A non-invasive approach to investigation of ventricular blood pressure using cardiac sound features

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Abstract
Heart sounds (HSs) are produced by the interaction of the heart valves, great vessels, and heart wall with blood flow. Previous researchers have demonstrated that blood pressure can be predicted by exploring the features of cardiac sounds. These features include the amplitude of the HSs, the ratio of the amplitude, the systolic time interval, and the spectrum of the HSs. A single feature or combinations of several features have been used for prediction of blood pressure with moderate accuracy.

Experiments were conducted with three beagles under various levels of blood pressure induced by different doses of epinephrine. The HSs, blood pressure in the left ventricle and electrocardiograph signals were simultaneously recorded. A total of 31 records (18262 cardiac beats) were collected. In this paper, 91 features in various domains are extracted and their linear correlations with the measured blood pressures are examined. These features are divided into four groups and applied individually at the input of a neural network to predict the left ventricular blood pressure (LVBP).

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The analysis shows that non-spectral features can track changes of the LVBP with lower standard deviation. Consequently, the non-spectral feature set gives the best prediction accuracy. The average correlation coefficient between the measured and the predicted blood pressure is 0.92 and the mean absolute error is 6.86 mmHg, even when the systolic blood pressure varies in the large range from 90 mmHg to 282 mmHg.

Hence, systolic blood pressure can be accurately predicted even when using fewer HS features. This technique can be used as an alternative to real-time blood pressure monitoring and it has promising applications in home health care environments.

Keywords: heart sound features, left ventricular blood pressure, back propagation neural network, continuous estimation, correlation analysis

(Some figures may appear in colour only in the online journal)

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| BP           | Blood pressure |
| SBP          | Systolic blood pressure |
| LVBP         | Left ventricular blood pressure |
| HS           | Heart sound |
| ECG          | Electrocardiograph |
| S1           | The first heart sound |
| S2           | The second heart sound |
| MSI          | Mechanical systolic interval |
| MDI          | Mechanical diastolic interval |
| CC           | Correlation coefficient |
| MAE          | Mean absolute error |
| ME           | Mean error |
| SD           | Standard deviation |

1. Introduction

Heart sounds (HSs) are a result of mechanical interaction between blood flow and the valves and great vessels of the cardiovascular system (Luisada et al 1958, Piette et al 1966). This sound is audible on the anterior and posterior sides of the chest. The two prominent events that occur in a cardiac cycle are the first HS (S1) and the second HS (S2). Despite significant inter-observer variability and need for habituation and training, auscultation of the heart provides important clinical clues in patient evaluation and serves as a guide for further diagnostic testing (Durand and Pibarot 1995).

Over the past 50 years, previous researchers have revealed some of the intrinsic relations between HS features and heart hemodynamics. These features are mainly connected to time, frequency or combinations of both. Shah et al (1963) and Sakamoto et al (1965, 1966) illustrated a linear relationship between the magnitude of S1 and the rising rate of left ventricular blood pressure (LVBP) using various experimental procedures for animal data sets. They concluded that the amplitude of S1 is a reliable indicator for the monitoring of cardiac contractility changes and cardiac performance (Luisada et al 1985, Hansen et al 1989). Blick et al (1979) and Mazumdar and Woodard-Knight (1984) proposed a one-dimensional mathematical
membrane model to identify the factors that affect valve vibration and sounds. The aortic valve was assumed to vibrate like a circular membrane undergoing a parabolic displacement. The force that drives the membrane was assumed to be the pressure difference that acts across the membrane. The membrane motion was described by a one-degree-of-freedom equation where the pressure gradient was approximated by a ramp function and an exponential function, respectively. Analytical solution and studies in vitro of the velocity of the centerline deflection of the membrane showed that the amplitude of HS pressure generated by the aortic valve appears to be linearly proportional to the rate of change of the pressure gradient. Tang et al (2013) conducted animal experiments and found that the relation in a global view could be better described by an exponential function. Ozcan Gulcur and Bahadirlar (1998) conducted experiments invasively for obtaining the systolic blood pressures at the aortic roots of human subjects and then found that the amplitude of the second HS has a positive linear relationship to the aortic pressure. Hoon Lim et al (2013) found that the ratio of $S_1$ to $S_2$ has a greater correlation with the systolic blood pressure than the amplitude of $S_1$ or $S_2$. A different study (Hsieh et al 2010) described the ratio of primary HSs as being more useful in calculating blood pressure.

Temporal features have been explored widely as an alternative means of measuring blood pressure. Zhang et al (2008) introduced a timing feature associated with the $S_2$ event. The timing feature was defined as the time delay between the onset of left ventricular pressure rise and the onset of $S_2$ and was denoted $R_{S_2}$. It was measured by the time interval from the $R$ wave of the electrocardiogram (ECG) to the peak of $S_2$. It was found that $R_{S_2}$ bore a strong negative correlation with blood pressure under the effect of changing peripheral resistance, heart rate, and contractility. Based on these results, a further experiment was carried out by Wong et al (2006a) and Castro et al (2015) on healthy adults. This approach performed satisfactorily for diagnosis of hypertensive subjects (Wong et al 2006b). The ratio of systolic time interval to diastolic time interval was also taken as an important time-domain feature and it was used as an indicator of cardiac reserve (Xiao et al 2003, Guo et al 2012).

Aside from temporal features, researchers have also employed spectral features to predict blood pressure. Sikarskie et al (1984) introduced a nonlinear, single-dimension, planar valve model to measure blood pressure using spectral domain features. The results showed that both the magnitude and frequency of the sound increase with increasing pressure gradient. Later on, Zhang and Zhang (2006) demonstrated that aortic pressure, frequency of vibration and amplitude of sound increase linearly with the help of a theoretical model. On the basis of this, the data sets acquired from Fourier transform and wavelet transform of HSs were also applied to estimate the blood pressure (Bartels and Harder 1992, Castro et al 2014, Peng et al 2015). Peng et al (2015) performed a cold-pressure experiment on a data set of 32 healthy subjects in order to investigate the prediction ability by spectral features.

In summary, previous studies have disclosed that many HS features have a strong correlation with blood pressure. However, the authors of this paper note that: (1) in previous studies the data on blood pressure are commonly measured via non-invasive methods. Blood pressure taken via indirect methods is less accurate, and inaccurate blood pressure is not sufficient as a benchmark to evaluate how accurately blood pressure can be predicted. (2) Features are separately analyzed. Previous features are usually from a sole domain and are studied individually. Features extracted from multi-domain are seldom comparatively studied in a same pressure benchmark. (3) The variations in blood pressure in the previous studies are usually small. They are normally induced by physical excitement, with systolic blood pressure (SBP) figures of 80–150 mmHg in a human experiment performed by Hoon Lim et al (2013), 119–152 mmHg induced by stair climbing in a study performed by Zhang and Zhang (2006), 90–140 mmHg induced by cold pressure in a study by Peng et al (2015), and 90–150 mmHg induced by physical exercise in a study by Wong et al (2006a, 2006b).
A question arises of how well the features correlate with blood pressure at the same benchmark and how to select preferable features to yield a higher accuracy of prediction. To address these questions, the authors designed animal experiments using various experimental procedures. Three beagles were involved in an experiment in which blood pressure was accurately measured by an invasive catheter inserted into the left ventricle and blood pressure was changed in a short time by different doses of epinephrine. The HSs on the chest, blood pressure in the left ventricle and ECG signals were simultaneously recorded. Some 31 records including 18,262 heart beats were collected. The minimum blood pressure in the experiments was 90 mmHg and the maximum was 282 mmHg. Therefore, the blood pressure range examined in this study was $282 - 90 = 192$ mmHg. To the best of our knowledge, it is the widest range of blood pressure considered in this field. We investigated 91 features at the same benchmark. The features are divided into four groups and used to train a neural network. The accuracy of the prediction has been evaluated using ten-fold cross-validation. This study suggests that the LVBP can be predicted by selected HS features even where the blood pressure exhibits fast changes in a wide range.

2. Materials and methods

2.1. Data acquisition

The experiments were carried out with three healthy adult beagles weighing 9–10 kg. They were given anesthesia and the procedure was repeated to obtain experimental results. The beagles were first anesthetized with Xylazine (0.2 ml kg$^{-1}$) and then laid down in the supine position for surgical operations. A catheter filled with a heparinized solution (500 units ml$^{-1}$) was inserted into the left ventricle via the carotid artery. A calibrated framework of catheter and high-fidelity blood pressure transducer (MLT0699, ADInstruments, Australia) was used to record the intraventricular blood pressure signal. To produce varying blood pressure signals, different doses of epinephrine were ejected into the upper limb vein of the beagle by a path formed by an intravenous infusion of 0.9% saline with an uncontrolled flow speed. This path remained open during the signal recording so that a new dose of epinephrine could be ejected at any required time. Meanwhile, a microphone transducer (MLT201, ADInstruments, Australia) was used to record external HSs at the apex of the heart. The blood pressure, HS signal, and ECG of lead II were simultaneously digitalized at sampling frequency 1 KHz (PL3508, PowerLab 8/35, ADInstruments, Australia) with a 16-bit resolution. The microphone, blood pressure transducer, ECG electrical node and associated electrical lines were kept fixed during the signal recording to avoid the influence of motion artifacts. The schematic diagram and experimental procedure of the measurement system are shown in figure 1.

The experimental procedure for one beagle was divided into three stages. In the first stage, the epinephrine dose of 0.5 µg kg$^{-1}$ was injected. The signals were collected 10 s prior to the injection and ended after 4–6 min. The injection of this dose was repeated 3–5 times. In the second and third stage, the operations were same as those in the first stage except that the epinephrine doses were 1 µg kg$^{-1}$ and 2 µg kg$^{-1}$, respectively. In each stage, epinephrine was injected with uncontrolled flow speed and a number of recordings were obtained (see table 1). A total of 37 records were obtained, but off-line data analysis found that record numbers 1, 2, 3, 12, 26 and 37 were unusable due to signal quality. In detail, the HS signals in records 1, 2 and 3 had low signal quality due to a bad connection between the sensor and the amplifier. Blood pressure signals in records 12, 26 and 37 were abnormal because the end of the catheter touched the ventricle wall. These six records were abandoned during further analysis. As shown in table 1, 31 signal records including 18,262 heart beats are considered in this study.
This study was supported in part by National Natural Science Foundation of China under grant 61471081. The obtained signals are shown in figure 2. The ECG R-waves are indicated by circles and used as the start marks of cardiac cycles. Therefore, the blood pressure value at the end of systolic stroke can be detected as the systolic blood pressure.

2.2. Response to epinephrine

Epinephrine is a hormone and a neurotransmitter, secreted by the medulla of the adrenal glands. It is also produced at the ends of sympathetic nerve fiber and serves as the chemical mediator for conveying nerve impulses to affected organs. Epinephrine could increase the heart contractility. Figure 3 shows the responses of SBP when ejecting different doses of epinephrine. Once ejecting epinephrine, a general observation is that the intraventricular SBP increases rapidly. In figure 3(a), the dose of epinephrine is 0.5 $\mu$g kg$^{-1}$. It is clearly noted from this figure that intraventricular SBP decreases quickly with metabolism going on. Figures 3(b) and (c) show the variation of blood pressure with metabolism for epinephrine doses of 1 $\mu$g kg$^{-1}$ and 2 $\mu$g kg$^{-1}$. For higher epinephrine doses, the intraventricular SBP declines more slowly than that of 0.5 $\mu$g kg$^{-1}$ because the subject takes more time to metabolize the epinephrine. It is observed from table 1 that some of the minimum SBPs are as high as 150–170 mmHg. However, the normal SBP of dog subject without epinephrine is about 100 mmHg. Hence, some of the minimum SBPs are higher than a normal SBP. The reason could be that a new dose of epinephrine was ejected before the SBP came down to the baseline. Table 1 shows that a relatively large SBP range is observed for 31 records and it extends from the minimum SBP of 90 mmHg to the maximum SBP of 282 mmHg. So, in this study, a varying BP range of 282–90 = 192 mmHg has been considered to analyze the relation between HS features and

![Figure 1](image-url)
blood pressure. To our best knowledge, it is the widest BP range used for this purpose. The local fluctuations illustrated in figure 3 in the SBP are caused by the uncontrolled respiration of the subject.

2.3. Identification of S1 and S2

The acquired HS recordings are first filtered by a Butterworth bandpass filter with cutoff frequency [5, 200] Hz to reduce baseline wandering and high-frequency noise. The filtering operation is implemented in both forward and backward directions to avoid group delay. An admissible method is used in this paper to segment HSs based on the Shannon energy envelope (Liang et al 1997).
The filtered signal is normalized to the range of $[-1, 1]$ by dividing its absolute maximum. Then, the Shannon energy is calculated according to

$$ E(n) = x^2(n) \log(x^2(n)) $$

where $x(n)$ is the normalized signal. The average Shannon energy is calculated by using a sliding time window of 20 ms with an overlap of 10 ms:

$$ E_A(n) = \frac{1}{N} \sum_{i=n-N/2}^{n+N/2} E(i) $$

where $E(i)$ is the Shannon energy, $E_A(n)$ is the average Shannon energy and $N$ is the total number of the time window. $N$ is equal to 20 because the sampling frequency is 1000 Hz. After that, $E_A$ is normalized by the following.
The HS envelope signal is segmented into cardiac cycles using the locations of the $R$-waves of the ECG signal. Then, two thresholds are applied to a single cardiac cycle envelope to identify the potential peaks of $S_1$ and $S_2$, respectively. Both the thresholds are manually set as the media of local maximums. Generally, there are only two dominant peaks in a single cardiac cycle envelope. They correspond to $S_1$ and $S_2$. In the first part of the cycle, a dominant peak whose magnitude is greater than that of the median belongs to $S_1$. Similarly, in the middle part of the cycle, a peak whose magnitude is greater than that of the median belongs to $S_2$. Medical knowledge on HS intervals is further used to tune the selection if multiple dominant peaks are detected. An example of the detection process of HSs is shown in figure 4.

2.4. Heart sound features

The HS features that depend upon blood pressure, summarized from previous studies, can be classified into four groups: features in the amplitude domain, features in the energy domain, features in the time domain and features in the frequency domain.

2.4.1. Features in the amplitude domain. The absolute maximum amplitude of $S_1$ is defined as

$$A_{\text{max } S_1} = \max(|S_1(n)|).$$

The absolute maximum amplitude of $S_2$ is defined as

$$A_{\text{max } S_2} = \max(|S_2(n)|).$$
where $S_1(n)$ and $S_2(n)$ are the HSs identified in section 2.4. The ratio of $A_{\text{max},S1}$ to $A_{\text{max},S2}$ is

$$R_{S1/S2} = A_{\text{max},S1}/A_{\text{max},S2}. \quad (6)$$

### 2.4.2. Features in energy domain.

The energy of $S1$ and $S2$ is defined as $E_{S1}$, $E_{S2}$, respectively. They are calculated by the following.

$$E_{S1} = \sum_n (S_1^2(n)) \quad (7)$$

$$E_{S2} = \sum_n (S_2^2(n)). \quad (8)$$

The Shannon energy of $S1$ and $S2$ is defined as $SE_{S1}$ and $SE_{S2}$, respectively. They are computed via

$$SE_{S1} = - \sum_n S_1^2(n) \log(S_1^2(n)) \quad (9)$$

$$SE_{S2} = - \sum_n S_2^2(n) \log(S_2^2(n)). \quad (10)$$

### 2.4.3. Features in the time domain.

Four features in the time domain are considered in this study. $RS_2$, that is, the time interval from the ECG $R$-wave to the start of $S2$, reflects the electromechanical systole of the heart. The mechanical systolic interval (MSI), which is the time interval from the start of $S1$ to the start of $S2$, measures the ejection time of the left ventricle as it pumps blood into the arteries. The mechanical diastolic interval (MDI), which is the time span from the start of $S2$ to the start $S1$ of the next cycle, measures the time intervals of the heart’s own blood supply. The ratio of MDI to MSI is denoted as $R_{DS}$

$$R_{DS} = \frac{\text{MDI}}{\text{MSI}}. \quad (11)$$

This ratio has been used as an indicator for measuring and evaluating cardiac function in previous studies (Xiao et al 2003, Guo et al 2012). An illustration of the measurement of $RS2$, MSI and MDI is shown in figure 5.
2.4.4. Features in the frequency spectrum. Once the HSs of each cardiac cycle are identified, the frequency spectrum is obtained by fast Fourier transform. Then, 40 spectral values at 5 Hz intervals in the frequency band \([5, 200] \text{ Hz}\) are selected as the spectrum features. The spectrum features for \(S_1\) and \(S_2\) are denoted

\[
R_{S1} = [p_{S1}^{S1}, p_{10}^{S1}, p_{15}^{S1}, \ldots, p_{200}^{S1}]_1 \times 40
\]

\[
R_{S2} = [p_{S2}^{S2}, p_{10}^{S2}, p_{15}^{S2}, \ldots, p_{200}^{S2}]_1 \times 40
\]

where \(p_{S}^{f}\) is the spectrum value of HSs at frequency \(f\) Hz.

In summary, three features in the amplitude domain, four features in the energy domain, four features in the time domain, and 80 features in the frequency domain are obtained in this study. The features are listed in table 2 for clarification. Each feature is considered as the response of the subject’s blood pressure. The correlations of the features with blood pressure are further analyzed and compared.

3. Results

3.1. Feature changes linked to blood pressure

A typical example of feature changes in response to systolic blood pressure is shown in figures 6 and 7 for data associated with record \#36. As shown in figure 6(a), the systolic blood pressure in the left ventricle was 114 mmHg before the ejection, suddenly increased to the maximum 264 mmHg under the effect of the medicine, and then went down slowly to the baseline. The feature changes linked to systolic blood pressure are shown in figures 6(b)–(l). Visual
inspection shows that RS2, MSI, MDI, SES1, and SES2 are negatively related to blood pressure. However, RD/S, AmaxS1, AmaxS2, RS1/S2, E51, and E52 are positively related to the blood pressure. Figures 7(b) and (c) show the spectral changes of S1 and S2 in response to blood pressure variations. We can observe that when the blood pressure increases, both the spectra of S1 and S2 are shifting upward to the higher frequency. The frequency shifting of S1 is greater than that of S2. It can also be found that both the frequency spectra become widely spread for high blood pressure. This phenomenon is more clearly noticeable for the cardiac cycle ranging from 25 to 250 for S1, where the blood pressure is higher.

3.2. Linear correlation analysis between features and blood pressure

The correlation coefficients (CCs) of each feature with respect to the records and subjects are shown in figure 8. The statistical results are listed in table 3. It can be seen that RS2, MSI, MDI, SES1, and SES2 have a negative correlation with blood pressure for all records where RS2 has the maximum absolute CC, −0.87. RS2 and MSI have high consistency between records and subjects, and SD is 0.10. AmaxS1, AmaxS2, E51, and E52 have a positive correlation with blood pressure. AmaxS1 has a correlation, 0.83, followed by E51 and E52. However, MDI and SES2 have an opposite correlation for different subjects. MDI has a negative correlation for the first and third subjects, and a positive correlation for the second subject. SES2 has a negative correlation for the second and third subjects, and a positive correlation for the first subject. Specifically, both MDI and SES2 are highly consistent in a subject. These opposite correlations show that MDI and SES2 have individual variability.

Figure 9 shows the statistical results of the CCs between spectral values and blood pressure at various frequencies over 31 records. It can be seen that the spectral values of both S1 and S2 have a positive correlation with blood pressure. The positive correlation obtained in this study is consistent with previous studies (Zhang and Zhang 2006, Castro et al 2014, Peng et al 2015), i.e. the spectrum of HSs shifts upward to higher frequency when the blood pressure is increasing. The overall observation shows that the spectrum values of S1 had higher coefficients than those of S2. Specifically, the coefficient curve for S1 shown in figure 9(a) has two prominent peaks. One peak appears at 20 Hz and another peak appears around 120 Hz, and their corresponding coefficients are 0.72 ± 0.13 (mean ± SD) and 0.75 ± 0.07 (mean ± SD),

| Table 2. Summary of the features used in this study. |
|-----------------|-----------------|-----------------|
| **Domain**      | **Feature abbreviation** | **Definition**   |
| Amplitude       | AmaxS1, AmaxS2, RS1/S2 | Absolute maximum amplitude of S1, Absolute maximum amplitude of S2, Ratio of AmaxS1 to AmaxS2 |
| Energy          | E51, E52, SE51, SE52 | Energy of S1, Energy of S2, Shannon energy of S1, Shannon energy of S2 |
| Time            | MSI, MDI, RD/S | Mechanical systolic interval, Mechanical diastolic interval, Ratio of MDI to MSI |
| Frequency       | P51, P52 | Frequency spectrum of S1. 40 spectral values with 5 Hz interval in the frequency band [5, 200] Hz, Frequency spectrum of S2. 40 spectral values with 5 Hz interval in the frequency band [5, 200] Hz |
respectively. The coefficient reduces as the frequency is below 20 Hz and beyond 120 Hz. The minimum coefficient of 0.45 occurs at 200 Hz. Meanwhile, the coefficient curve for $S_2$ shown in figure 9(b) has one flat prominent peak over the frequency band from 40–70 Hz, the magnitude of which is approximately $0.61 \pm 0.2$. The minimum coefficient is 0.17 occurring at a frequency around 165 Hz. Figures 9(a) and (b) indicate that the SD of $S_1$ are somewhat lower than those of $S_2$. So, it can be concluded that the spectral values of $S_1$ can track the changes of blood pressure with smaller fluctuations than those of $S_2$.

3.3. Blood pressure prediction by selected features

Since some features are highly correlated with blood pressure, it is possible to predict blood pressure by selected features. However, the authors do not apply a linear regression model because somewhat unknown nonlinear relations may exist. In this study, a back propagation artificial neural network is applied to approximate the link between the features and blood pressure, the structure of which with two hidden layers is shown in figure 10. A back propagation neural network is a feed-forward network with its weights adjusted through the method of a back propagation learning algorithm, and it can achieve arbitrary nonlinear mapping from input to output, generally with good performance. Each net node in the network is a neuron
whose function is to calculate the inner product of the input vector and weight vector by a nonlinear transfer function to get a scalar result. The value of a node is expressed as

\[ \text{Node}_j = \sum_{k=1}^{n} x_k w_{kj} \]  

where \( x_k \) is the input which applies to node \( j \), \( n \) is the dimension of input \( x_k \), and \( w_{kj} \) represents the weight between node \( k \) and \( j \).

### Table 3. Distribution of correlation coefficients for the features. Significant level was set to \( p < 0.05 \).

| Features | Min.  | Median | Max.  | Mean  | STD   |
|----------|-------|--------|-------|-------|-------|
| RS2      | -0.67 | -0.88  | -0.99 | -0.87 | 0.10  |
| MSI      | -0.68 | -0.85  | -0.99 | -0.86 | 0.10  |
| SE_{S1}  | -0.39 | -0.71  | -0.81 | -0.67 | 0.11  |
| A_{maxS1}| 0.43  | 0.87   | 0.92  | 0.83  | 0.11  |
| E_{S1}   | 0.42  | 0.80   | 0.91  | 0.78  | 0.10  |
| E_{S2}   | 0.37  | 0.78   | 0.88  | 0.73  | 0.15  |
| A_{maxS2}| 0.15  | 0.76   | 0.92  | 0.72  | 0.19  |
| R_{DWS}  | 0.31  | 0.74   | 0.87  | 0.68  | 0.17  |

**Figure 8.** Distribution of the feature correlation coefficients with respect to records. The indicators of ‘O’, ‘+’, and ‘△’ are for the first, the second and third subject, respectively.
The dimension of input to the network is the number of features selected, and the output SBP to be predicted corresponds to the target vector. The number of the neurons for hidden layer 1 and hidden layer 2 are empirically chosen to be 11 and 6, respectively. To approximate the nonlinear relationship between the features and blood pressure, the sigmoid activation function is used in hidden layer 1 and the linear activation function is applied to hidden layer 2. In the output layer, the linear activation function is used.

The sigmoid and linear activation functions are given by (15) and (16), respectively.

\[
O_j = \frac{1}{1 + e^{\theta_{j}(x_i + b_j)}}
\]  

\[
O_j = x_i + b_j
\]  

\[\text{Figure 9.} \ \text{Statistical results of the correlation coefficients (CCs) between spectral value and blood pressure. (a) Changes of SBP; (b) statistical results for spectral values of } S_1; \ \text{(c) statistical results for spectral values of } S_2.\]

\[\text{Figure 10.} \ \text{Structure of the neural network.}\]
\[ O_j = \text{Node}_j + \beta_j \]  
\[ \text{where } \beta_j \text{ is the threshold for the node } j. \]

Equation (15) was applied to hidden layer 1. Equation (16) was applied to hidden layer 2 and the output layer.

In this study, a back propagation learning algorithm is preferred because of its higher prediction probability with minimization error. The outputs and the errors of a neural network can be calculated by employing the features of its input. For the aim of reducing timely errors, weights are iterated over and over until the best weights are detected based on the minimum error energy, as expressed by

\[ E_{\text{error}} = \frac{1}{2} \sum_m (d_m - y_m)^2 \]

where \( m \) is the index number of the input–output pairs, \( d \) is the desired output and \( y \) is the actual output. During the iteration of weights, a negative gradient direction of error function is used.

To evaluate the prediction accuracy, a ten-fold cross-validation (Pierre and Josef 1982) is used to test how accurately the predictive model will perform. For each recording, the input data (the features) and target output (SBP values) are divided into ten subsets of equal size. Nine of them are used to train the model and the other one to test the accuracy of the model. This cross-validation process is repeated ten times for one recording such that each instance is tested exactly once.

The performance of the predictive model is quantitatively evaluated by the indicators concerned, for instance, Pearson CC, mean absolute error (MAE), mean error (ME) and SD. These indicators were calculated as below.

\[ \text{CC} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2} \sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}} \]

\[ \text{MAE} = \frac{1}{n} \sum_{i=1}^{n} |y_i - x_i| \]

\[ \text{ME} = \frac{1}{n} \sum_{i=1}^{n} (y_i - x_i) \]

\[ \text{SD} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (y_i - x_i - \text{ME})^2} \]

where \( x \) is the measured value, \( y \) is the predicted value, and \( \bar{x} \) and \( \bar{y} \) are the mean values. The variable \( n \) is the number of samples involved.

A total of 91 features have been considered in this study and each feature has a specific correlation to SBP, as shown in section 3.2. Theoretically, the prediction performance of the model must depend on the features selected as the input to the model. To analyze the effect of feature selection, the features are divided into four groups which have been examined in the following four cases.
Case 1 Non-spectral features used as input
The non-spectral features (11 dimensions), i.e. three features in the amplitude domain, $A_{max S1}$, $A_{max S2}$, $R_{S1/S2}$, four features in the time domain, $RS_2$, MSI, MDI, $RD/S_1$, and four features in the energy domain, $ES_1$, $ES_2$, $SES_1$, $SES_2$, are used as input to the network.

Case 2 Spectral features of $S1$ used as input
The spectral features of $S1$ (40 dimensions) are used as input to the network.

Case 3 Spectral features of $S2$ used as input
The spectral features of $S2$ (40 dimensions) are used as input to the network.

Case 4 All features used as input
All features (91 dimensions) are used as input to the network.

The prediction performance of the four cases has been visually represented by a typical record, #30 in figure 11. The correlation analysis shows that the CCs of the four cases are 0.99, 0.90, 0.86, and 0.96. It is found that the predicted SBP in case 1 has the maximum coefficient and least deviation, as shown in figure 11(a). Meanwhile, the predicted value in case 3 has the least coefficient and maximum deviation, as shown in figure 11(c). The distribution of CCs, MAE, ME and SD for all the cases with respect to all the records is given in figure 12 and table 4. The averages of the CCs, MAE, ME and SD for case 1 are 0.92, 6.86, 0.65 and 8.96, respectively, which is the best among the four cases. Case 4 is the second best case in which the averages of the CCs, MAE, ME and SD are 0.87, 9.47, 1.08, and 12.33, respectively. The indicators of case 2 are approximately close to those of case 4. Meanwhile, case 3 is the worst case where the average of the CCs, MAE, ME and SD are 0.67, 16.30, −0.32 and 20.97.

Figure 11. A typical example of the correlation between measured SBPs and predicted SBPs (record #30). (a) Case 1; (b) case 2; (c) case 3; (d) case 4.
Table 4. Prediction performance for the four cases.

| Case index | Indicators | Min. | Median | Max. | Mean |
|------------|------------|------|--------|------|------|
| Case 1     | CCs        | 0.68 | 0.94   | 0.99 | 0.92 |
|            | MAE (mmHg) | 4.03 | 6.40   | 12.96| 6.86 |
|            | ME (mmHg)  | −1.86| 0.74   | 4.18 | 0.65 |
|            | SD (mmHg)  | 5.39 | 8.13   | 15.72| 8.96 |
| Case 2     | CCs        | 0.69 | 0.87   | 0.95 | 0.86 |
|            | MAE (mmHg) | 5.47 | 12.22  | 19.47| 11.26|
|            | ME (mmHg)  | −5.22| 1.24   | 6.97 | 1.5 |
|            | SD (mmHg)  | 7.17 | 15.17  | 25.19| 14.70|
| Case 3     | CCs        | 0.24 | 0.68   | 0.91 | 0.67 |
|            | MAE (mmHg) | 8.15 | 14.83  | 26.81| 16.30|
|            | ME (mmHg)  | −6.66| 0.10   | 4.28 | −0.32|
|            | SD (mmHg)  | 10.65| 20.40  | 33.25| 20.97|
| Case 4     | CCs        | 0.55 | 0.90   | 0.99 | 0.87 |
|            | MAE (mmHg) | 4.96 | 9.32   | 22.3 | 9.47 |
|            | ME (mmHg)  | −1.81| 0.90   | 4.13 | 1.08 |
|            | SD (mmHg)  | 6.67 | 12.38  | 27.30| 12.33|

Figure 12. Comparison of prediction performances for four cases. (a) CCs, (b) mean absolute error (MAE); (c) mean error (ME); (d) standard deviation (SD).
4. Discussion

HSs are mixed mechanical vibrations generated by the interaction between blood hemodynamics and the heart valves, chambers, and great vessels. So HSs are believed to have a natural link to heart hemodynamics. Over the past 50 years, previous researchers have found, using animal experiments, clinical experiments or theoretical models, that features in the amplitude domain (Shah et al 1963, Sakamoto et al 1965, 1966, Blick et al 1979, Mazumdar and Woodard-Knight 1984, Luisada et al 1985, Hansen et al 1989, Ozcan Gulcur and Bahadirlar 1998, Hsieh et al 2010, Hoon Lim et al 2013, Tang et al 2013), time (Xiao et al 2003, Wong et al 2006a, 2006b, Zhang et al 2008, Guo et al 2012, Castro et al 2015) and frequency (Sikarskie et al 1984, Bartels and Harder 1992, Zhang and Zhang 2006, Castro et al 2014, Peng et al 2015) of HSs are linked to blood pressure or rising rates of blood pressure, quantitatively or qualitatively. A further practical application has been carried out to predict blood pressure in chambers invasively by the selected HS features (Ozcan Gulcur and Bahadirlar 1998, Xiao et al 2003, Wong et al 2006a, 2006b, Zhang and Zhang 2006, Hoon Lim et al 2013, Castro et al 2015, Peng et al 2015). In this study, experiments were conducted with three beagles under different blood pressure levels induced by various doses of epinephrine. The blood pressure signal, HS signal, and ECG signal were simultaneously recorded and sampled at the same rate. To the best of our knowledge, the most comprehensive features are analyzed at the same benchmark to show how well the features are linked to blood pressure and how accurately the blood pressure can be predicted by selected features.

The results suggest that the features have different degrees of correlation with blood pressure. Correlation analysis for the non-spectral features has been illustrated in figure 8 and table 3. These results show that the time domain feature $RS_2$ has a maximum absolute coefficient ($-0.87 \pm 0.1$, mean $\pm$ SD) with blood pressure. This result is in coincidence with that obtained by Zhang et al (Guo et al 2012). From the viewpoint of physiology, $RS_2$ reflects the systolic function of a heart directly. Under the effect of epinephrine, the heart pumps blood with greater force than usual. Consequently, $RS_2$ takes less time than usual. The metric MSI gives the second highest CC and its value is $-0.86 \pm 0.1$. In fact, the sum of MSI and electromechanical delay constitutes $RS_2$. The electromechanical delay is commonly a small fraction of the $RS_2$ interval. So, it is not surprising that the CC of the MSI is close to that of $RS_2$. $A_{maxS1}$ ($0.83 \pm 0.11$) is third in order based on the degree of correlation from high to low. The experimental result obtained in terms of CC has been validated by physical findings since the 1960s (Luisada et al 1958, Shah et al 1963, Sakamoto et al 1965, 1966, Piemme et al 1966), because the amplitude of the HS signal is linearly correlated to heart hemodynamics. A recent study shows that this relation is positively linear locally but nonlinear globally (Tang et al 2013). It can be noted that the CC of $A_{maxS1}$ ($0.83 \pm 0.11$) is higher than that of $A_{maxS2}$ ($0.72 \pm 0.19$), and the CC of $ES_1$ ($0.78 \pm 0.10$) is higher than that of $ES_2$ ($0.73 \pm 0.15$).

There are two unusual non-spectral features, MDI and $SE_{S2}$. These are positively correlated to blood pressure for one subject but negatively correlated to the others. Therefore, these feature sets are not applicable for all subjects due to this discrepancy. However, both features were highly correlated to blood pressure within a subject.

The correlation analysis of the spectral values of both $S1$ and $S2$ with blood pressure is illustrated in figure 9. All the spectral values from both $S1$ and $S2$ are found, in general, to have a positive correlation with blood pressure. This matches with the results of the mathematical model of valve vibration (Blick et al 1979, Mazumdar and Woodard-Knight 1984), i.e. increasing blood pressure results in an increase of both the frequency and magnitude of the vibration produced.
Since the features are correlated to blood pressure by different degrees, it is reasonable to predict blood pressure by the selected features. Four cases have been considered for the purpose of prediction as described in section 3.3. The features in case 1, which have the least dimension amongst the four cases, are in the time, amplitude and energy domains, and have very low computational load. The features in case 2 and case 3 are in the frequency domain, which need more calculation compared to case 1 due to the involvement of the Fourier transform operation. Case 4 includes all the features, which are the most complex and have the highest computational load. It is found that the prediction performance from using non-spectral features (case 1) is the best among the four cases. Comparatively, case 2 and case 4 give similar performance. Case 3 has the worst performance.

The differences in performance between the four cases can be explained by checking the correlation analysis. Figure 9 shows that the spectral values of $S_1$ generally have a higher degree of correlation than those of $S_2$ where the maximum coefficient of $S_1$ is $0.75 \pm 0.07$ occurring at $120$ Hz and the maximum coefficient of $S_2$ is $0.61 \pm 0.12$ occurring around $50$ Hz. A further inspection of the two subplots of figure 9 shows that the SDs of $S_1$ are somewhat lower than those of $S_2$. It means that the spectral values of $S_1$ can follow the changes of blood pressure with less fluctuation than the spectral values of $S_2$. The authors believe that this is the reason why case 2 outperforms case 3.

The correlation analysis related to non-spectral and spectral features is illustrated in figure 9. Table 3 gives an insight into the performance difference between case 1 and the others. It is found that the non-spectral features generally have higher CCs than the spectral features. Simultaneously, a comparison between table 3 and figure 9 illustrates that the CCs of non-spectral features have less SD than those of spectral features. This result implies that the non-spectral features can track changes in blood pressure with higher stability. In other words, the non-spectral features are more sensitive than the spectral features to changes in blood pressure. Hence, we can conclude that case 1 has the best prediction performance. The comparison of performance for the four cases demonstrates that it is not necessary to make predictions using complex and comprehensive features. It is possible to achieve good prediction with only a few simple and effective features, such as the features in case 1.

The authors note that four MAEs in case 1 are greater than 10 mmHg. This is higher in absolute magnitude than the results in previous studies (Peng et al 2015), where the MAE is commonly less than 8 mmHg. However, the variation range of blood pressure in this study is usually up to 120 mmHg, while the range in previous studies is 50 mmHg. The range in this study is therefore much greater than that in previous ones. From the point of view of relative MAE, the prediction error in this study is even smaller.

5. Conclusions

In this paper, the correlation between various HS features and systolic blood pressure in the left ventricle has been investigated based on animal experiments at various pressure differences induced by different doses of epinephrine. The analysis confirms that $R_S$ has a maximum CC, followed by $M_1$, $A_{max_1}$ and $E_{S1}$. The computer simulations for all the four cases show that blood pressure can be accurately predicted even when using a lesser number of features. It demonstrates that continuous non-invasive SBP prediction by extracting the features of HSs is promising. It is easy to handle and execute with low computational load. This technique has potential applications for beat-to-beat blood pressure monitoring or supporting home health care.
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Authors’ contributions

HT carried out the study design and statistical analysis, and drafted the manuscript. JZ and HC analyzed part of the data. AM helped to draft the manuscript and gave suggestions. YP proofread the manuscript and gave suggestions. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics statement

This study obtained full approval from the Animal Care Committee of Chongqing Medical University and all experiments were performed in accordance with the ‘Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research’ developed by the American Psychological Association. Experiments were conducted at the Affiliated Animal Experiment Center of Chongqing Medical University.

Availability of data and supporting materials

The authors have made the data described in the manuscript available to any scientist wishing to reproduce the results.

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