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● *Original Contribution*

FEASIBILITY OF NON-INVASIVE PULSE PRESSURE MEASUREMENT USING THE PHASED-TRACKING METHOD

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Abstract—Phased tracking (PT) is a high-precision ultrasonic technology that enables measurements of pulse pressure (PP). The aim of this study was to verify the accuracy of estimated PP using PT. Estimated PPs were compared with measured PPs in three sheep fetuses that were connected to an artificial placenta system. Similarly, estimated and measured PPs of 30 human neonates were compared. PP was calculated using the Water−-Hammer equation (PP = ρ × PWV (pulse wave velocity) × ΔU). PWV was estimated by measuring the transit times of pulse waves at two sites along the aorta using the PT method, and ΔU was obtained by subtracting end-diastolic velocity from peak systolic velocity. The correlation between the estimated and measured PPs of the sheep fetuses was strong ($r = 0.95$, $p < 0.01$), as was the case with the human neonates ($r = 0.88$, $p < 0.05$). It can be concluded from the results of this study that PT may be a non-invasive alternative method used to predict PP. (E-mail: masa_saito_lizard@yahoo.co.jp)

Key Words: **Ultrasound, Sheep, Fetal, Neonate.**

INTRODUCTION

Through measurement of fetal blood pressure (BP), it becomes possible to better understand the condition of the pathologic fetus in more detail. However, at present, it is not possible to measure fetal BP non-invasively. Additionally, because fetal blood vessels are small, it may not be possible to accurately monitor the movement of fetal blood vessels through conventional ultrasonography. A previous study revealed that the diameter of the aorta in human fetuses at 20−40 wk of gestation changed by approximately 300−500 μm depending on the pressure exerted by the pulse waves (Miyashita et al. 2015). To determine the pulse wave velocity (PWV) accurately, the transition of the fetal blood vessel wall must be measured with an accuracy of a few micrometers. The distance resolution (5 MHz) of the M-mode used in obstetrics is approximately 300 μm. The distance resolution of the echo tracking method has been found to be 20 μm (Struijk et al. 2013). However, the issue remains that regardless of the method used, it is difficult to capture small changes in fetal blood vessel walls.

Strujik et al. (2013) previously attempted to measure fetal pulse pressure (PP) using the echo tracking method. The basic principles of echo tracking technology include first determining the echo radiofrequency (RF) signals of the vessel wall, which contain both the amplitude and original phase information, and then automatically tracking vessel wall movement *via* the phase trajectory tracking method. However, this method is technically limited in measuring the movement of fetal blood vessels, and therefore, the PP values that are obtained may vary. Kanai et al. (1996, 1997) developed a different ultrasonic tracking system, called the phased-tracking (PT) method, which can accurately trace fine movements with a significantly high spatial resolution of 0.5 μm. Miyashita et al. (2015) reported that this PT method more accurately monitored fetal blood vessels and measurement of fetal PP. However, in previous studies (Struijk et al. 2013; Miyashita et al. 2015), no attempt

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was made to compare the measured fetal PP values with the values estimated using the PT method, and thus, the accuracy of the PT method remains uncertain.

The objective of this study was to evaluate the accuracy of the PT method in measuring sheep fetal PP through comparisons of measured versus estimated PP values in sheep fetuses and human neonates.

METHODS

Accuracy of the PT method in sheep fetus

All procedures involving animals were approved by the Animal Care and Use Committee of the Tohoku University School of Medicine (Sendai, Japan). Suffolk ewes (n = 5, term at 147 d) underwent laparotomy at gestational days 90 and 137 under artificial ventilation and anesthesia with 1.5% isoflurane. Sheep fetuses born at 137 d were considered almost term fetuses, while those born at 90 d are preterm. We examined whether the PP measurement method using ultrasound is valid for both term and preterm sheep fetuses. A polyvinyl cannula (8 Fr, Duraflo II, Edwards Lifesciences, Irvine, CA, USA) was inserted into the two umbilical arteries of each sheep fetus delivered from the ewes, while a second polyvinyl cannula (12 Fr, Argyle Trocar catheter; Covidien, Dublin, Ireland) was inserted into the umbilical vein. The cannulas were connected to an artificial placenta (AP) system (Miura et al. 2016). As illustrated in Figure 1, the AP system consists of two outflow tubes: a flow tube and membranous oxygenator. Appropriate oxygenation is supplied through the membranous oxygenator. The AP system uses the fetal heart pump to circulate the blood in the tubes. A catheter was inserted into the internal carotid artery of the sheep fetuses to measure central arterial pressure. In addition, a superior vena cava catheter was inserted into the internal jugular vein of the sheep fetuses for central venous delivery of nutrition. The sheep fetuses were placed in a bag containing artificial amniotic fluid. Lipo-prostaglandin E_1 was used to prevent closure of the ductus arteriosus. Non-invasive PP measurements of the sheep fetuses were performed three times for a total of 10 min every 8 h until 72 h after introduction of the AP system. Afterward, the measured and estimated PP values were compared.

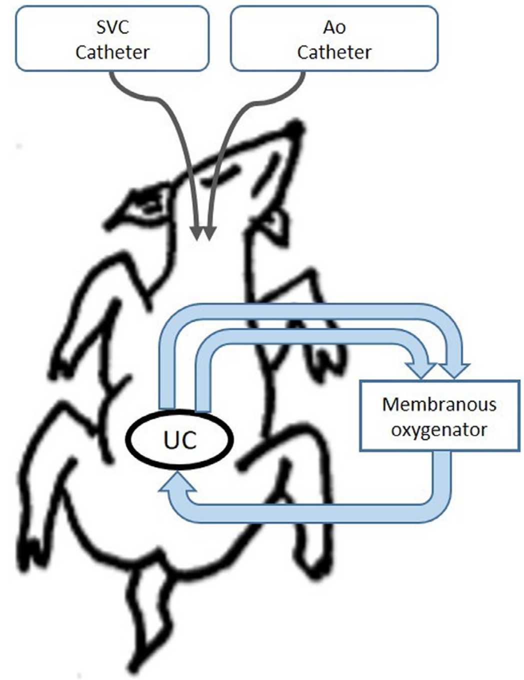

Fig. 1. Layout of the AP system. The AP system consists of two outflow tubes: an inflow tube and a membranous oxygenator. Two tubes were connected to the umbilical arteries, and one tube was connected to the umbilical vein. The AP system used the fetal heart pump to circulate the blood in the tubes. Appropriate oxygenation was supplied through the membranous oxygenator. Blood flowed through the two umbilical arteries and two outflow tubes to the membranous oxygenator. The blood was oxygenated in the membranous oxygenator and sent systemically through an inflow tube and an umbilical vein. The SVC catheter was inserted into the internal jugular vein of the sheep fetus for central venous delivery of nutrition. AP = artificial placenta: SVC = superior vena cava; Ao = aorta; UC = umbilical cord.

Accuracy of the PT method in human neonates

The human study protocol was approved by the institutional ethics committee. Measurements were performed after obtaining written informed consent from the participants at the Department of Maternal and Fetal Medicine of Miyagi Children's Hospital (Sendai, Japan). Thirty normal neonates were enrolled in the study from April 2017 to April 2018. No maternal complications were observed. Non-invasive PP measurement by ultrasound was performed after giving milk to the newborn infants at postpartum hour 12. The median gestational age was 37.6 (range: 36−39) wk. Ideally, a catheter should have been inserted into the inferior aorta of the newborn to measure the PP to compare with the aortic PP measured by the ultrasound. However, the catheter is not usually inserted into the inferior aorta of a normal healthy newborn, in clinical practice, so in this case the PP was measured using ultrasound and was compared with the PP measured with an oscillometric electronic sphygmomanometer. A BP cuff was applied to the left upper arm to measure PP. Estimated PP was calculated by measuring PWV and blood flow velocity at the descending aorta of the neonates. The measured and estimated PP values were then compared.

Ultrasonic PT method and PP measurement

An ultrasonic beam scanned different directions at a frame rate of 500 Hz using the Prosound F75 Premier

Ultrasound Processor (Hitachi-ALOKA, Tokyo, Japan) with a 5-MHz convex array probe (Hitachi). The RF signals from the beam were applied perpendicularly to the descending aorta at the diaphragm level. The RF signal of each scan line was captured for 2−4 s. The fine motions of the vessel wall in each beam obtained from the RF signals were analyzed offline using PT. In conventional ultrasonographic techniques, deviations of a point of interest that are smaller than the wavelength cannot generally be detected because they are measured based on the amplitude of the reflected waves. For this reason, the minimum wavelength measured by a probe (5 MHz) that is often used for obstetric examinations is said to be approximately 300 μm. The measurement principle of the PT method is different from that of conventional methods. For example, in the PT approach, an ultrasonic pulse is transmitted from the ultrasound probe and reflected by the aortic wall with a slight movement. By the time it returns to the probe, a phase delay has occurred in the ultrasound pulse because of propagation length. By detecting the phase difference between two ultrasonic pulses that are continuously transmitted and received, it is possible to estimate the displacements of a point of interest that are smaller than the wavelength with a distance measurement precision of 0.5 μm (Ozawa et al. 2015).

Aortic PPs of the sheep fetuses and human newborns were estimated using the PWV and blood flow velocity change (ΔU) of the descending aorta. All motions of the proximal and distal borders of the lumen of the descending aorta in sheep fetuses and human newborns were analyzed at each point using the PT method. PWV was estimated using measurements of the pulse wave's transit time at two sites along the aorta using the PT method. The transit time of the pulse wave traveling from the proximal site to the distal site through the arterial wall was analyzed and defined as the peak-to-peak interval in the systolic phase (Fig. 2). PWV was obtained by dividing the distance between the two sites by the transit time of the pulse waves. ΔU was measured with the pulse Doppler method using the same ultrasonographic probe at the same level as the descending aorta. The beam-to-flow angle of the ultrasound beam was kept as low as possible (<30°). RF signals and ΔU were to measured separately. ΔU is obtained by subtracting end-diastolic velocity from peak systolic velocity. The sample volume was set to 2 mm to measure blood flow and the sample gate, which is located just at the center of the blood vessel. According to the Water−Hammer equation (Gary 2015), the relationship between the changes in pressure ΔP and velocity ΔU is obtained as

$$\mathrm{PP}(\Delta P)(\mathrm{Pa}) = \rho(\mathrm{g/cm^3}) \times \mathrm{PWV}(\mathrm{m/s}) \times \Delta U(\mathrm{m/s})$$

where ρ is blood density, and ΔU is the blood flow velocity change. The equation assumes that blood density is a constant value (1.05 g/mL) that is independent of gestational age. PP is obtained by subtracting diastolic BP from systolic blood pressure. Similarly, ΔU is obtained by subtracting end-diastolic velocity from peak systolic velocity. The Water−Hammer equation is a result of applying the conservation of mass and momentum to the wave. It indicates that the pressure and velocity waveforms in the arteries are not independent of each other as is often thought. In the context of the unidirectional wave, there is a simple linear relationship between ρ and U. In the Water−Hammer formula, the unit of pressure is expressed in Pascals, so it becomes necessary to multiply the right side of the equation by 7.51 to convert to millimeters of mercury.

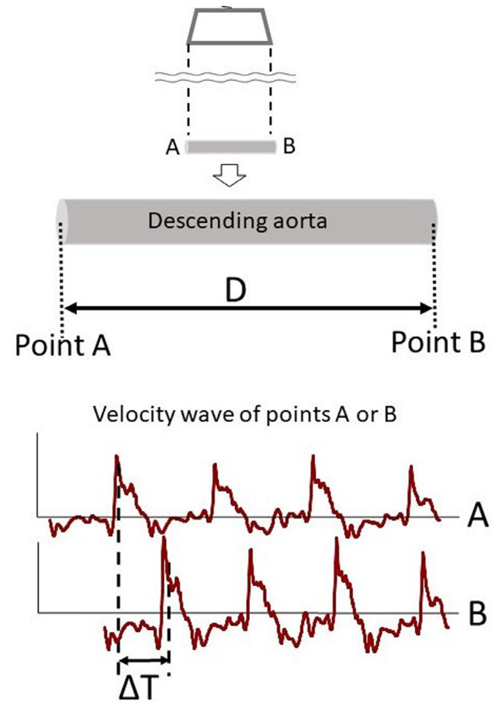

Fig. 2. Ultrasonic measurement using the phased-tracking method was performed at 90° on fetal blood vessels. The RF signals were captured simultaneously from different directions. All motions of the proximal (A point) and distal (B point) borders of the lumen of the fetal descending aorta were analyzed using the phased-tracking method at each point, and the time delay was measured. Pulse wave velocity was obtained by dividing the distance between the analyzed points by the time delay of the pulse wave.

$$\begin{aligned} &PP(mmHg) \\ &= \rho \times PWV \times \Delta U(g/cm^3 \times m/s \times m/s) = \rho \times PWV \times \Delta U(1000kg/m^3 \times m^2/s^2) \\ &= \rho \times PWV \times \Delta U(1000N/m^2) = \rho \times PWV \times \Delta U(1000Pa) \\ &= \rho \times PWV \times \Delta U(7.51mmHg) \end{aligned}$$

For example, the ΔU of the descending aorta obtained with the Doppler method is 0.8 (m/s), and the PWV obtained with the PT method is 4 (m/s). In this case, PP (mm Hg) is $1.05 \times 0.8 \times 4 \times 7.51 = 25.23$.

All ultrasonic examinations were performed by one examiner. The intra-rater reliability of the measured values of the sheep fetuses and human neonates was evaluated accordingly.

Statistical analysis

Reported values are presented as the group mean (range). Statistical analyses were performed using IBM SPSS Software for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). To compare the two groups, median differences were tested for significance using the Mann−Whitney *U*-test. Spearman's correlation coefficient was used to determine the strength of the links between the two data sets. Intra-rater reliability was examined using intra-class correlation coefficient (ICC) and was considered moderate to good if ICC was between 0.50 and 0.75 and good to excellent if ICC was between 0.75 and 1.00. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Accuracy of the PT method: Sheep fetus

Cardiac arrest occurred in two of the five fetuses (40%) involved in the study before the introduction of the AP system. The estimated and measured PP values of sheep fetuses born on days 137 (n = 1) and 90 (n = 2) of the gestational period were compared. Of the sheep fetuses born on day 90 of the gestational period, one died within 8 h, and the other died within 36 h. The sheep fetus born on day 137 of the gestational period died in 32 h. An analysis of the non-invasive PP measurements was possible 60 of 89 times. Measurement failures were caused by disappearance of the descending aorta from the screen because of a large fetal body movement. The correlation between the estimated and measured PP values was highly significant ($y = 1.03x$, $R = 0.95$, $p < 0.01$) (Fig. 3). The measurement error of the estimated PP was within ±3 mm Hg for almost all measurements. The ICC (95% confidence interval [CI]) was 0.987 (0.977−0.992).

Accuracy of the PT method in human neonates

Non-invasive PP measurements were performed for all 30 neonates. There were no maternal complications. Three newborns (3/30) were considered small for gestational age. The median birth weight was 2460 (range: 2120−3120) g. The correlation between the estimated and measured PP values was strong ($y = 0.86x$, $R = 0.88$, $p < 0.05$) (Fig. 4). The ICC (95% CI) was 0.928 (0.848−0.966). However, the estimated PP value was slightly lower than the measured PP value.

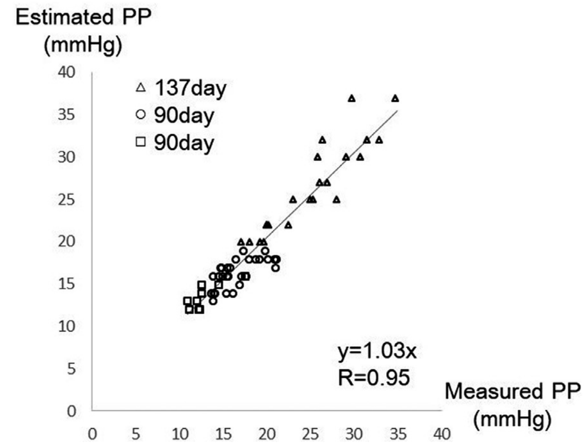

Fig. 3. Correlation between the estimated and measured PP values of sheep fetuses (term at 147 d) at gestational days 137 (n = 1) and 90 (n = 2). Estimated PP was measured by ultrasound. Measured PP was measured with the catheter. It appears that the PPs of 90-d fetuses were significantly lower than the PPs of the 137-d fetus. The PPs of the 137-d fetus ranged from 20−40 mm Hg over its 32-h lifetime, and this provided most of the points on the graph. The others are clustered in in a 5+ mm Hg range. PP = pulse pressure.

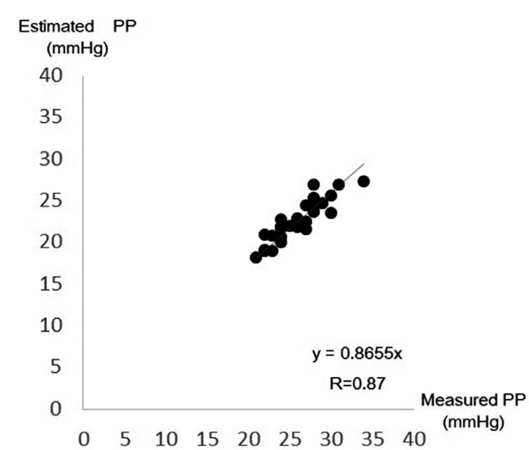

Fig. 4. Correlation between estimated and measured pulse pressure values of human fetuses.

DISCUSSION

The results from this study indicate that there was a strong correlation between the estimated and measured PP values of sheep fetuses and human neonates. It was confirmed that PP measurement using ultrasound was highly accurate. This study is the first of its kind as there are currently no studies comparing measured and estimated PP values in sheep fetuses or neonates.

Struijik et al. (2013) previously measured the rate of change in the diameter of the descending aorta of the fetus using the echo tracking method and calculated fetal PP using the Moens−Korteweg equation. However, it was technically difficult to obtain the rate of change in the diameter of blood vessels using the echo tracking method. Miyashita et al. (2015) measured the change in diameter of the descending aorta of the fetus using the PT method and calculated the fetal PP value using the Moens−Korteweg equation. Although the accuracy of the measurement had improved, it was higher than the assumed PP value (Johnson et al. 2000). In previous studies (Langewouters et al. 1984), when pressure was applied to the aorta, the aortic diameter exhibited no linear change in pressure. This may have been owing to the error caused by diameter-dependent estimates from the Moens−Korteweg equation. The present study used the Water−Hammer formula to calculate the PP value wherein the PP value is calculated only from the PWV and blood flow velocity of the descending aorta. In the Water−Hammer equation, the change in pressure as it occurs when a water flow is blocked by a valve can be calculated from the change in blood flow velocity. Similarly to blood vessels, the change in BP that occurs when the blood flow generated during systole is resisted by the peripheral narrow blood vessels is calculated as the change in blood flow velocity. According to the Water−Hammer formula, the PP can be measured by subtracting the lowest blood flow velocity from the highest blood flow velocity and multiplying that value by the density and change in PWV. Although the conventional method may have involved more complex measurements and calculations, the Water−Hammer formula was simple and made it possible to measure the PP value in a shorter time (Struijk et al. 2013; Miyashita et al. 2015). The PP values measured with ultrasound in this study were considered more reproducible than those in previous reports doing the same.

It was concluded that the sheep model may be superior to the human neonate model because the arterial catheter is inserted into the aorta through the internal carotid artery for BP measurements. Non-invasive PP measurements can be performed in conformity to the insertion site. In this experiment, the estimated and measured PP values of the sheep fetuses were approximately the same. It has been widely recognized that aortic BP more accurately reflects the hemodynamic status of adult patients than peripheral BP and, thus, is used as the most reliable hemodynamic parameter (Gary 2015). The method proposed in this study is a non-invasive technique used to measure the central BP of a fetus; therefore, it is considered that the results obtained with this method most accurately reflect the hemodynamic status of a fetus.

In this experiment, the measured PP value of the brachial artery of a newborn strongly correlated to the estimated PP value of the descending aorta, but the estimated PP values were lower by approximately 4 mm Hg. It has been argued that, in adults, BP is higher in the brachial artery than in the central artery because of differences in vessel diameters (Learoyd and Taylor 1965). It can also be inferred that the differences in our results between estimated and measured PP values were owing to the same cause. For adults, there exists an algorithm to convert peripheral arterial pressure into central arterial pressure (Munir et al. 2008). According to the algorithm, a value obtained by multiplying the PP of the brachial artery by 0.79 can be approximated to the PP of the central artery. In this study, the value obtained by multiplying the PP of the brachial artery measured using the oscillometric method by 0.79 strongly agreed with the value obtained by multiplying the PP of the central artery measured using ultrasound ($y = 1.06x$, $r = 0.89$, $p < 0.01$).

In the study described here, we chose to conduct the experiment on a sheep fetus because it had a circulation pattern similar to that of a human fetus (Schrauben et al. 2019). Initially it was hypothesized that the accuracy of the PT methods would depend largely on the size of the fetal blood vessels, and therefore, the PPs of sheep fetuses were measured on days 90 and 137 of the gestational period. The human newborns were selected on the basis of whose blood vessels were small enough to illustrate that PP measurements can be applied to “fine and tiny” blood vessels of the human fetus.

Although there are two umbilical veins in a sheep fetus, one umbilical vein was ligated to achieve the same circulation as a human fetus in this study. Ligation of one umbilical vein is thought to increase the internal pressure of the catheter in the artificial placenta. We compared measured PPs with estimated PPs in the central artery, and we thought that ligation of the umbilical vein did not affect this study.

Because the pulse Doppler method has an angle correction function, it is possible to measure from any angle. Because the phase-tracking method does not have an angle correction function, it is necessary to measure perpendicularly to the blood vessel. If measured obliquely, the delay time calculated will be too large, and the PWV will be measured smaller than it actually is. Moreover, the wall displacement detected by ultrasound becomes small, and the accuracy of measurement becomes low.

This method can be applied only to the normal cardiovascular system. For example, if there was a stenosis of blood vessels or regurgitation in the human fetus, PP could not be measured correctly. In this study, a sheep newborn was connected to the AP rather than a sheep fetus. After delivery of the sheep by cesarean section, it was possible to insert a catheter into the carotid artery of the sheep, return it into the uterus of the maternal sheep and perform ultrasound measurements from the abdominal wall of the maternal sheep. At first, this model was used to take ultrasound measurements from the abdominal wall of the maternal sheep, but it was not realistic to do so because the sheep moved violently. Therefore, research was conducted using sheep that were connected to an AP. It remains to be seen to what extent PP reflects fetal well-being. A multi-institutional joint research program is currently being conducted to measure fetal PP in human fetuses for conditions such as anemia, twin-to-twin transfusion syndrome and intrauterine growth retardation in comparison with those in healthy newborns. It is thought that the results of this joint research will elucidate fetal pathologies of these fatal conditions in a more comprehensive way from the viewpoint of PP.

CONCLUSIONS

The results of this study indicate that there is a strong correlation between the estimated and measured PPs of sheep fetuses. This was also the case with human neonates. It was confirmed that PP measurement using the ultrasound technique is highly accurate.

Conflict of interest disclosure—None of the authors have a conflict of interest.

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