

## Original Article

## New non-invasive approach to detect cardiac contractility using the first sound of phonocardiogram

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**Aim:** During surgery, a non-invasive and easy-to-use method is required for evaluating left ventricular status. The systolic time interval, including pre-ejection period (PEP), of left ventricle has been known to be correlated with cardiac contractility. In this study, we focused on the non-invasive time interval from the Q wave of an electrocardiogram to the third component in the first heart sound (QS<sub>1</sub>-3rd) and evaluated the correlation between PEP and peak differentiated left ventricular pressure (LV dp/dt).

**Methods:** Six adult anesthetized pigs were intubated. Mechanical ventilation was started. An electrocardiogram, carotid artery blood pressure, left ventricular pressure, and phonocardiogram on the fourth left intercostal space were monitored using a polygraph system. Cardiac output was measured by the thermodilution method. Data were simultaneously measured at baseline and after the infusion of noradrenaline, nitroprusside, esmolol sulfate, and dobutamine, respectively. Data were analyzed by Spearman's rank correlation coefficient using four-quadrant plot analysis.

**Results:** A total of 270 points were simultaneously measured. The QS<sub>1</sub>-3rd showed a significant correlation with PEP (QS<sub>1</sub>-3rd = 7.62 + 0.92 PEP;  $\rho = 0.91$ ,  $P < 0.0001$ ). Concordance rate was 92% between PEP and QS<sub>1</sub>-3rd (excluded zones were set within  $\pm 5$  ms). Both PEP and QS<sub>1</sub>-3rd showed a good correlation with LV dp/dt (LV dp/dt = 3861.3–24.4 PEP;  $\rho = 0.85$ ,  $P < 0.0001$ , LV dp/dt = 3763.6–23.5 QS<sub>1</sub>-3rd;  $\rho = 0.82$ ,  $P < 0.0001$ ).

**Conclusion:** This non-invasive and easy-to-use hemodynamic parameter (QS<sub>1</sub>-3rd) could be helpful for continuous monitoring of left cardiac contraction performance.

**Key words:** Performance, phonocardiogram, pre-ejection period, left ventricular contraction

## INTRODUCTION

TO OPTIMIZE THE hemodynamic status, a non-invasive and easy-to-use method is required for evaluating cardiac contractility during surgery. Echocardiography (ECG) is a useful device to evaluate cardiac performance. However, this technology requires specialized training for image acquisition and interpretation and is not always readily available. Therefore, especially during surgery, a novel, easy-to-use, and non-operator-dependent technique is needed to monitor hemodynamics for evaluating left ventricular contractility. Systolic time intervals are well-evaluated indicators of heart failure<sup>1</sup> and ventricular dyssynchrony.<sup>2</sup>

These indicators could be measured non-invasively using ECG, aortic blood pressure waveform, and/or phonocardiogram. Among these parameters, the pre-ejection period (PEP) of left ventricle is known to be correlated with peak differentiated left ventricular pressure (LV dp/dt).<sup>3</sup> Originally, PEP was measured by subtracting left ventricular ejection time in the carotid arterial pulse tracing from the time interval from the ECG Q wave to the second sound (S<sub>2</sub>) in the phonocardiogram.<sup>4–6</sup> Therefore, PEP had not been used in the clinical setting because the S<sub>2</sub> sound was so small to detect exactly. On the contrary, the S<sub>1</sub> sound was large enough for routine monitoring and known to change according to cardiac contractility.<sup>7</sup> Recently, the electromechanical activation time, which is defined as the time interval from the ECG Q wave to the first sound (S<sub>1</sub>), has been reported to identify cardiac function.<sup>8,9</sup> In the S<sub>1</sub> sound, the following three components were recognized: the first component occurs when the left ventricular wall and the septum have reached a certain tension, the second component occurs when the aortic valve opens, and the third component occurs when the peak of the aortic pulse flow has been reached.<sup>10–12</sup>

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Therefore, we hypothesized that the third component in the first sound ( $S_1$ -3rd) could detect the carotid artery pressure waveform upstroke. In this study, we focused on the non-invasive systolic time interval from the Q wave of ECG to  $S_1$ -3rd from the phonocardiogram ( $QS_1$ -3rd) and evaluated the ability for detecting left ventricular contractility.

## METHODS

### General procedure

**T**HE PRESENT STUDY was carried out at the Kochi Medical School (Kochi, Japan) and was approved by the Institutional Animal Research Ethics Committee (H-00094). All experiments were carried out according to the National Institutes of Health guidelines for the use of experimental animals. We studied six domestic pigs (mean weight,  $46.0 \pm 3.5$  kg).

### Animal preparation

Six domestic pigs were fasted overnight with free access to water. Anesthesia was induced with an i.m. injection of midazolam (0.2 mg/kg), ketamine (5 mg/kg), medetomidine hydrochloride (0.04 mg/kg), and atropine sulfate (0.05 mg/kg). Anesthesia was maintained using isoflurane in 0.5 L/min oxygen and 1.5 L/min air, ketamine (5 mg/kg/h), and vecuronium bromide (0.2 mg/kg/h). An adequate depth of anesthesia was evaluated with the maintenance of physiological variables (heart rate and arterial pressure) and unresponsiveness to stimuli during surgical treatment. Supplementary boluses of 1 mg/kg ketamine were given if the animals developed unexpected tachycardia or arterial hypertension. All the measurements were undertaken at least 5 min after anesthesia was given, to minimize the effects of the drugs on the measured parameters.

Tracheal intubation and mechanical ventilation were carried out with the following baseline ventilator settings: a tidal volume of 12 mL/kg with positive end-expiratory pressure of 3 cmH<sub>2</sub>O. Ventilatory frequency was adjusted to maintain an end-carbon dioxide (EtCO<sub>2</sub>) value between 35 and 45 mmHg (Ultima; Datex/Instrumentarium, Helsinki, Finland), and inspiratory fraction of oxygen was adjusted to maintain arterial saturation over 95%. These settings were considered as initial ventilation.

A standard three-lead electrocardiography (II lead), carotid artery blood pressure (ARTcarotid), left ventricular pressure, and phonocardiogram were monitored by the polygraph system (RMT-1000; Nihon Kohden, Tokyo, Japan) ( $f_s = 1$  kHz). Phonocardiogram was recorded on the fourth left intercostal space by a microphone using a piezoelectric

element (TA-701T; Nihon Kohden). Vascular pressures were measured using calibrated pressure transducers (Blood Pressure Monitoring Kit SCKD-5005 [S568]; Becton Dickinson Critical Care Systems, Singapore) positioned at the level of the left atrium. Left ventricular pressure was measured through the left ventricular catheter (BeaconTip Royal Flush Plus High-flow Catheter; Cook Medical, Bloomington, IN, USA). A 7-Fr pulmonary artery catheter (774HF75; Edwards Lifescience, Irvine, CA, USA) was inserted by pressure curve visualization through the internal jugular vein. Cardiac output (CO) was measured by the thermodilution method. Ten milliliters of ice-cold saline was injected three times into the proximal port of the pulmonary artery catheter to calculate CO, and mean CO values were recorded. After surgical preparation, a continuous infusion of 2 mL/kg/h lactated Ringer's solution was given during the entire experimental period. After data collection, the animals were killed with potassium chloride overdose while under deep anesthesia.

### Study protocol

Noradrenaline and nitroprusside were infused to achieve a >10% increase or decrease in mean arterial pressure. Dobutamine and esmolol sulfate were infused to achieve a >30% increase or decrease in carotid artery blood flow. Data were simultaneously measured at baseline and after the infusion of noradrenaline, nitroprusside, esmolol sulfate, and dobutamine while maintaining the hemodynamic stability for 15 min, respectively (five datasets in each phase) (Fig. 1).

### Measurements

All signal processing, detecting ECG Q wave, peak LV dp/dt and the third component in the first sound ( $S_1$ -3rd), and subsequent data analysis was carried out in Labchart 7 (ADInstruments, Bella Vista, New South Wales, Australia) (Fig. 2).

### Statistics

A priori, we undertook a pilot study and obtained a mean PEP value of  $113 \pm 4$  ms (mean  $\pm$  standard deviation) and a mean difference value between PEP and  $QS_1$ -3rd of  $4 \pm 3$  ms. From these data, power analysis was carried out. Six pigs were predicted to be required to detect a 10 ms difference between PEP and  $QS_1$ -3rd, considered clinically significant, with  $\alpha = 0.05$  and a power of 80%. Accordingly, six pigs were used in the present study. Data were analyzed in an offline manner. Hemodynamic values were presented as mean  $\pm$  standard deviation and analyzed by repeated measures analysis of variance with Bonferroni's correction

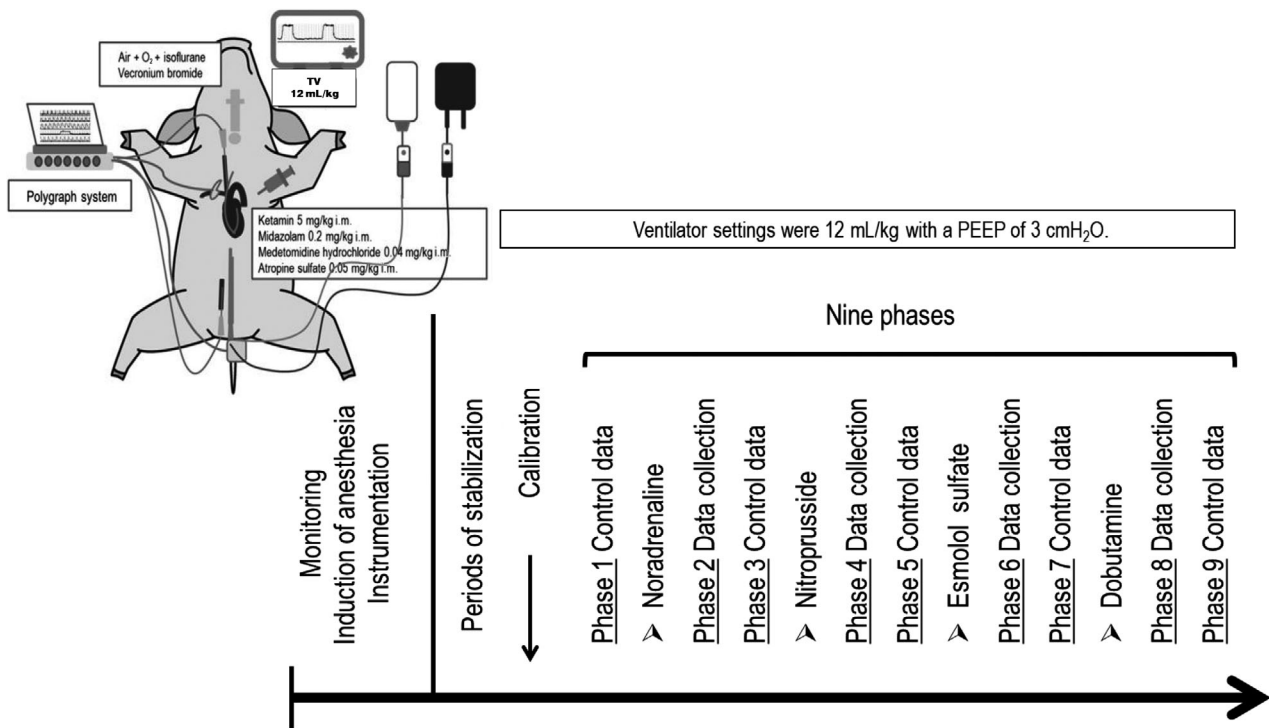


Fig. 1. Study protocol. PEEP, positive end-expiratory pressure; TV, tidal volume.

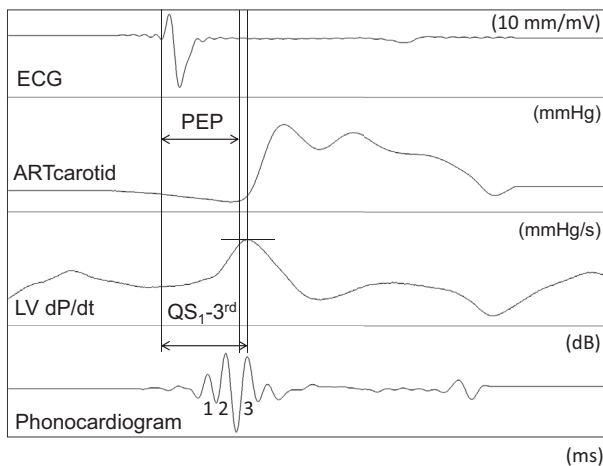


Fig. 2. In the lowest line, 1, 2, and 3 indicate the component in the first sound. ARTcarotid, carotid arterial pressure; ECG, electrocardiogram; LV dp/dt, peak differentiated left ventricular pressure; PEP, pre-ejection period; QS<sub>1-3rd</sub>, time interval from the Q wave of ECG to the third component in the first heart sound.

as post hoc analysis. Spearman’s rank correlation coefficient was calculated to determine the correlation between PEP and QS<sub>1-3rd</sub> against LV dp/dt. A four-quadrant plot analysis

was used to evaluate the tracking ability in QS<sub>1-3rd</sub> for PEP.<sup>13</sup> Excluded zones were set within  $\pm 5$  ms.  $P < 0.05$  was considered statistically significant. Concordance rate of  $>92\%$  was considered reliable for trending ability against reference values<sup>14</sup> (JMP (r) Sample JSL Scripts 2009 and JMP 11 2014; SAS Institute, Cary, NC, USA).

**RESULTS**

**H** EART RATE WAS significantly increased in Phase 8 (after dobutamine infusion) and Phase 9. The ARTcarotid (systolic, diastolic, and mean) values were significantly increased in Phase 4 (after noradrenaline infusion) and Phase 8 (after dobutamine infusion) and significantly decreased in Phase 2 (after nitroprusside infusion) and Phase 6 (after esmolol infusion). Cardiac output values were significantly increased in Phase 2 (after nitroprusside infusion), Phase 4 (after noradrenaline infusion), and Phase 8 (after dobutamine infusion) and significantly decreased in Phase 6 (after esmolol infusion) (Table 1). A total of 270 points were simultaneously measured; QS<sub>1-3rd</sub>, PEP, and LV dp/dt were measured in an offline manner. For securing the reliability of the result, these parameters were measured by a person irrelevant to this study. QS<sub>1-3rd</sub> showed a significant

**Table 1.** Hemodynamic variables before and after drug infusion

Phase	HR (b.p.m.)	ARTcarotid (mmHg)			CO (L/min)	BT (°C)
		Systolic	Diastolic	Mean		
Phase 1 (control)	84 ± 9	91 ± 5	50 ± 11	64 ± 8	5.1 ± 0.5	37.5 ± 0.5
Phase 2 (nitroprusside)	80 ± 12	70 ± 7*	35 ± 11*	43 ± 10*	5.6 ± 0.9*	37.4 ± 0.4
Phase 3 (control)	78 ± 13	89 ± 8	45 ± 14	61 ± 12	5.0 ± 1.3	37.2 ± 0.4
Phase 4 (noradrenaline)	86 ± 25	142 ± 43*	88 ± 32*	116 ± 35*	7.7 ± 2.8*	37.0 ± 0.6
Phase 5 (control)	85 ± 11	99 ± 17	56 ± 8	64 ± 7	5.9 ± 1.5	36.9 ± 0.7
Phase 6 (esmolol)	77 ± 9	80 ± 6*	47 ± 8*	52 ± 7*	4.5 ± 0.3*	36.8 ± 0.5
Phase 7 (control)	87 ± 9	87 ± 5	47 ± 5	59 ± 6	5.5 ± 0.4	36.7 ± 0.4
Phase 8 (dobutamine)	134 ± 22*	117 ± 21*	79 ± 6*	97 ± 3*	10.8 ± 1.0*	36.6 ± 0.4
Phase 9 (control)	85 ± 4*	91 ± 6	51 ± 12	62 ± 9	5.2 ± 0.5	37.5 ± 0.5

Values are expressed as mean ± standard deviation.

ARTcarotid, carotid arterial pressure; BT, body temperature; CO, cardiac output; HR, heart rate.

\* $P < 0.05$  versus Phase 1.

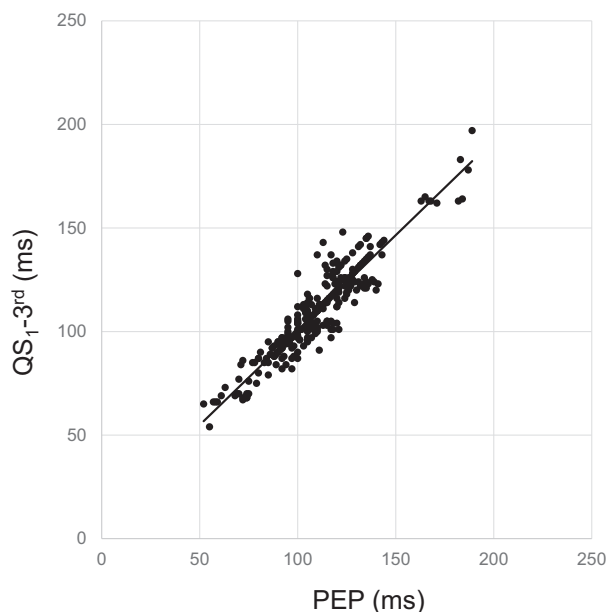
correlation with PEP ( $QS_{1-3rd} = 7.62 + 0.92 \text{ PEP}$ ;  $\rho = 0.91$ ,  $P < 0.0001$ ) (Fig. 3). The concordance rate was 92% between PEP and  $QS_{1-3rd}$  (Fig. 4). Pre-ejection period showed a good correlation with LV dp/dt (LV dp/dt =  $3861.3 - 24.4 \text{ PEP}$ ;  $\rho = 0.85$ ,  $P < 0.0001$ ) (Fig. 5).  $QS_{1-3rd}$  also showed a significant correlation with left

cardiac contraction performance (LV dp/dt =  $3763.6 - 23.5 \text{ QS}_{1-3rd}$ ;  $\rho = 0.82$ ,  $P < 0.0001$ ) (Fig. 6).

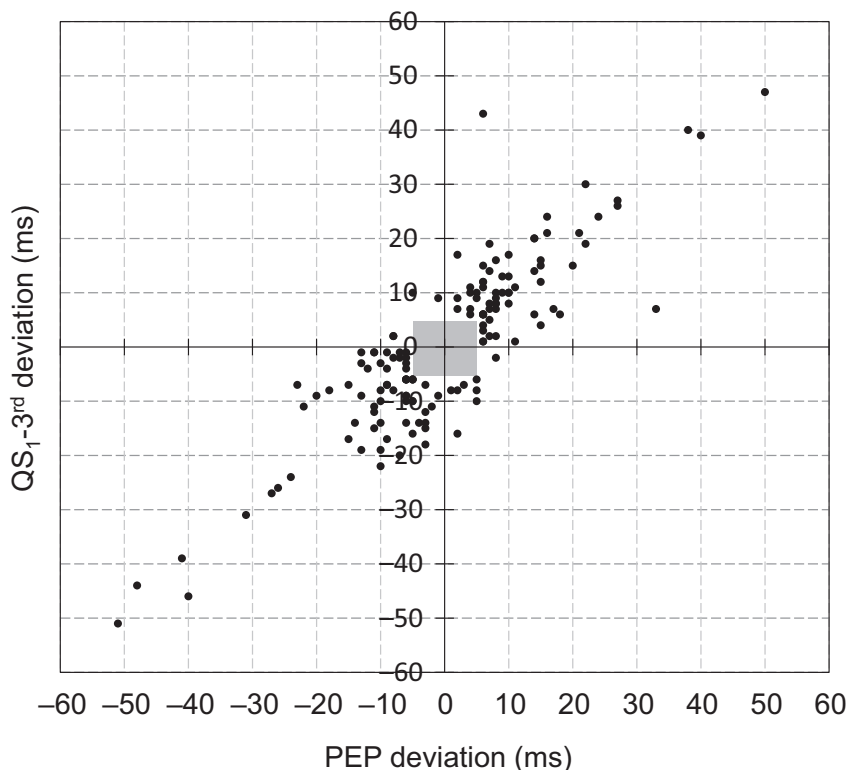
## DISCUSSION

IN THE PRESENT animal study, we showed that  $QS_{1-3rd}$  showed a good correlation with PEP with an acceptable tracking ability and also an ability for estimating the left ventricular contractility with a significant correlation with LV dp/dt. From a non-invasive point of view,  $QS_{1-3rd}$  is considered as a superior hemodynamic parameter.

Pre-ejection period was reported to inversely correlate with LV dp/dt.<sup>1</sup> Peak differentiated left ventricular pressure was believed to be a sensitive direct measure of cardiac performance.<sup>15,16</sup> Therefore, PEP might indicate left ventricular function. However, LV dp/dt is also influenced by preload, afterload, heart rate, and myocardial hypertrophy.<sup>17</sup> In other words, LV dp/dt increases with increases in afterload and preload. A normal dp/dt could be present in hypertension and aortic stenosis even with impaired LV function and vice versa. Therefore, PEP and LV dp/dt might not directly indicate the regional cardiac contractility but the global function of the heart, including LV contractility. Especially during surgery, anesthesiologists require more information about the hemodynamic status other than blood pressure and heart rate. From the changes in LV dp/dt and PEP, we could identify new cardiac complications. Therefore,  $QS_{1-3rd}$  might indicate the global function of the heart, including LV contractility. However, from the result of this study,  $QS_{1-3rd}$  and PEP underestimate LV dp/dt under 50 ms or over 150 ms. Inotropic and/or chronotropic agents, such as



**Fig. 3.** Scatter plots for pre-ejection period (PEP) and time interval from the Q wave of electrocardiogram to the third component in the first heart sound ( $QS_{1-3rd}$ ). PEP versus  $QS_{1-3rd}$ , including lines of identity.

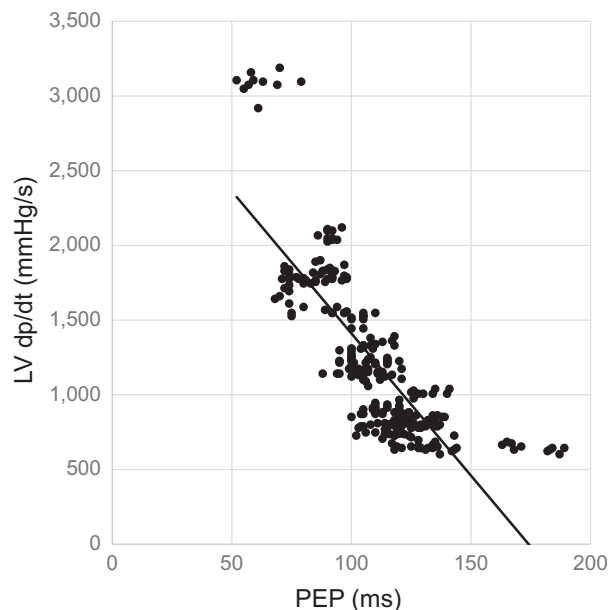


**Fig. 4.** Four-quadrant plots for pre-ejection period (PEP) and time interval from the Q wave of electrocardiogram to the third component in the first heart sound (QS1-3rd). Each data point represents the change (ms) in PEP and QS1-3rd (PEP deviation and QS1-3rd deviation, respectively). Gray square indicates the exclusion zone of 5 ms.

dobutamine and esmolol sulfate, might have an influence on this relationship. Further study was required to make sure the characteristics of this parameter.

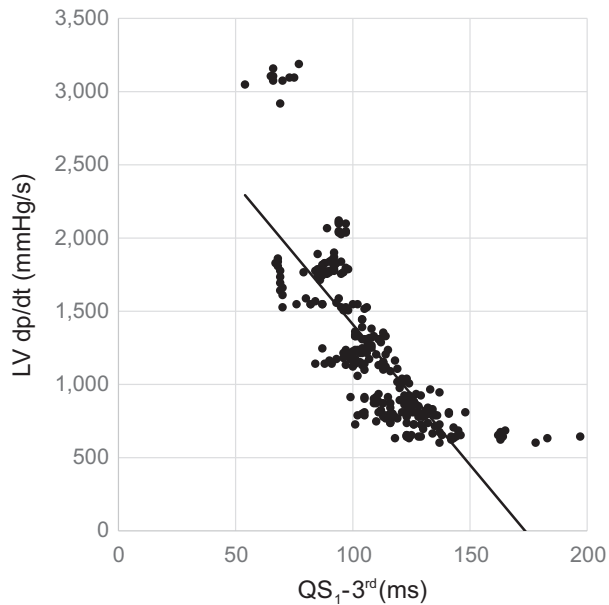
In this study, we focused on the first sound of the phonocardiogram. With advancements in digital techniques, the phonocardiogram has been able to characterize heart sounds and murmurs by their acoustic components, pattern, timing, frequency, and intensity.<sup>7</sup> However, an online analysis algorithm for detecting the component of the first sound has not been reported. Therefore, in the present study, we detected the time interval from the ECG Q wave to the third component of the first sound in an offline manner. Further study is required to detect the component of the first sound in an online manner. However, the phonocardiogram is influenced by endogenous and exogenous noises, including breathing and surgical procedures. It is essential that the subject is quiet and still during recording. However, in patients undergoing surgery, it is quite difficult to maintain stable conditions. Another study needs to be carried out to reduce these noises. Noise reduction technology might be useful for this monitoring system.

In the present study, we used the four-quadrant plot analysis. This method was originally proposed to show a tracking



**Fig. 5.** Scatter plots for the pre-ejection period (PEP) and peak differentiated left ventricular pressure (LV dp/dt). PEP versus LV dp/dt, including lines of identity.





**Fig. 6.** Scatter plots for time interval from the Q wave of electrocardiogram to the third component in the first heart sound ( $QS_{1-3rd}$ ) and peak differentiated left ventricular pressure (LV dp/dt). PEP versus LV dp/dt, including lines of identity.

ability of CO monitoring technology. However, a problem with this method was a lack of clearly defined cut-off values for definition of good, acceptable, and poor agreement in existing reports.<sup>13</sup> Another problem was that the exclusion zone was not clearly defined. The exclusion zone was needed to reduce the noise from small changes in reference values. In previous reports of CO monitoring technology, a >10% CO change was thought to be significant in the clinical setting.<sup>14</sup> Therefore, the exclusion zone was defined within 5 ms, because the deviation of PEP was within 50 ms in this study. Based on the results of a >92% of concordance rate, we believe that  $QS_{1-3rd}$  was interchangeable from PEP.

Finally, in the present study, we studied young subjects. Therefore, cardiac function, vessel reactivity, and other organ functions were absolutely normal. Further studies are required using older subjects with cardiovascular diseases.

## CONCLUSIONS

**T**HIS NON-INVASIVE and easy-to-use hemodynamic parameter ( $QS_{1-3rd}$ ) might be valuable in the management of perioperative patients, especially when other investigations such as echocardiography are not feasible or immediately available.

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## DISCLOSURE

Approval of the research protocol: The present study was carried out at the Kochi Medical School (Kochi, Japan) and was approved by the Institutional Animal Research Ethics Committee (H-00094).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: All animal experiments were carried out following the national guidelines and the relevant national laws on the protection of animals.

Conflict of interest: None.

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