박사학위논문

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# Heart sound S1/S2 component as a surrogate index for myocardial contractility: An experimental animal study

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이 논문을 박사학위 논문으로 제출함

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박용석의 박사학위 논문을 인준함

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## 국문요약

서론: 심음도는 심장 판막 기능 및 혈역학에 대한 중요한 정보를 제공할 수 있는 심장 소리를 기록하는 검사이다. 식도 청진기는 전신 마취 중 지속적인 청진에 사용되지만, 지속적인 혈역학 지표로서의 심음 데이터를 조사한 연구는 흔하지 않다. 본 연구에서는 동물 실험 연구를 통해 혈역학적 변화를 유도하고 심음과 혈역학적 변수 간의 관계를 밝히고자 하였다.

방법: 마취된 돼지에 도부타민, 에스몰롤, 페닐에프린, 니카르디핀을 투여하여 심근 수축력과 혈관 저항성의 변화를 유도하였다. 또한 하대정맥 클램핑을 통해 정맥 환류를 제한하여 심박출량의 감소를 유도하였다. 혈역학적 변화와 심음 지표의 변화 사이의 관계를 분석하였다.

결과: 돼지 8 마리의 실험 데이터를 분석하였다. 도부타민 투여는 수축기 혈압 (SBP), 맥압 (PP), $dP/dt_{max}$를 각각 평균 40.0 ± 10.9 mmHg, 19.8 ± 6.1 mmHg, 933.4 ± 281.9 mmHg/sec 증가시켰으며, 심음의 S1 진폭(S1amp)은 2840.4 ± 1401.8 AU 증가시켰다. 도부타민 투여 중 ΔS1amp 와 ΔSBP, ΔPP 및 $\Delta dP/dt_{max}$ 의 상관 계수의 평균값은 각각 0.94, 0.96 및 0.96 이었다. 에스몰롤 투여는 SBP, PP, $dP/dt_{max}$ 를 각각 평균 30.1 ± 23.8 mmHg, 14.9 ± 20.9 mmHg, 619.1 ± 760.1 mmHg/sec 감소시킨 반면 S1amp 는 1340.1 ± 1714.9 AU 감소시켰다. 에스모롤 투여 중 ΔS1amp 와 ΔSBP, ΔPP 및 ΔdP/dt 의 상관 계수의 평균값은 각각 0.80, 0.82 및 0.86 이었다. 페닐에프린 및 니카르디핀 투여로 인한 혈역학적 변화는 심박수 변화와 유의미한 상관관계가 없었다. 하대정맥 클램핑으로 인한 SBP 및 PP 의 변화는 S1amp 의 변화와 양의 상관관계를 보였으며, 평균 피어슨 상관관계 계수는 각각 0.70 및 0.67 이었다.

결론: 심음의 S1 진폭은 심근 수축성 변화로 인한 혈역학적 변화와 유의한 상관관계가 있었지만 혈관 저항의 변화와는 유의한 상관관계가 없었다. 심음은 잠재적으로 혈역학적 변화의 원인을 감별할 수 있는 비침습적 모니터링 방법을 제공할 가능성이 있다.

차례

표 목차

그림 목차

**Abstract**

*Introduction:* Phonocardiography is a recording of heart sounds that can provide valuable information about heart valve function and hemodynamics. Despite the esophageal stethoscope being used for continuous auscultation during general anesthesia, studies investigating phonocardiographic data as a continuous hemodynamic index are limited. In this study, we aimed to induce hemodynamic changes and to clarify the relationship between heart sounds and hemodynamic variables through an experimental animal study.

*Methods:* Changes in cardiac contractility and vascular resistance were induced in anesthetized pigs by administering dobutamine, esmolol, phenylephrine, and nicardipine. In addition, a decrease in cardiac output was induced by restricting venous return through inferior vena cava (IVC) clamping. The relationship between hemodynamic changes and changes in heart sound indexes was analyzed.

*Results:* Experimental data from 8 pigs were analyzed. Dobutamine administration increased systolic blood pressure (SBP), pulse pressure (PP), and $dP/dt_{max}$ by an average of 40.0±10.9 mmHg, 19.8±6.1 mmHg, and 933.4±281.9 mmHg/sec, respectively, while S1 amplitude of the heart sound (S1amp) increased by 2840.4±1401.8 AU. The mean values of the correlation coefficients of ΔS1amp with ΔSBP, ΔPP, and ΔdP/dt during dobutamine administration were 0.94, 0.96, and 0.96, respectively. Esmolol administration decreased SBP, PP, and $dP/dt_{max}$ by an average of 30.1±23.8 mmHg, 14.9±20.9 mmHg, and 619.1±760.1mmHg/sec, respectively, while S1amp decreased by 1340.1±1714.9 AU. The mean values of the correlation coefficients of ΔS1amp with ΔSBP, ΔPP, and $\Delta dP/dt_{max}$ during esmolol administration were 0.80, 0.82, and 0.86, respectively. The hemodynamic changes caused by phenylephrine and nicardipine administration did not correlate significantly with changes in heart rate. Changes in SBP and PP caused by IVC clamping were positively correlated with changes in S1amp, with mean Pearson coefficients of 0.70 and 0.67, respectively.

*Conclusion:* S1 amplitude of the heart sound was significantly correlated with hemodynamic changes caused by changes in cardiac contractility, but not with changes in vascular resistance. Heart sounds have the potential to provide a non-invasive monitoring method to differentiate the cause of hemodynamic changes.

## Introduction

Phonocardiography, which involves recording heart sounds, provides valuable information about the functioning of heart valves and the hemodynamics of the heart [1]. It has the potential to detect various heart diseases and to monitor cardiac function [2, 3]. Despite the long-standing use of esophageal stethoscopes (ESS) for continuous auscultation during general anesthesia, there have been limited studies investigating the use of phonocardiographic data as an indicator of cardiovascular function or continuous hemodynamic measurements [4-6]. In previous studies, we proposed that monitoring the phonocardiogram during surgery could provide useful clinical information as a non-invasive measure of hemodynamic status [7, 8]. In the two studies, we analyzed the time-domain and frequency-domain characteristics of heart sound signals obtained from digitalized recordings of ESS in patients under general anesthesia. The two studies have shown that heart sounds change differently depending on the mechanism of hemodynamic changes, and that changes in heart sound interval index follow a similar trend of changes in pulse pressure (PP) [8].

However, our previous studies have been retrospective observational studies of patients undergoing surgery, so it was not possible to induce hemodynamic changes in a controlled environment due to study design and ethical concerns. In addition, electrical or acoustic noise from the surgical situations interfered, making it difficult to acquire a clean signal. To overcome these limitations, we planned to conduct animal experiments using pigs. In this study, we induced hemodynamic changes in the study animals by administering various drugs that affects myocardial contractility or vascular resistance, and determined whether there were differences in the changes in heart sounds depending on the mechanism of the drugs. In addition, we simulated massive intraoperative blood loss by restricting venous return through surgical intervention and measured the changes in heart sounds during the process. The purpose of these experiments and analyses is to quantitatively determine the relationship between heart sounds and hemodynamic

variables and to identify the differences in heart sound changes by different mechanisms of hemodynamic changes.

## Methods

### *Subjects and experiment preparation*

This experiment was reviewed and approved by the Institutional Animal Care and Use Committee of the Asan Medical Center (Protocol No. 2020-12-114). Ten male Yorkshire pigs weighing from 34.1 to 36.7kg (35.5 ± 0.8 kg) were selected as the experimental subjects. Anesthesia was induced by intramuscular injection of Zoletil$^{TM}$ (zolazepam + tiletamine) 5mg/kg and xylazine 2mg/kg. After endotracheal intubation, mechanical ventilation was applied, and anesthesia was maintained by inhalation of 1%vol isoflurane. An intravenous catheter was placed for fluid and drug administration and an arterial catheter was inserted into the femoral artery for arterial blood pressure (ABP) monitoring. After inserting the ESS into the esophagus, an X-ray was taken to adjust the depth so that the tip of the ESS positioned at the center of the heart shadow.

### *Interventions to induce hemodynamic changes*

After anesthesia and preparation for the experiment is complete, dobutamine was administered with continuous intravenous (IV) infusion at a rate of 10 mcg/kg/min for 10 minutes to induce increased myocardial contractility. In the next phase, esmolol 0.5 mg/kg single IV dose induced a decrease in contractility. Phenylephrine 1 mcg/kg IV was administered to induce an increase in vascular resistance in the third phase, followed by nicardipine 10 mcg/kg IV induced a decrease in vascular resistance in the fourth phase. In the last phase, Inferior Vena Cava (IVC) clamping was performed to limit venous return to simulate a decrease in cardiac output due to acute blood loss. A 20-minute interval or more was allowed between each phase to minimize the effects of the previous phase's administration and to return hemodynamic status to baseline.

### *Signal acquisition, processing, and analysis*

We measured three biosignals: heart sounds, ABP, and electrocardiogram (ECG). Heart sounds were measured as sound signals with an electret microphone connected to an ESS inserted through

the esophagus near the heart, and ECG was measured from lead II electrodes. Heart sounds and ECG were converted to audio signals using a stereo sound analog-to-digital converter (ADC) and stored into an Android app. ABP was measured using a patient monitor from an arterial catheter inserted into the femoral artery via a pressure transducer. Finally, all signals were collected and recorded simultaneously using SignalTAB, an in-house developed Android application that can record multiple biosignal waveforms simultaneously (Figure 1).

To extract the heart sound features, we first applied a band-pass filter from 25 to 100 Hz using a second-order Chebyshev II FIR filter to separate the heart sound from the lung sounds. The envelope of the heart sound signal was calculated by squaring the absolute value of the filtered signal and using the Hilbert transform [9]. We detected the first heart sound (S1) and the second heart sound (S2) every cardiac cycle which were defined using a temporal relationship with the R peak of the synchronized ECG signal: Two peaks were extracted in each cardiac cycle and the first and second peak points were defined as S1 and S2, respectively, and heights of S1 and S2 were defined as S1 amplitude (S1amp) and S2 amplitude (S2amp), respectively. The R peaks of the ECG signal were extracted using simple peak detection algorithm (peak_detection function in SciPy python package) with manually calibrated thresholds for each recording. To extract the ABP features, systolic blood pressure (SBP) and diastolic blood pressure (DBP) points, we used feature extraction algorithm that proposed by Sun et al. [10], which uses the empirically defined threshold with rule-based algorithm.

All the signal processing analyses were performed using Python (Python Software Foundation, https://www.python.org).

***Statistical analysis***

Hemodynamic and heart sound signal data were expressed as mean ± standard deviation. All the statistical measures were analyzed using two-tailed paired-sample t-tests. The differences before and after each intervention were assessed by the paired t-test. Correlation between

variables were evaluated using Pearson correlation coefficients. All statistical analyses were performed using Python.

## Results

### *Hemodynamic and heart sound changes between pre- and post-intervention*

Of the 10 subjects, 2 were excluded due to poor heart sound signal, leaving 8 subjects whose data were included in final analysis. Different hemodynamic changes were observed pre- and post-intervention depending on the type of drug (Table 1). For dobutamine, SBP, pulse pressure (PP), and $dP/dt_{max}$ increased significantly after injection due to increased myocardial contractility ($\Delta$SBP 40.0 ± 10.9 mmHg: $t(8) = -10.4$, $p < 0.001$; $\Delta$PP 19.8 ± 6.1 mmHg: $t(8) = -9.2$, $p < 0.001$; $\Delta dP/dt_{max}$ 933.4±281.9: $t(8) = -9.4$, $p < 0.001$). Simultaneously, S1amp also increased significantly ($\Delta$S1amp 2840.4±1401: $t(8) = -5.7$, $p < 0.001$) (Figure 2). For esmolol, SBP, PP, and $dP/dt_{max}$ decreased after injection due to decreased contractility ($\Delta$SBP -30.1 ± 23.8 mmHg: $t(8) = 3.6$, $p = 0.009$; $\Delta$PP -14.9 ± 20.9 mmHg: $t(8) = 2.0$, $p = 0.084$; $\Delta dP/dt_{max}$ -619.1 ± 760.1: $t(8) = 2.3$, $p = 0.055$). At the same time, the S1amp also decreased ($\Delta$S1amp -1340.1 ± 1714.9: $t(8) = 2.2$, $p = 0.063$) (Figure 4). For phenylephrine, SBP and PP increased significantly after injection due to increase in vascular resistance ($\Delta$SBP 27±14.4 mmHg; $\Delta$PP 9.7±8.6 mmHg), while changes in heart sounds were not significant. For nicardipine, the change in SBP was -20.7±16.0 mmHg and was statistically significant ($p = 0.034$), while the changes in heart sounds were not significant (Table 1). After IVC clamping, SBP, PP, and S1amp decreased rapidly, and PPV increased rapidly. After IVC declamping, hemodynamic and cardiac variables returned to pre-clamping levels (Table 2 and Figure 8).

### *Correlation between hemodynamic changes and changes in heart sound indexes*

Changes in S1 amplitude due to dobutamine administration showed a good positive correlation with changes in SBP, PP, and $dP/dt_{max}$. The mean values of the correlation coefficients of $\Delta$S1amp with $\Delta$SBP, $\Delta$PP, and $\Delta dP/dt_{max}$ during dobutamine administration were 0.94, 0.96, and 0.96, respectively (Figure 3). Changes in S1 amplitude due to esmolol administration also showed a good positive correlation with changes in SBP, PP, and $dP/dt_{max}$. The mean values of the

correlation coefficients of ΔS1amp with ΔSBP, ΔPP, and ΔdP/dt during esmolol administration were 0.80, 0.82, and 0.86, respectively (Figure 5). However, the hemodynamic changes caused by phenylephrine and nicardipine administration did not correlate significantly with any changes in S1amp or S2amp, with the mean correlation coefficients ranging only between -0.09 and 0.59 for all cases. (Figure 6 and 7). Changes in SBP and PP caused by IVC clamping were positively correlated with changes in S1amp, with mean Pearson coefficients of 0.70 and 0.67, respectively (Figure 9).

## Discussion

In the current study, we identified changes in hemodynamic parameters induced by different mechanisms and their correlation with heart sound index. In particular, we found a strong correlation between changes in S1amp and in hemodynamic parameters caused by changes in myocardial contractility. On the other hand, changes in hemodynamic parameters due to changes in vascular resistance did not consistently correlate with changes in heart sound indexes.

The primary component of the heart sound is the vibration caused by the abrupt acceleration or deceleration of blood within the cardiovascular system [11]. Heart sounds are broadly categorized into S1 and S2 sounds: S1 is a sound with a slightly lower pitch and occurs when the atrioventricular valves close. On the other hand, S2 is a sound with a slightly higher pitch and produced by the closure of the arterial valves [12, 13]. In our previous work, we found that S1amp increased in cases where ephedrine was administered [7]. Ephedrine is a drug derived from the ephedra plant that has a predominant β-adrenergic effect with additional vasoconstrictor activity [14, 15]. Cases in which ephedrine was injected was analyzed in the previous study because the ephedrine is commonly administered to treat hypotension during anesthesia, making it easier to collect data from electric medical record. However, the downside is that it can be difficult to see the effect of pure changes in myocardial contractility. Dobutamine, on the other hand, is a direct-acting agent that acts on the $\beta_1$-adrenoreceptor, making it more suitable for determining the effectiveness of pure increase in contractility [16]. Indeed, in this experiment, dobutamine administration was successful in producing a significant increase in cardiac output due to a large increase in contractility and resulted in a strongly correlated change in S1amp. Since the pressure from the contraction of the ventricle is the primary force that closes the atrioventricular valve, this provides an explanation for why changes in myocardial contractile force change S1amp and raises the possibility that S1 sound could be a monitoring modality specific to cardiac contractility.

Hemodynamic changes with changes in systemic vascular resistance induced by administration of phenylephrine and nicardipine, however, did not show a correlation with heart sound parameters in our study. This was inconsistent with what we expected based on our previous research, in which administration of phenylephrine and nicardipine significantly affected the S2amp. One possible explanation for this is that the correlation between vascular resistance and S2amp is actually weaker than that between myocardial contractility and S1amp. In the previous study, the correlation between S2amp and SVR ($r^2 = 0.285$) was relatively weak compared to the correlation between S1amp and dP/dt ($r^2 = 0.679$), even though the correlation is described as statistically significant [7]. Therefore, it is possible that the changes in vascular resistance produced by the administration of phenylephrine and nicardipine in this experiment were insufficient to produce significant changes in heart sounds. If this is true, it suggests that changes in vascular resistance that typically occur in surgical patients do not produce detectable changes in heart sounds, and therefore monitoring changes in vascular resistance with heart sound measurements may be inappropriate. Another explanation is that anatomical or physiological differences between humans and pigs have led to these disparities. The shape of the porcine organ resembles a traditional 'Valentine heart,' which is influenced by its position within the thorax and the pig's unguligrade stance. In contrast, the human heart has a trapezoidal silhouette, reflecting our upright posture [17]. Another report revealed that the diameter of the great vessels, including the ascending aorta and main pulmonary artery, is relatively smaller in pigs compared to humans [18]. This is important because the way we acquire heart sounds is by inserting the ESS through the esophagus and receiving sound signals through it, so these anatomical variations and differences in the positioning of the ESS relative to the heart and great vessels can affect the shape and amplitude of the acquired heart sound signal. The difference may also be due to the condition of the subjects. In this study, the drug was administered to animals with normal vital signs, whereas the drug was administered to patients with abnormal vital signs in previous studies. This

is because the patients were given the drug only to correct some abnormal vital condition, which may have contributed to the greater effect of S2amp.

In hemodynamic changes due to IVC clamping, changes in S1amp were more strongly correlated with changes in SBP and PP compared to changes in $dP/dt_{max}$. IVC clamping is a technique that can reduce bleeding by reducing central venous pressure during liver resection, but it is known to cause intraoperative hemodynamic instability due to reduced venous return [19-21]. Whereas dobutamine caused similar or slightly stronger correlation between S1amp and $dP/dt_{max}$ than between S1amp and PP, IVC clamping caused a rapid reduction in cardiac output through venous return restriction without a significant effect on contractility, resulting relatively weak correlation between S1amp and $dP/dt_{max}$. Although arterial $dP/dt_{max}$ is influenced by various central and peripheral arterial factors, radial or femoral $dP/dt_{max}$ is known to provide a good tracking of changes in left ventricular contractility as loading and inotropic conditions were altered [22]. Therefore, this phenomenon (relative weak correlation of $dP/dt_{max}$ with S1amp) is likely to reflect the mechanism of action of IVC clamping on hemodynamic changes (reduction in cardiac output not attributable to myocardial contractility). Given these correlations, it seems likely that the analysis of heart sounds can be used to differentiate the cause of hemodynamic changes, i.e., whether they are due to change in myocardial contractility or other causes.

This study has several limitations. First, as noted above, we did not find a consistent correlation between changes in S2amp and changes in vascular resistance. It is possible that this result actually reflects a weak or no correlation between the variables, or that physiological differences between humans and pigs may be responsible, but further research is needed to determine the exact fact. Second, although the intra-individual correlations were strong, the inter-individual variability was quite large that generalized relationships between cardiac and hemodynamic variables could not be established. Compared to the correlations between the variables in each case, the correlations between the variables in all cases combined were relatively weak

(Supplementary figures 1, 2, and 3). In addition to this inter-individual variation, the fact that there is no absolute baseline value for the heart sound itself makes it difficult to use it as a monitoring indicator. Therefore, in order to develop this as a practical monitoring tool, it should be a way to use trend based on the initial baseline value. Third, due to the rapid decrease in cardiac output during IVC clamping, the heart sound signal became very weak, resulting in poor peak detection performance and failure to measure the respiratory variation of beat-to-beat heart sound. In other words, the goal of finding a non-invasive alternative to fluid responsiveness monitoring was not achieved. In future studies, partial or gradual clamping of the IVC or fluid loading to drive slow, incremental changes in cardiac output may help to overcome this limitation. Fourth, data from two subjects were excluded due to poor heart sound signals. The equipment we used to acquire the heart sounds was an initially developed Android-based software on tablet computer, which could not check the signal acquisition status during the experiment but should check the signal sent to the server after the experiment ended. Currently, with the update, it is possible to see the signal in real-time on the tablet as it is being acquired, so we do not think this will happen in future clinical trials. Finally, cardiac pressure-volume loop analysis could be performed to determine end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR), which reflects actual myocardial contractility and ventricular compliance, respectively, but was not performed in this experiment.

**Conclusion**

In conclusion, hemodynamic changes related to myocardial contractility were significantly correlated with changes in S1 amplitude, but changes related to vascular resistance did not correlate with changes in heart sound parameters. This suggests that heart sounds can be used to monitor changes in myocardial contractility and cardiac output, and may be a way to differentiate the cause of hemodynamic changes.

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**Table 1.** Changes in hemodynamic and heart sound indexes by administration

| | **Dobutamine** | **Esmolol** | **Phenylephrine** | **Nicardipine** |
|---|---|---|---|---|
| **Hemodynamic changes** | | | | |
| ΔSBP (mmHg) | 40.0±10.9*** | -30.1±23.8** | 27±14.4* | -20.7±16.0* |
| ΔHeart Rate (bpm) | 51.3±13.9*** | -24.6±19.8** | -1.6±10.0 | -0.1±6.2 |
| ΔPulse Pressure (mmHg) | 19.8±6.1*** | -14.9±20.9 | 9.7±8.6* | -4.3±6.8 |
| ΔPulse Pressure Variation | 1.0±5.1 | -0.14±7.9 | 3.4±11.1 | 3.0±4.5 |
| $\Delta dP/dt_{max}$ | 933.4±281.9*** | -619.1±760.1 | 143.5±239.1 | -30.2±244.0 |
| **Heart Sound changes** | | | | |
| ΔS1 amplitude (AU) | 2840.4±1401.8*** | -1340.1±1714.9 | 220.5±539.4 | -90.8±201.2 |
| ΔS2 amplitude (AU) | 687.5±786.6* | -358.7±337.8* | 65.0±163.2 | -148.2±181.5 |
| ΔS1-S2 interval (ms) | -39.2±100.8 | -1.7±55.1 | -1.9±24.8 | 0.3±16.6 |
| ΔS1-S2 interval variation | -1.8±31.1 | 2.9±31.4 | -0.3±15.5 | 1.9±4.6 |

Δ difference between before and after intervention; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; AU, arbitrary unit.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$: p-value comparing pre- and post-intervention variables using a t-test.

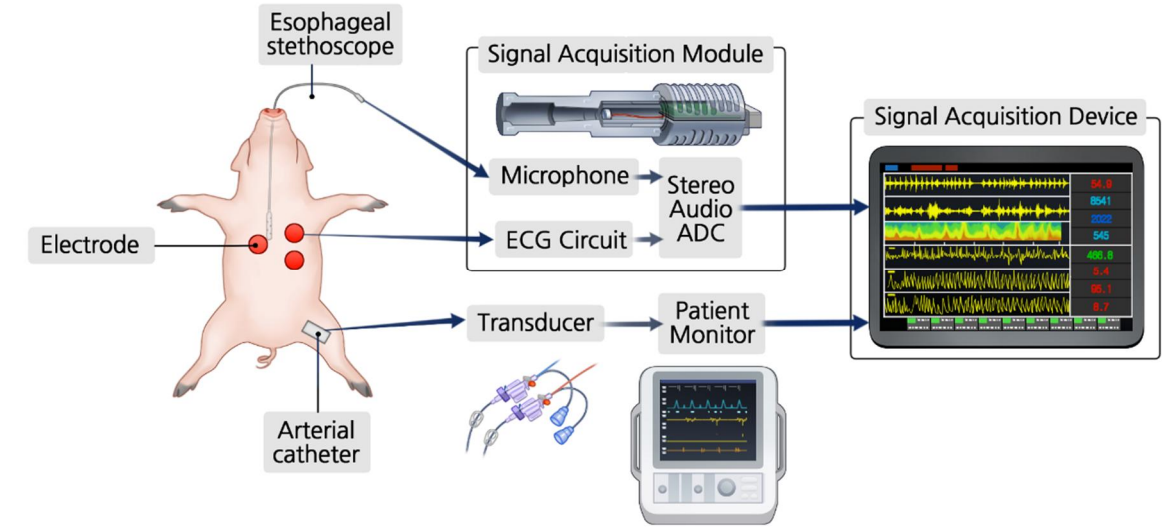
**Table 2.** Changes in hemodynamic and heart sound indexes by IVC clamping

| | **Before clamping** | **During clamping** | **After declamping** |
|---|---|---|---|
| **Hemodynamic variables** | | | |
| Systolic Blood Pressure (mmHg) | 92.5±17.1 | 61.1±11.7* | 86.5±12.6** |
| Heart Rate (bpm) | 87.1±13.7 | 83.8±12.0 | 82.6±11.5 |
| Pulse Pressure (mmHg) | 38.6±8.6 | 22.7±8.2*** | 34.6±10.2** |
| Pulse Pressure Variation | 11.8±4.3 | 26.8±10.1* | 11.2±4.7*** |
| $dP/dt_{max}$ | 843.5±323.6 | 510.8±154.0 | 768.9±284.7* |
| **Heart sound variables** | | | |
| S1 amplitude (AU) | 773.2±299.1 | 483.2±187.9 | 639.9±296.6 |
| S2 amplitude (AU) | 531.5±396.5 | 476.6±258.9 | 660.3±442.8 |
| ΔS1-S2 interval (ms) | 279.2±119.5 | 269.1±76.1 | 263.3±111.1* |
| ΔS1-S2 interval variation | 33.2±19.4 | 42.1±25.8 | 39.9±24.3 |

$dP/dt_{max}$, peak rate of rise of arterial pressure; AU, arbitrary unit.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$: p-value compared to the previous step by t-test.

**Figure 1.** Schematic illustration of the esophageal stethoscope system and heart sound signal processing process. ECG, electrocardiography; ADC, analog-to-digital converter; ABP, arterial blood pressure; S1, first heart sound; S2, second heart sound; SBP, systolic blood pressure; DBP, diastolic blood pressure.



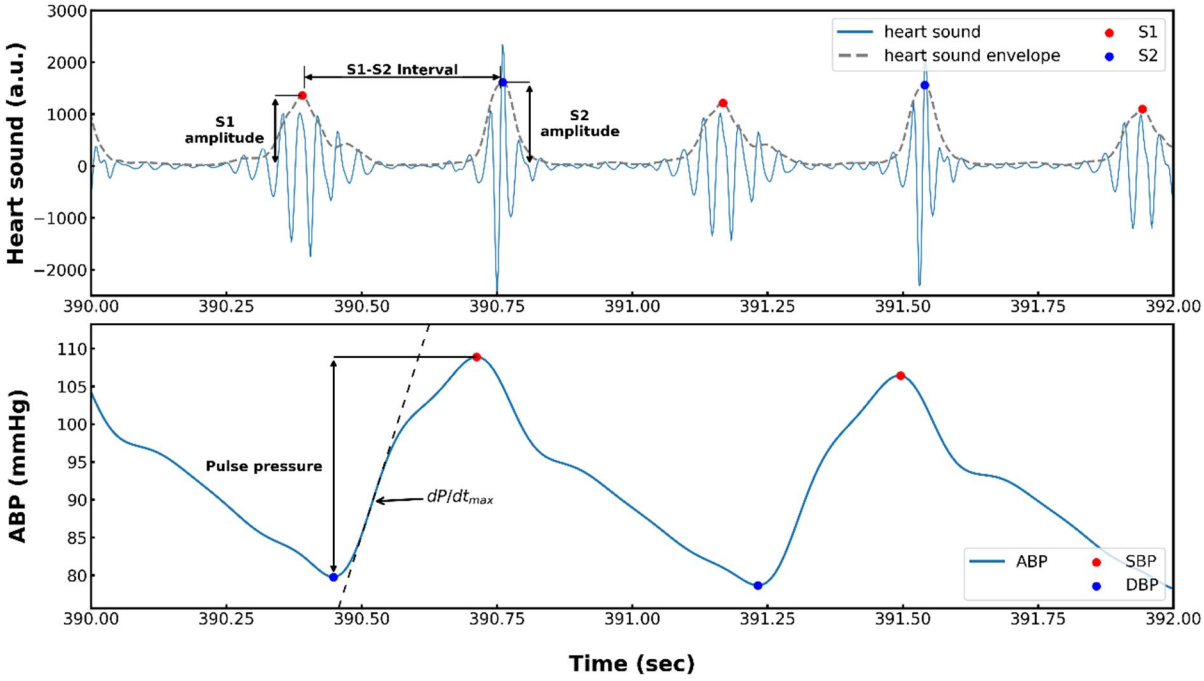



**Figure 2.** Representative plot of changes in hemodynamic status and heart sounds by dobutamine administration. ABP, arterial blood pressure; PP, pulse pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; S1, first heart sound; S2, second heart sound.

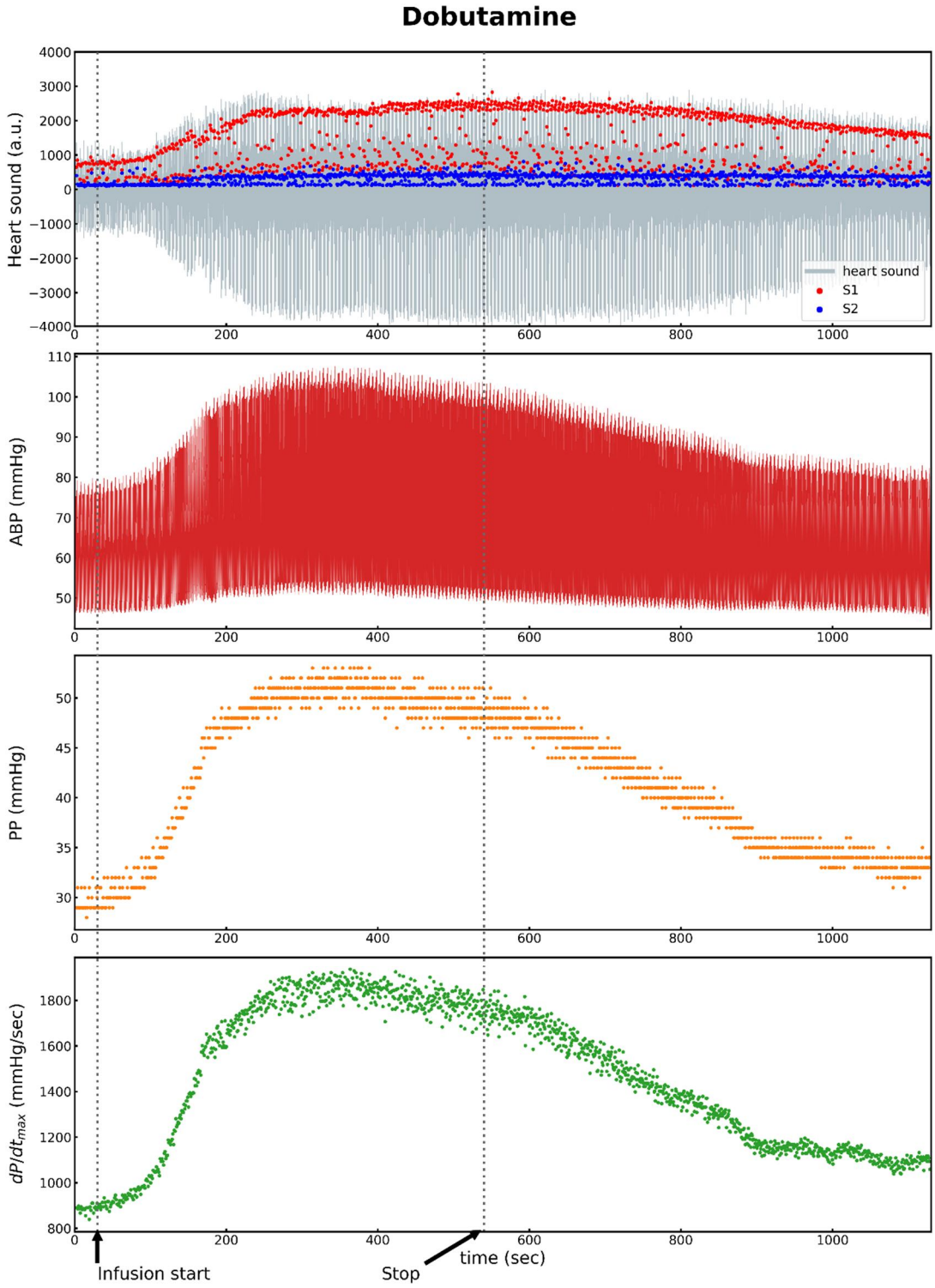


**Figure 3.** Correlations between dobutamine-induced changes in hemodynamic status and heart sound index. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; $\bar{r}$, average of the correlation coefficient in each case.

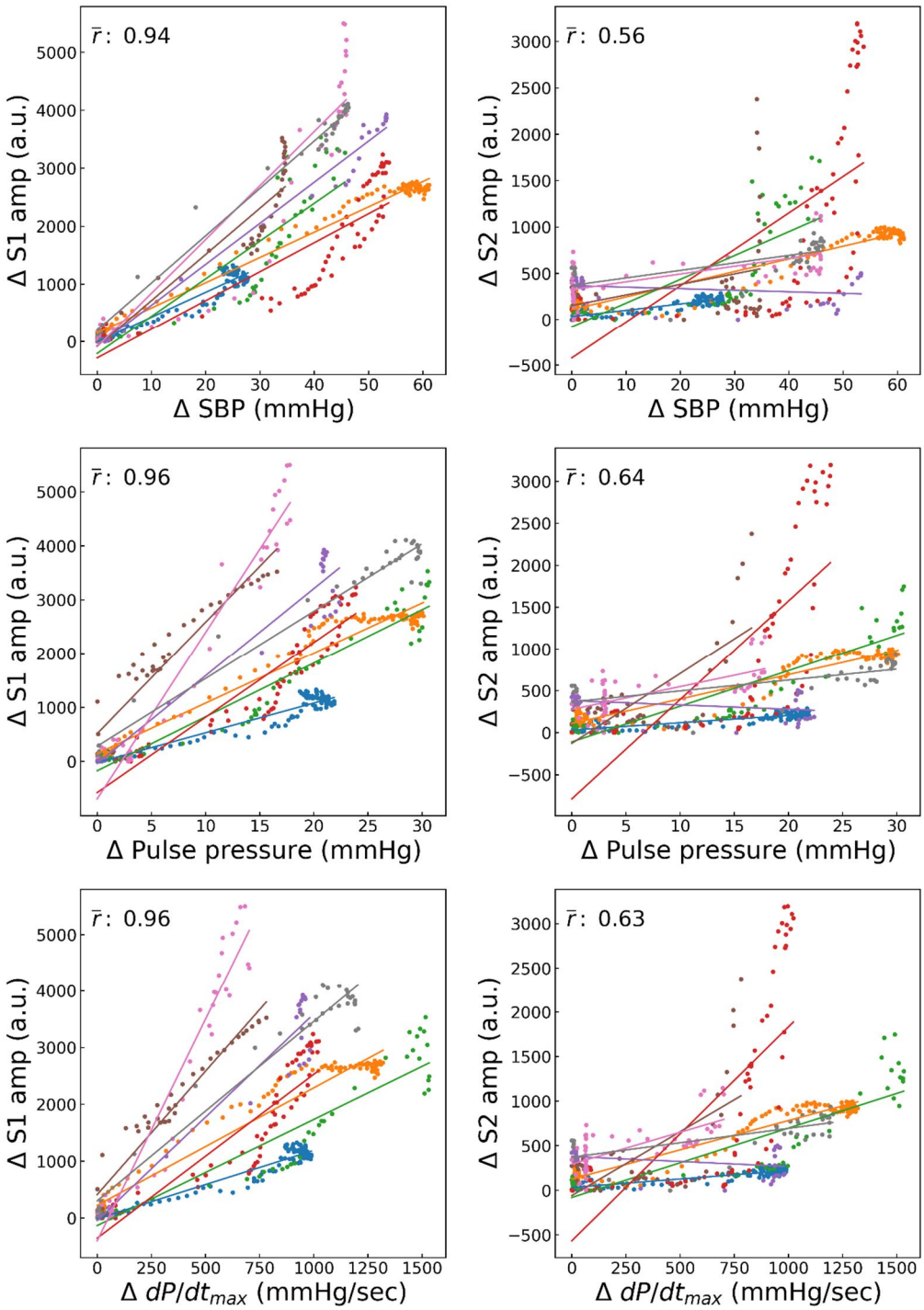


**Figure 4.** Representative plot of changes in hemodynamic status and heart sounds by esmolol administration. ABP, arterial blood pressure; PP, pulse pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; S1, first heart sound; S2, second heart sound.

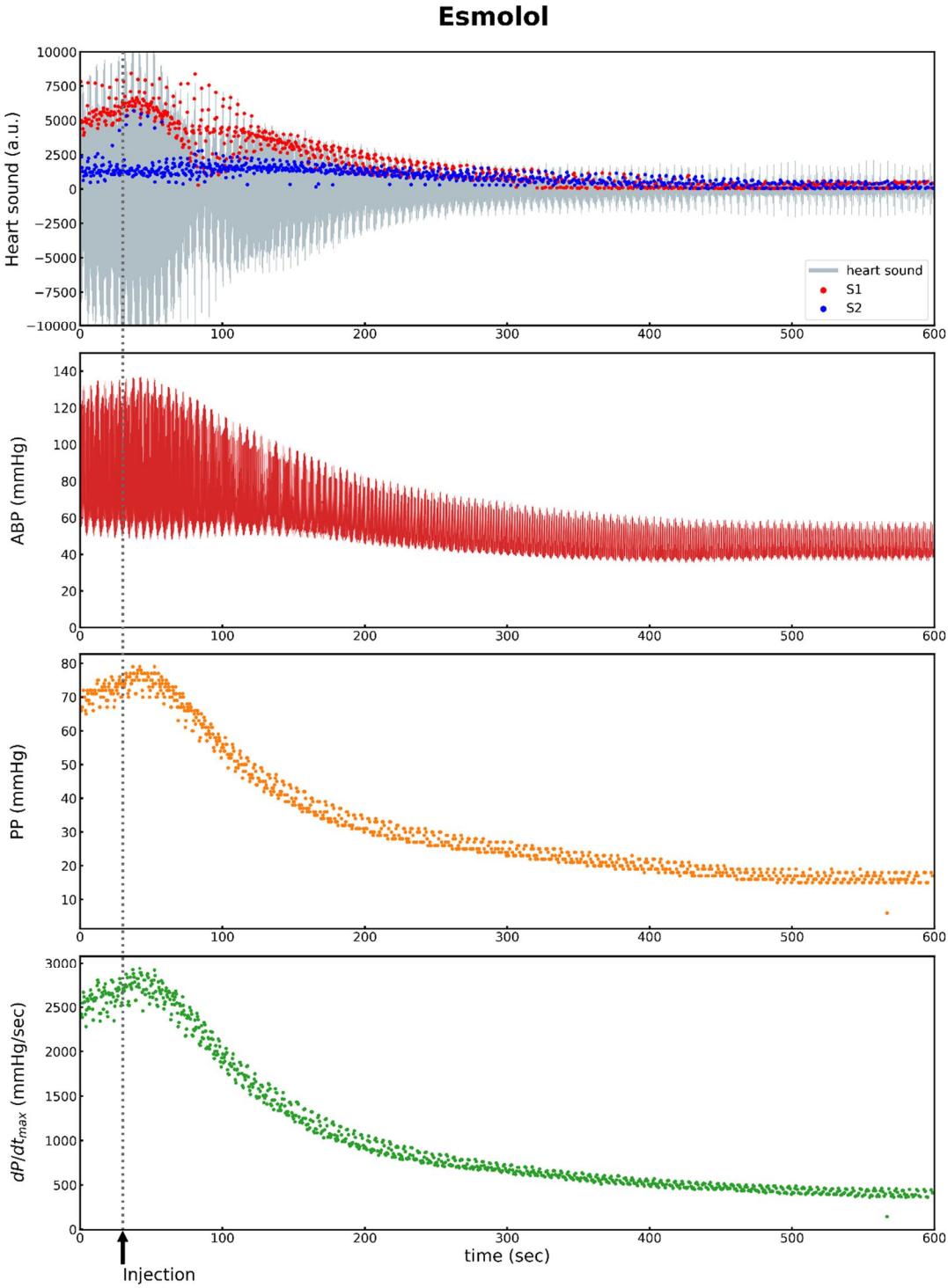


**Figure 5.** Correlations between esmolol-induced changes in hemodynamic status and heart sound index. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; $\bar{r}$, average of the correlation coefficient in each case.

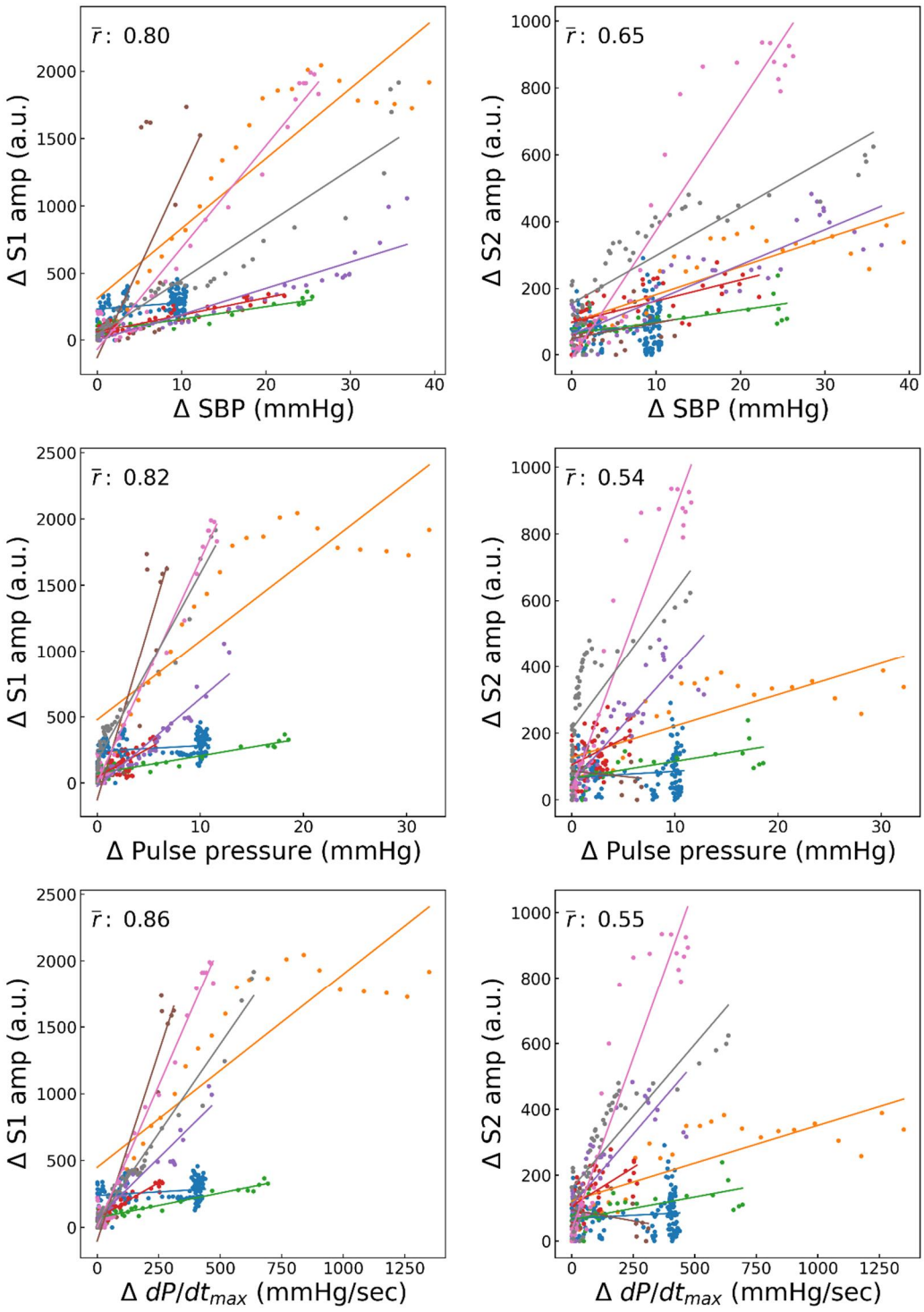


**Figure 6.** Correlations between phenylephrine-induced changes in hemodynamic status and heart sound index. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; $\bar{r}$, average of the correlation coefficient in each case.

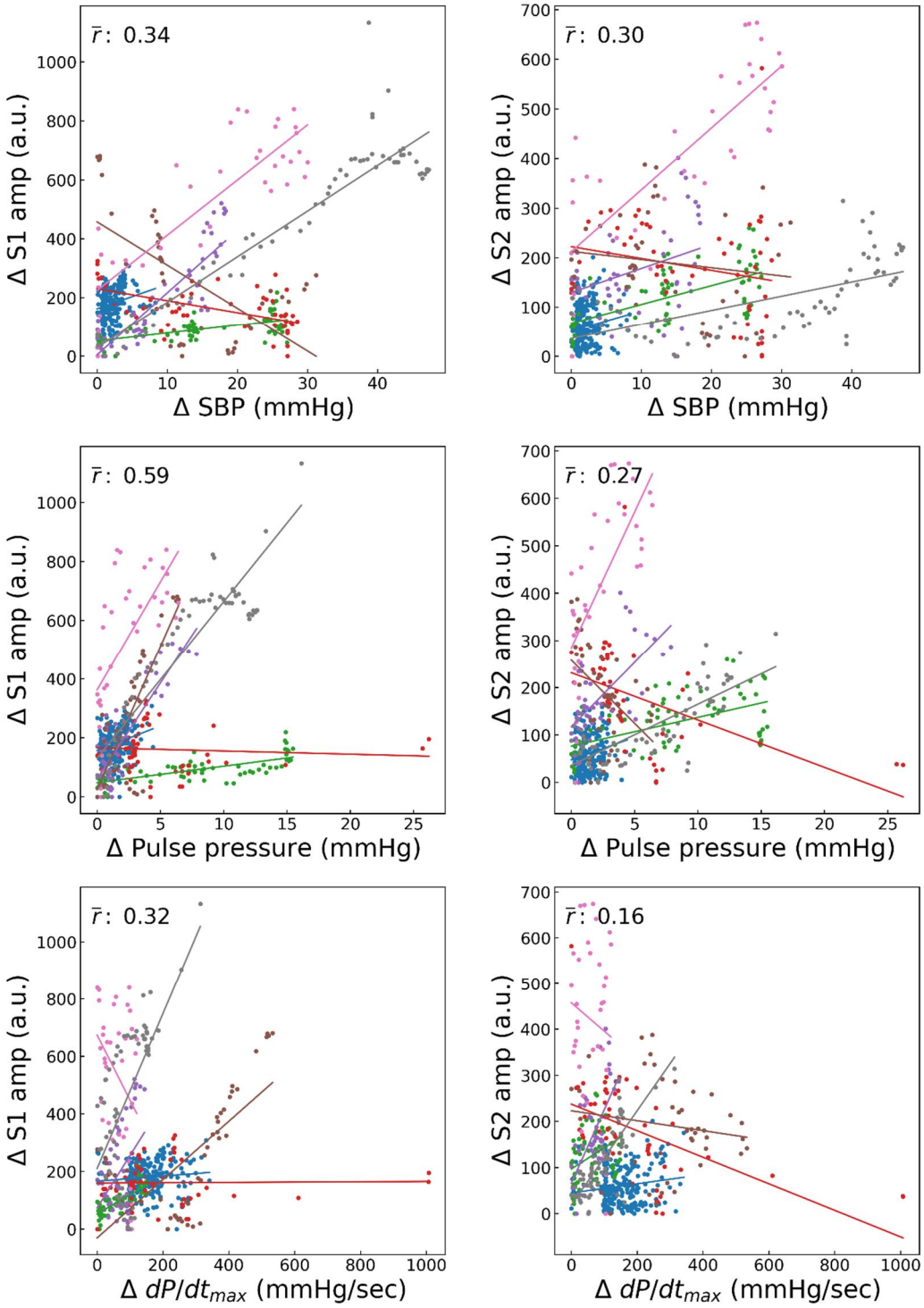


**Figure 7.** Correlations between nicardipine-induced changes in hemodynamic status and heart sound index. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; $\bar{r}$, average of the correlation coefficient in each case.

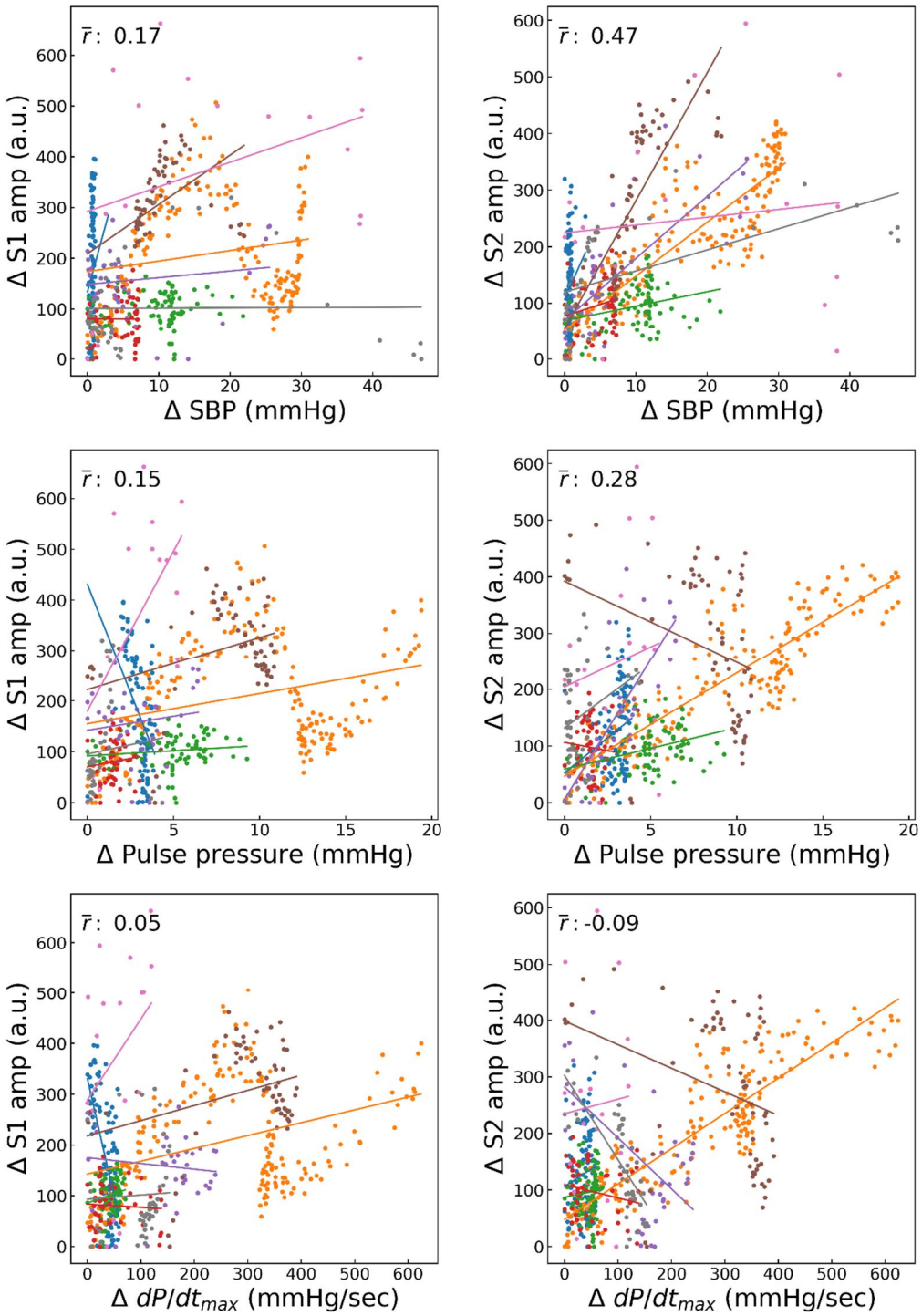


**Figure 8.** Representative plot of changes in hemodynamic status and heart sounds by IVC clamping. IVC, inferior vena cava; ABP, arterial blood pressure; PP, pulse pressure; S1, first heart sound; S2, second heart sound.

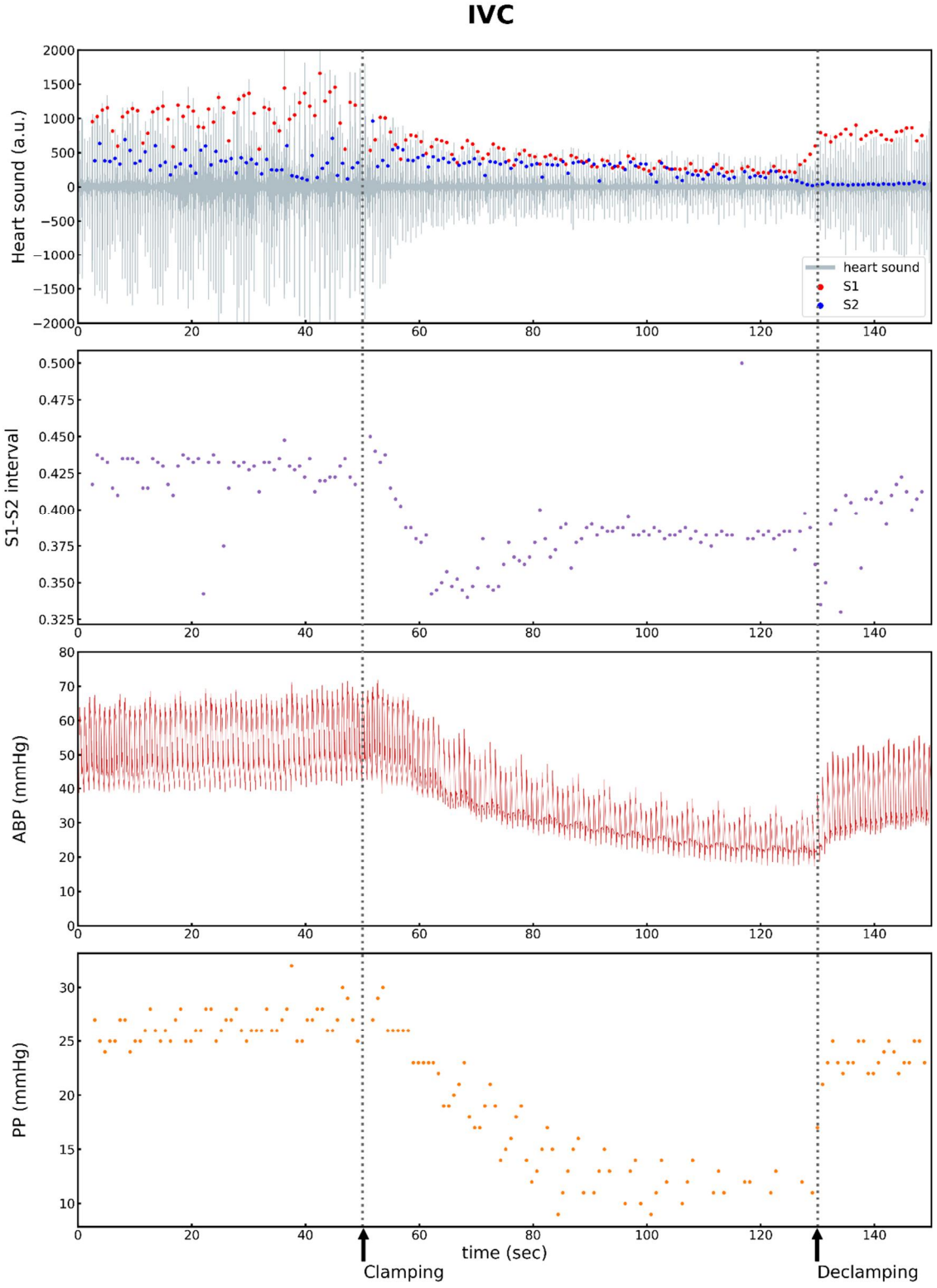
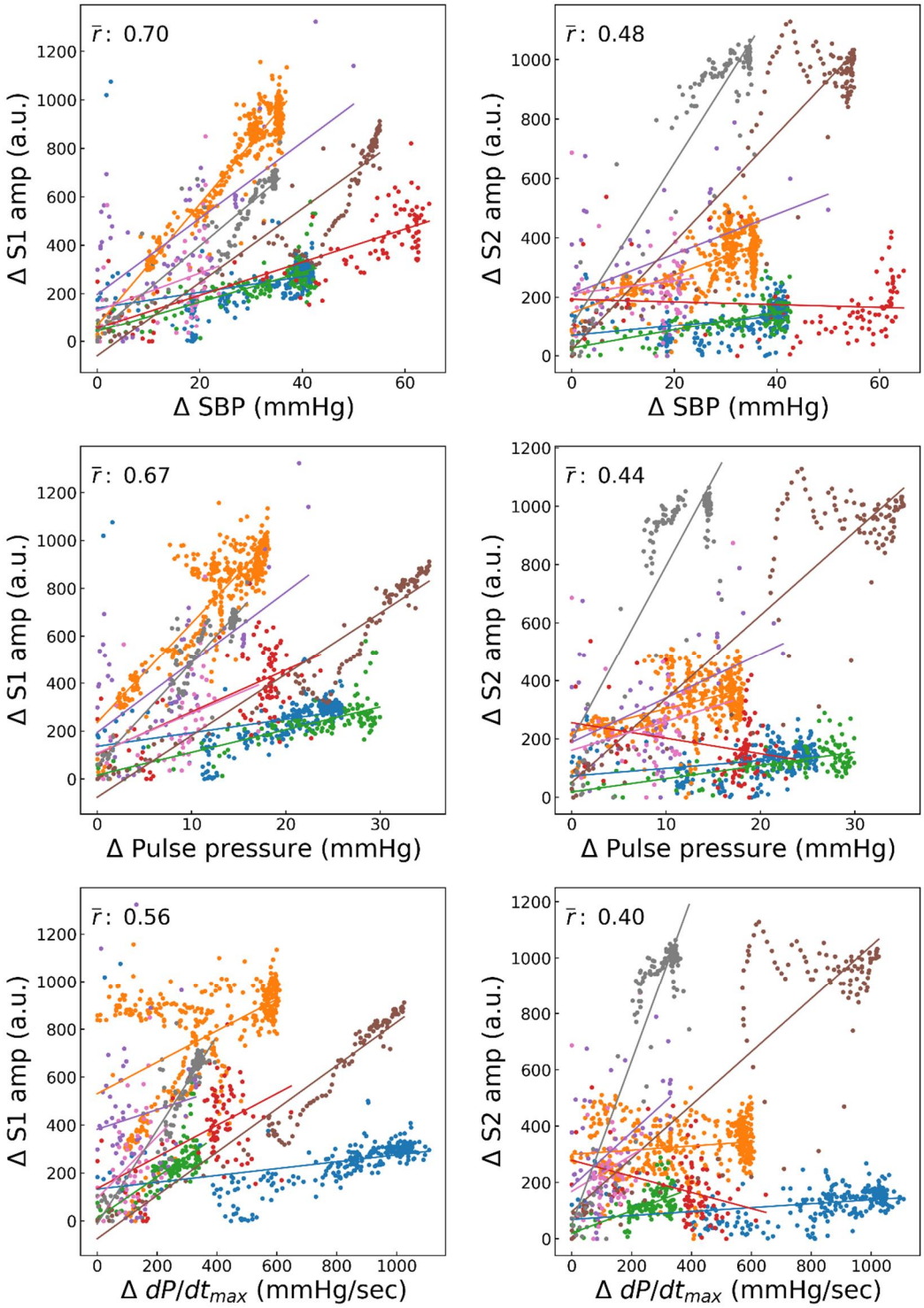


Figure 9. Correlations between changes in hemodynamic status due to IVC clamping and heart sound index. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure; $\bar{r}$, average of the correlation coefficient in each case.



**Supplementary Table 1.** Correlations between changes in each variable by dobutamine administration. Described for each case.

| | **ΔS1amp and ΔSBP** | | **ΔS1amp and ΔPP** | | **ΔS1amp and ΔdP/dt$_{max}$** | |
|---|---|---|---|---|---|---|
| Case | r | *p*-value | r | *p*-value | r | *p*-value |
| 1 | 0.952 | < 0.001 | 0.957 | < 0.001 | 0.964 | < 0.001 |
| 2 | 0.995 | < 0.001 | 0.985 | < 0.001 | 0.981 | < 0.001 |
| 3 | 0.888 | < 0.001 | 0.963 | < 0.001 | 0.945 | < 0.001 |
| 4 | 0.855 | < 0.001 | 0.912 | < 0.001 | 0.894 | < 0.001 |
| 5 | 0.995 | < 0.001 | 0.979 | < 0.001 | 0.981 | < 0.001 |
| 6 | 0.909 | < 0.001 | 0.901 | < 0.001 | 0.961 | < 0.001 |
| 7 | 0.949 | < 0.001 | 0.978 | < 0.001 | 0.977 | < 0.001 |
| 8 | 0.990 | < 0.001 | 0.983 | < 0.001 | 0.975 | < 0.001 |

S1amp, amplitude of first heart sound; SBP, systolic blood pressure; dP/dt$_{max}$, peak rate of rise of arterial pressure.

**Supplementary Table 2.** Correlations between changes in each variable by esmolol administration. Described for each case.

| | **ΔS1amp and ΔSBP** | | **ΔS1amp and ΔPP** | | **ΔS1amp and ΔdP/dt$_{max}$** | |
|---|---|---|---|---|---|---|
| Case | r | *p*-value | r | *p*-value | r | *p*-value |
| 1 | 0.214 | 0.011 | 0.218 | 0.010 | 0.219 | 0.009 |
| 2[†] | NA | NA | NA | NA | NA | NA |
| 3 | 0.918 | < 0.001 | 0.930 | < 0.001 | 0.935 | < 0.001 |
| 4 | 0.916 | < 0.001 | 0.716 | < 0.001 | 0.918 | < 0.001 |
| 5 | 0.922 | < 0.001 | 0.951 | < 0.001 | 0.966 | < 0.001 |
| 6 | 0.226 | 0.115 | 0.641 | < 0.001 | 0.748 | < 0.001 |
| 7 | 0.979 | < 0.001 | 0.989 | < 0.001 | 0.988 | < 0.001 |
| 8 | 0.954 | < 0.001 | 0.967 | < 0.001 | 0.986 | < 0.001 |

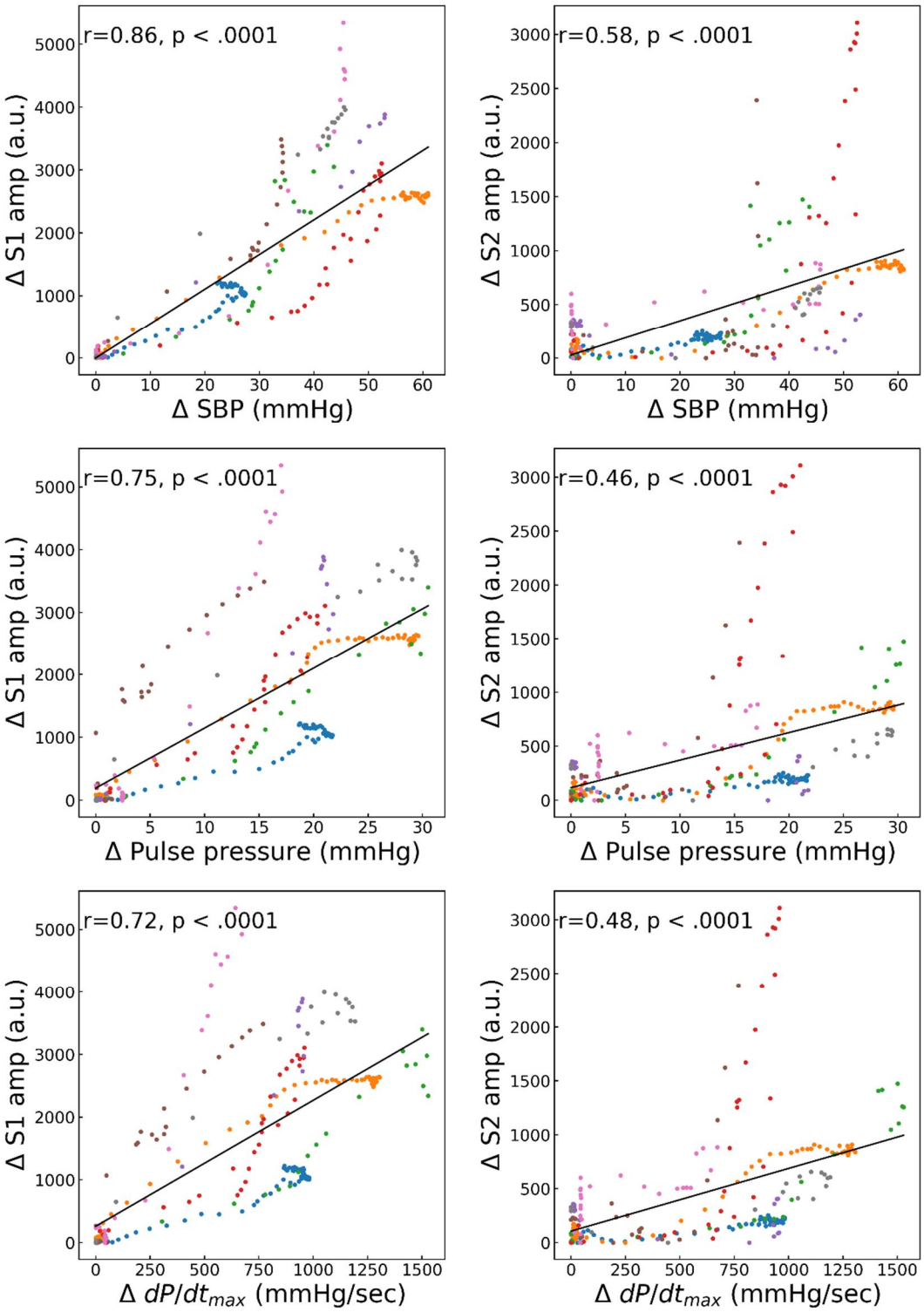
S1amp, amplitude of first heart sound; SBP, systolic blood pressure; dP/dt$_{max}$, peak rate of rise of arterial pressure. [†]Case #2 not available due to missing signal record.

**Supplementary Table 3.** Correlations between changes in each variable by clamping inferior vena cava. Described for each case.

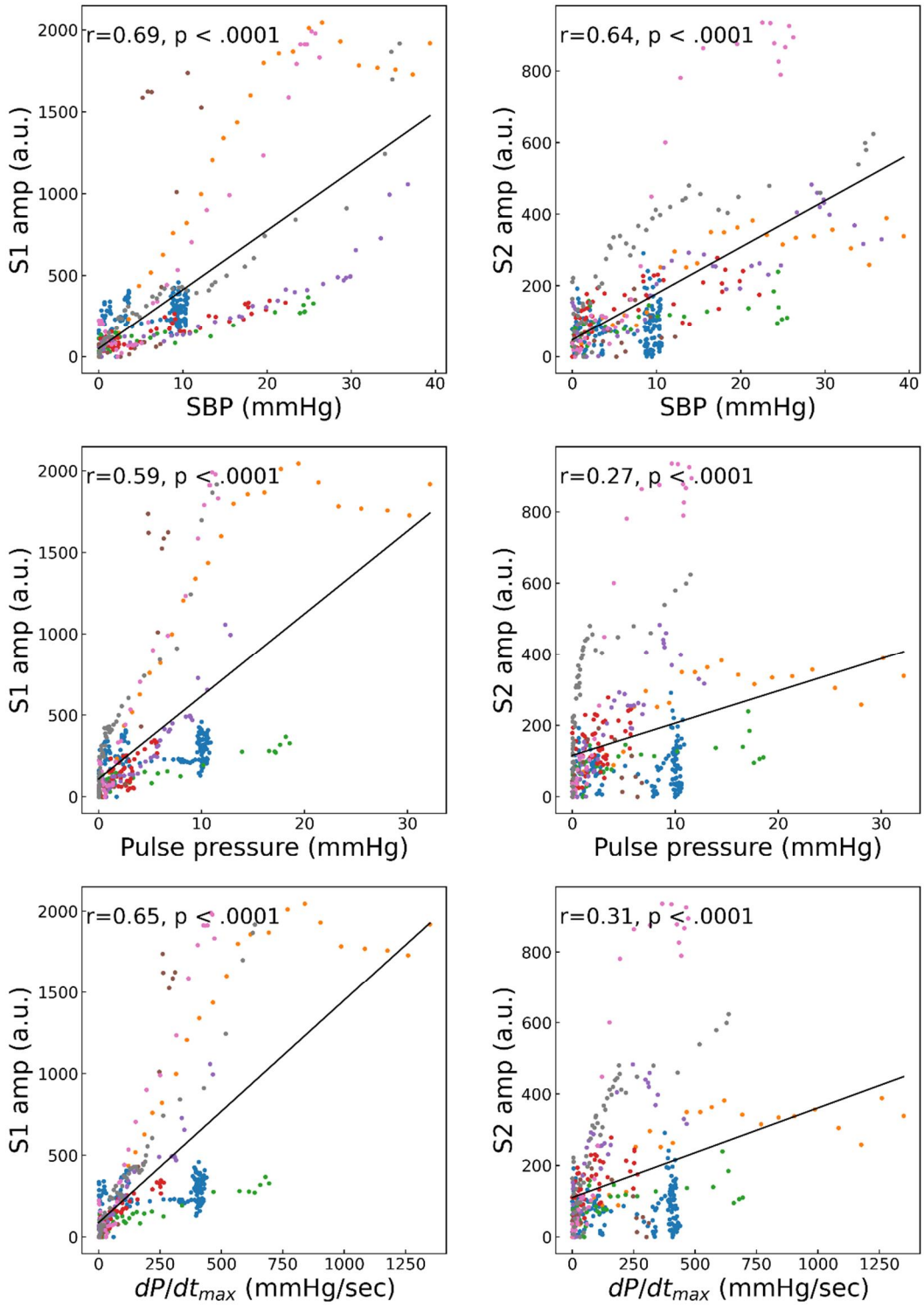
| | **ΔS1amp and ΔSBP** | | **ΔS1amp and ΔPP** | | **ΔS1amp and ΔdP/dt$_{max}$** | |
|---|---|---|---|---|---|---|
| Case | r | *p*-value | r | *p*-value | r | *p*-value |
| 1 | 0.307 | < 0.001 | 0.303 | < 0.001 | 0.322 | < 0.001 |
| 2 | 0.946 | < 0.001 | 0.878 | < 0.001 | 0.545 | < 0.001 |
| 3 | 0.743 | < 0.001 | 0.750 | < 0.001 | 0.721 | < 0.001 |
| 4 | 0.792 | < 0.001 | 0.585 | < 0.001 | 0.503 | < 0.001 |
| 5 | 0.661 | < 0.001 | 0.644 | < 0.001 | 0.159 | 0.243 |
| 6 | 0.935 | < 0.001 | 0.958 | < 0.001 | 0.973 | < 0.001 |
| 7 | 0.319 | 0.025 | 0.331 | 0.020 | 0.371 | 0.009 |
| 8 | 0.926 | < 0.001 | 0.933 | < 0.001 | 0.926 | < 0.001 |

S1amp, amplitude of first heart sound; SBP, systolic blood pressure; dP/dtmax, peak rate of rise of arterial pressure.

**Supplementary Figure 1.** Correlations between dobutamine-induced changes in hemodynamic status and heart sound index, plotting single regression lines that summarizes changes in all cases. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure.



**Supplementary Figure 2.** Correlations between esmolol-induced changes in hemodynamic status and heart sound index, plotting single regression lines that summarizes changes in all cases. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure.



**Supplementary Figure 3.** Correlations between changes in hemodynamic status and heart sound index by clamping of inferior vena cava, plotting single regression lines that summarizes changes in all cases. S1amp, amplitude of the first heart sound; S2amp, amplitude of the second heart sound; SBP, systolic blood pressure; $dP/dt_{max}$, peak rate of rise of arterial pressure.