSI}}$$  \hspace{1cm} \text{Equation (3)}$$

where $a = -21.6$ and $b = 26.3$ for systolic PAP, $a = -13.7$ and $b = 19.2$ for mean PAP, and $a = -11.1$ and $b = 15.8$ for diastolic PAP. The systolic systemic pressure also varied widely during the protocol with the systolic pressure ranging from 65–122 mm Hg. It cannot be excluded that changes in systemic arterial pressure also had an effect on the duration of the left ventricular systole and thus on NSI. Nonetheless, there was no correlation ($r = 0.17$, $p = 0.29$) between NSI and systemic arterial pressure.

#### Clinical study
Among the 23 patients in the study, the systolic PAP varied between 20–70 mm Hg and 10 patients (43%) had pulmonary hypertension as defined by a systolic PAP > 35 mm Hg. The systolic aortic pressure varied between 98–220 mm Hg and nine patients (39%) had systemic arterial hypertension as defined by a systolic aortic pressure > 140 mm Hg. The mean

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**Figure 2** Method for the estimation of the splitting interval (SI) between the aortic (A2) and pulmonary (P2) components of the second heart sound (S2). (A) The original S2 signal in the time domain. (B) A2 and P2 components detected and reconstructed using a spectral dechirping approach. (C) Measurement of SI on the cross correlation function (CCF) between A2 and P2. In panels A and B, time zero is a relative temporal reference corresponding to the beginning of the 100 ms temporal window containing S2; in panel C, time zero corresponds to the onset of A2, as shown in panel B.

**Figure 3** Relation between the normalised A2-P2 splitting time interval (NSI) and the systolic (A) or mean (B) PAP in pigs.
SNR was 21 (10) dB. NSI was measurable in 21 patients (91%) and the NSI values were between 2.0–8.4%. NSI could not be measured in three patients because of poor SNR in two patients (SNR < 8 dB) and inability to detect P2 in one patient. As in the animal study, there was a strong relation between NSI and systolic PAP (r = 0.84, SEE = 7.8 mm Hg; fig 4A), mean PAP (r = 0.85, SEE = 5.8 mm Hg; fig 4B), or diastolic PAP (r = 0.82, SEE = 5.6 mm Hg). The equation describing this relation was also identical to that obtained in animals (equation 3) except for small differences in the coefficients: a = −18.3 and b = 26.7 for systolic PAP, a = −13.0 and b = 21.5 for mean PAP, and a = −20.9 and b = 18.6 for diastolic PAP. The optimal threshold for detecting pulmonary hypertension (defined by systolic PAP > 35 mm Hg) by the acoustic method was NSI > 4%. The resulting sensitivity and specificity were 100% and 91%, respectively.

DISCUSSION

The S2 results from the interplay of the dynamic events associated with the relaxation of the left and right ventricles, the closure of the aortic and pulmonary valves, and the compliance of the aorta and main pulmonary artery. Indeed, similarly to pulmonary hypertension, this disease is associated with an increase in the right ventricular systolic pressure, thus causing prolongation of the right ventricular systole and a delay in the onset of P2. The same limitation also applies to the estimation of PAP by Doppler echocardiography based on the gradient of the tricuspid regurgitation signal. Indeed, this method provides an estimation of the right ventricular systolic pressure that is considered to be equivalent to the systolic PAP in the absence of pulmonary stenosis. In this context it should, however, be considered that pulmonary stenosis has a low incidence and can be excluded by physical examination, to the type of catheter used for PAP measurement (Millar catheter in pigs versus fluid filled catheter in patients), and to the timing of PAP measurement and heart sound recording (simultaneous in pigs versus serial in all patients except four). Although NSI correlated well with systolic, mean, and diastolic PAPs, the acoustic method is somewhat superior for the estimation of mean PAP as suggested by the slightly higher correlation coefficients, relatively lower SEE, and high concordance of the PAP–NSI equations in animals and in patients.

In patients breathing spontaneously, a cyclic variation of NSI was usually noticed during the respiratory cycle. In this context, it is important to consider that this was expected because the PAP also varies with respiration. Since the PAP in the clinical setting is generally measured by averaging the pressure over several heart beats despite the inherent beat to beat variation, it is logical to use the same approach in an instrument based on NSI.

Limitations

Recording external noise in the clinical environment may compromise the quality of the phonocardiogram and thus preclude the measurement of NSI in some patients. However, the use of a contact-type microphone and of de-noising processing techniques may help reduce the background noise and enable the measurement of NSI even in noisy environments.

Pulmonary valve stenosis may also increase the NSI. Indeed, similarly to pulmonary hypertension, this disease is associated with an increase in the right ventricular systolic pressure, thus causing prolongation of the right ventricular systole and a delay in the onset of P2. The same limitation also applies to the estimation of PAP by Doppler echocardiography based on the gradient of the tricuspid regurgitation signal. Indeed, this method provides an estimation of the right ventricular systolic pressure that is considered to be equivalent to the systolic PAP in the absence of pulmonary stenosis. In this context it should, however, be considered that pulmonary stenosis has a low incidence and can be excluded by physical and Doppler echocardiographic examination.

It is possible that other concomitant diseases such as aortic valve stenosis, systemic arterial hypertension, or left bundle
branch block have an effect on the NSI independently of the PAP. These conditions may cause a prolongation of the left ventricular systole and thus a delay in the onset of A2. This would result in a decrease in the NSI and possibly an underestimation of the PAP. Nonetheless, the mean (SD) relative difference between the mean PAP directly measured by catheter and the mean PAP estimated from NSI using the regression equation obtained in fig 2B was not significantly different in the patients (n = 7) with severe aortic stenosis (–3 (26)% v –1 (16)%, p = 0.89) or in those (n = 9) with systemic hypertension (–6 (24)% v 2 (21)%, p = 0.49). This finding is also in agreement with the results of the animal study showing that the impact of the systemic arterial pressure on NSI is minimal. Pending further confirmation in a larger group of patients, these findings suggest that estimation of PAP by the acoustic method would be valid in the patients with severe aortic stenosis or systemic hypertension. Relatively good results may have been obtained in these patients because the right ventricle—as a result of its distinctive anatomical and physiological features—is much more sensitive to an increase in afterload than the left ventricle. Hence, an increase in systolic wall stress as a result of valve stenosis or hypertension likely has a lesser impact on left ventricular function and thus on the timing of A2 than on right ventricular function and timing of P2.

Other spectral features of S2 such as the dominant frequency of P2 may be less sensitive to the aforementioned concomitant diseases that may influence NSI independently of the PAP. Indeed, based on the valve theory for the genesis of heart sounds, the dominant frequency of P2 increases with increasing PAP similarly to a stretch drumhead: the more the drumhead is stretched, the higher is the frequency of the sound. Further studies are necessary to evaluate the performance of NSI and dominant frequency of P2 for PAP estimation in patients with specific conditions such as left or right bundle branch block, pulmonary stenosis, and aortic mechanical valves.

Clinical implications
The acoustic method proposed in this study may lead to the development of a low cost and accurate instrument for non-invasive estimation of PAP. Also, in contrast with other non-invasive methods, it may be used for continuous monitoring of PAP in acutely ill patients. It should be emphasised that pulmonary arterial catheters are associated with significant morbidity and mortality and that they should be left in place as briefly as possible. Hence, the acoustic instrument can potentially replace the catheter or allow for a briefer insertion since it would allow PAP monitoring to be maintained after the removal of the pulmonary arterial catheter. We are optimising this computer assisted method to develop an instrument that would measure NSI in real time and would be completely automated. On the basis of this parameter and the equations described in the present study, the instrument may provide a non-invasive and inexpensive estimation of PAP both in acutely ill patient and in patients with suspected pulmonary hypertension.

Conclusion
This study shows that this new non-invasive method based on advanced signal processing of S2 provides an accurate estimation of the PAP.

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APPENDIX
Assuming that the reconstructed aortic (A2) and pulmonary (P2) components of the second heart sound are digital real signals A(n) and P(n), the cross correlation function (CCF) between A2 and P2 can be estimated by using the following equation:

\[ \text{CCF}(m) = \frac{1}{N - |m|} \sum_{n=0}^{N-1} A_2(n)P_2(n + m) \]

where N is the total number of samples of A2 and P2, n is the sampling interval, and m is the temporal index of the CCF.

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