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Prediction of self-terminating Ventricular Tachycardia in isolated rat heart experiments by using wavelet analysis

Le Duy Manh[1, 2, 3, *], Bui Phuong Thuy[2, 3], Bui Van Hai[4], Man Minh Tan[2, 3], Trinh Xuan Hoang[5], C. K. Chan[6], Pik-Yin Lai[7]

[1]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, Viet Nam*

[2]*Institute of Theoretical and Applied Research, Duy Tan University, Trang An Complex, 01 Phung Chi Kien, Ha Noi Viet Nam*

[3]*Faculty of Natural Sciences, Duy Tan University, 254 Nguyen Van Linh, Da Nang, Viet Nam*

[4]*Le Quy Don Technical University, 236 Hoang Quoc Viet, North Tu Liem Dist, Hanoi, Viet Nam*

[5]*Institute of Physics, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, Viet Nam*

[6]*Institute of Physics, Academia Sinica, Taipei, Taiwan 115, ROC*

[7]*Department of Physics and Center for Complex Systems, National Central University, Chung-Li District, Taoyuan City, 320, Taiwan, ROC*

[*]Email: *leduymanh@duytan.edu.vn*

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Abstract. This study investigates whether self-terminating and prolonged ventricular tachycardias (VT) can be differentiated using cross-wavelet analysis. VT is a type of arrhythmia that may persist or transform into other arrhythmias. In this study, 40 VT samples from 7 isolated rat hearts are analyzed, including 19 prolonged VTs and 21 self-terminating VTs (STVTs). Bivariate time series of left ventricular and right atrium are analyzed using cross-wavelet analysis to find correlations between the signals. The results show that self-terminating VT occurs most frequently when there is a weak correlation between the signals, while prolonged VT is associated with a strong correlation between ventricular and atrial signals. The study suggests that mechano-electrical interaction between the right atrium and left ventricle may be the underlying mechanism for this connection. The findings may have implications for understanding the underlined mechanism and treatment of VT in clinical practice.

Keywords: Ventricular tachycardia, wavelet analysis, bivariate time series, mechano-electrical coupling.

Classification numbers: 4.2.3, 3.7.2, 3.7.4.

1. INTRODUCTION

Arrhythmia is a prevalent and serious health issue that affects millions of people worldwide [1]. It is characterized by an abnormal heartbeat that may be too fast, too slow, or irregular, even chaotic, leading to inefficient blood flow and possibly heart failure or sudden cardiac death [2]. Ventricular tachycardia (VT) and ventricular fibrillation (VF) are two of the most dangerous forms of arrhythmia, both of which can result in sudden cardiac death. Ventricular tachycardia is a type of arrhythmia that is characterized by a rapid and regular heartbeat, often originating in the ventricles of the heart, the VT can progress to more severe conditions, such as fibrillation or cardiac failure, if left untreated [3 - 4]. On the other hand, ventricular fibrillation (VF) is a more severe type of arrhythmia, in which the heartbeat becomes highly irregular and chaotic. VF is caused by the rapid, disorganized propagation of electrical impulses throughout the ventricles, leading to an inability of the heart to pump blood effectively. Research studies have shown that VF almost always follows VT and can last from a few beats to hundreds of beats or more [5 - 7]. Self-terminating ventricular tachycardia (STVT) is a type of VT that spontaneously converts back to a normal rhythm without any external intervention. Prolonged ventricular tachycardia (prolonged-VT) is a more sustained and dangerous form of VT and requires medical, electrical or physical interventions to terminate [8 - 9].

Various analysis methods have been studied to analyze both types of tachycardia such as Fourier transform [10], empirical mode decomposition [11, 12], machine learning [12 - 14], and information entropy [15, 16] etc. All these methods have shown promise for the detection and classification of tachycardia. However, each method has its own strengths and limitations. For example, the Fourier transform method is traditionally well-known for fast computation, but is not good for non-stationary signals of the heart time series [11]. Empirical mode decomposition and information entropy methods can be used for non-stationary and non-linear signals [11, 15]. However, the accuracy of these methods can be affected by mode mixing, noise and artifacts in the signals, and the quality of an analysis will depend on the experience of the analyst.

In this study, we assess the correlation between the left-ventricular and right atrial signals by utilizing the cross-wavelet power spectrum and wavelet coherence. Using the cross-wavelet power spectrum and its derivative – the wavelet coherence - is a good way of analysis to study the relationships between two time-varying signals and represent them in the time-frequency domain [17, 18]. One of the strengths of cross-wavelet spectrum and wavelet coherence is that it can be used to analyze non-stationary and transient signals. However, a limitation of the wavelet method is that it needs a proper selection of appropriate wavelet functions and scales. In addition, the interpretation of results can be challenging due to the complex nature of the time-frequency domain. Despite of these difficulties, by using wavelet analysis, we aim to identify any potential relationship between the left-ventricular and right atrial signals during STVT and prolonged VT, which could provide valuable insights into the underlying mechanisms of cardiac arrhythmias. Our results support the concept that self-terminating ventricular tachycardia is only achievable when the signals from the sinoatrial node (the heart pacemaker unit) are not significantly impacted by the ventricular signals. Based on the obtained results, a new algorithm based on these quantities for predicting self-terminating ventricular tachycardia has been developed.

2. DATA AQUISITION AND ANALYSIS METHODS

2.1. Data aquisition

The rat heart was excised and perfused in a nutrient and oxygen-enriched Krebs-Henseleit solution at 37°C using a Langendorff system. Experiments were conducted over a 3 - 4 hour period while the heart remained in a healthy state. The heart's baseline rate was approximately 3 - 6 Hz, varying according to body weight. Three simultaneous signals were recorded at a sampling rate of 4000 Hz: (1) right atrial activity (Va) via an electrode placed near the sinoatrial node in the right atrium, (2) ventricular electrical activity (Vv) using an electrode on the right ventricle, and (3) left ventricular pressure (LVP) measured with a water-filled balloon connected to a pressure transducer inside the left ventricle. LVP signals and ventricular waveforms were used to classify arrhythmias as fibrillation or tachycardia [19]. Arrhythmias were induced through rapid, low-amplitude electrical stimulation (20 to 62.5 Hz) via a pacing electrode inserted into the interventricular septum. All animal procedures were approved by the Academia Sinica Board of Ethics [20]. Experiments setup and details can be found in [19, 21]. Additionally, a table summarizing the number of normal beats and VT beats for each rat heart is included in the appendix.

2.2. Analysis methods

In order to quantify the correlation/relation between ventricular and atrial signals, the wavelet transform and wavelet analysis methods were used. For nonstationary time series as found in most biological systems, the wavelet transform is ideal since it is localized in both time and frequency. If a time series of a signal in equal time steps is given by X = {x_n, n = 0, 1, ..., N − 1}, then its continuous wavelet transform is defined as [17]

$$\begin{cases} W_n^X(s) = \sqrt{\dfrac{\delta t}{s}} \displaystyle\sum_{n'=0}^{N-1} x_{n'} \Psi_0\left[(n-n')\dfrac{\delta t}{s}\right] \\ \Psi_0(\eta) = \pi^{-1/4} e^{i\omega_0\eta} e^{-1/2\eta^2} \end{cases} \tag{1}$$

where δt is the time step, *N* is the total number of data point; *s* is a wavelet scale (can be understood as period) that can be converted to frequency; ψ_0 is the mother (or basic) wavelet function with a dimensionless variable η. For a better balance in the time and frequency resolutions, the Morlet mother wavelet [18] is selected in our analysis, that is corresponding to a dimensionless frequency of ω_0=6.

If W_X and W_Y are continuous transforms of two time series of equal length, X and Y, then the cross-wavelet (XWS) transform is defined as $XWS_{XY}=|W_X.W_Y^*|$ (where * denotes the complex conjugation) [17]. The XWS_{XY} shows how the bivariate time series X and Y signals are connected in time and frequency, highlighting their interdependence.

After obtaining the wavelet transforms W_X, W_Y and cross-wavelet transform XWS_{XY}, a derivative quantity named the wavelet coherence is given by the following formula [17]

$$WC(s) = sqrt(\frac{\left|S\left(s^{-1}W^{XY}(s)\right)\right|^2}{S\left(s^{-1}\left|W^X(s)\right|^2\right)S\left(s^{-1}\left|W^Y(s)\right|^2\right)} \tag{2}$$

in equation (2), the smoothing operator $S(W) = S_{scale}(S_{time}(W(s)))$ acts on both scale and time axes. Wavelet coherence is also used to quantify the interaction between right ventricular and atrium signals. In addition to the cross-wavelet spectrum, the wavelet coherence can effectively identify regions of high co-movements in the time–frequency space.

Both XWS and wavelet coherence of bivariate signals are used to quantify the correlation of two time series that are assumed to be related. These quantities are computed by using a Matlab package [18] that is utilized as a standard Matlab toolbox in recent versions (R2018 or later).

3. RESULTS AND DISCUSSION

In our process of identifying ventricular tachycardia, we employed waveform analysis, taking into account both duration (frequency) and LVP. A data segment is categorized as VT if it satisfies the following conditions: i) the beating frequency exceeds 2.0 times its normal rhythm (or the period is less than half of the normal rhythm), ii) it displays a regular waveform, and iii) the LVP is notably lower (less than half) compared to normal LVP levels. Figure 1 illustrates a typical time series of self-terminating VT, graphically demonstrating our criteria for identifying ventricular tachycardia.

3.1. Results

For depiction, one typical self-terminating tachycardia sample used in this study is shown in Fig. 1. This sample contains three signals of LVP, Vv and Va. As indicated in Fig. 1, this sample shows a STVT that can recover back to its sinus rhythm within seconds without any medical intervention; For the prolonged VT, we decided not to show it here, however, in our analysis, a VT that is sustained for more than 3 minutes was regarded as a prolonged-VT.

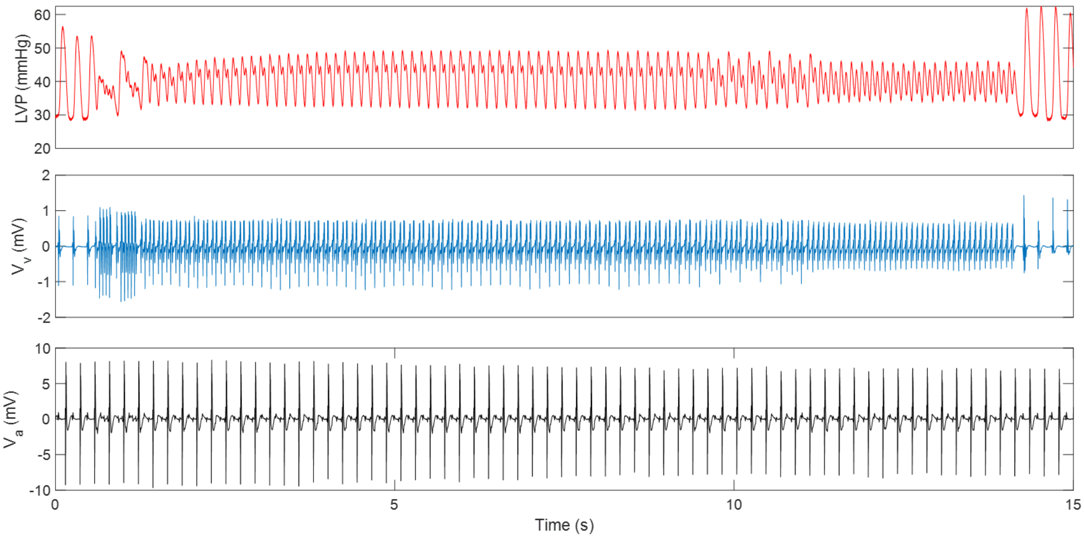

Figure 1. Time series of three simultaneous signals showing a self-terminating ventricular tachycardia (STVT). The top signal is the left ventricular pressure LVP (mmHg). The middle signal is the left ventricular signals Vv (mV), and the bottom one is the right atrial signal Va (mV). The tachycardia started at 1.5 s, and terminated at 15 s. This graph is created from raw, original data.

More specifically, we collected a total of 40 VT episodes from 7 isolated rat hearts; 21 of these were STVTs, whereas the other 19 were prolonged VTs. We utilized just the final 5 seconds of data before the sinus rhythm recovery for STVT and the last 5 seconds of 3-minute selected data for prolonged VT.

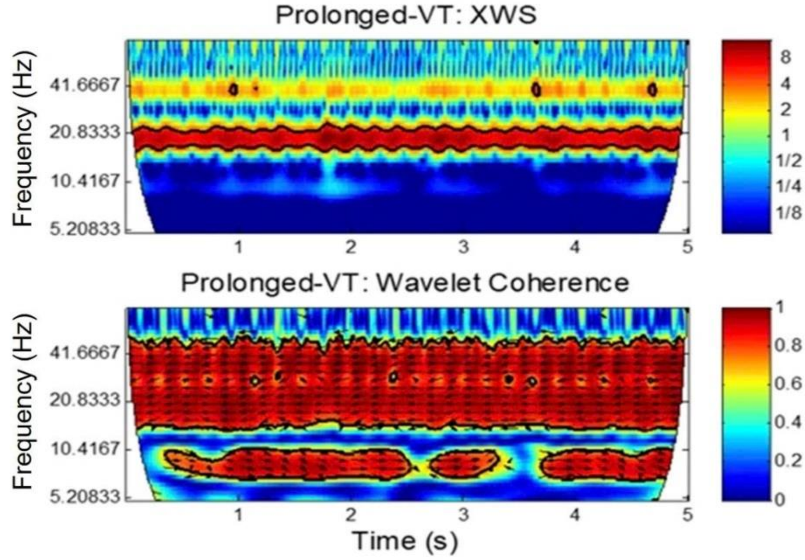

Figure 2. A typical prolonged-VT shown by the cross-wavelet power spectrum (XWS - top graph) and the wavelet coherence (bottom graph). The vertical axis represents frequency (Hz), ranged from 5 to 80 Hz. The horizontal axis represents time (second – s). Values of the XWS and the wavelet coherence are indicated by colors as defined in the color bars (right).

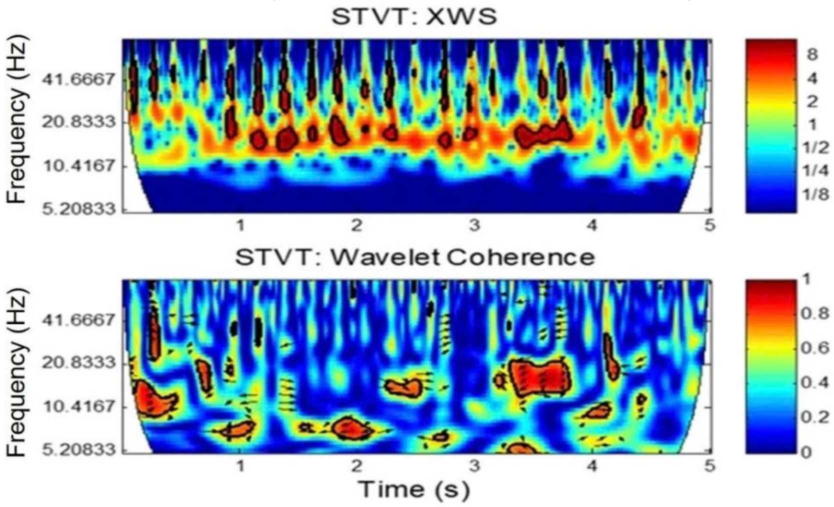

Figure 3. A self-terminating VT (STVT) shown by the cross-wavelet power spectrum (top graph), and the wavelet coherence (bottom graph). Axes and color properties are the same as in Fig. 2.

Figures 2 and Fig. 3 illustrate the equivalence of XWS and wavelet coherence (between Vv and Va) to assess the impact of VT on right atrium. The behaviors of XWS and wavelet coherence distributions in time and frequency can be used to define the effect. For both the XWS and wavelet coherence, the areas of top 5 % significant power [18] in the spectrum are delineated by black boundaries. For all samples, we used the frequency range of 5 - 80 Hz (about 1 to 15 times of a normal frequency of rat heartbeats) to study the relationship between Vv and

Va. For the prolonged VT shown in Fig. 2, the XWS and wavelet coherence have strong powers that are localized at a certain frequency range, i.e. 15-20 Hz for XWS and 10-50 Hz for wavelet coherence. This means that there is a strong correlation between the bivariate signals of the right atria and ventricle. In contrast, for the STVT shown in Fig. 3, both the XWS and wavelet coherence powers are small and dispersed in time and frequency.

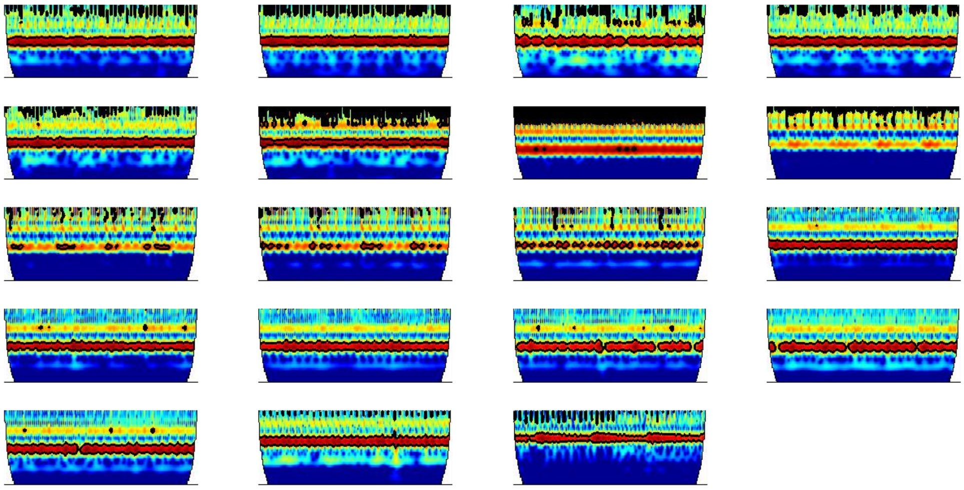

Figure 4. Cross-wavelet power spectra (XWS) shown for all 19 samples of prolonged VT. For each subfigure, axes and color properties are the same as in Fig. 2.

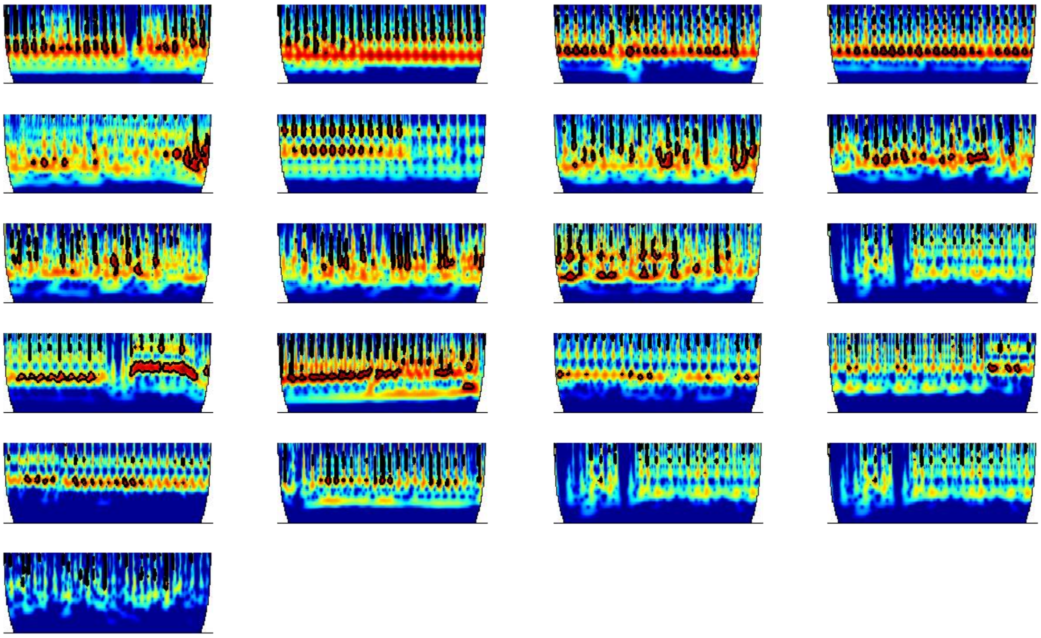

Figure 5. Cross-wavelet power spectra shown for all 21 samples of STVT. For each subfigure, axes and color properties are the same as in Fig. 2.

There are a total of 40 samples of 19 prolonged VTs and 21 STVTs. The XWS of all 19 prolonged VTs and 21 STVTs are plotted in Figure 4 and Figure 5. Similarly, the wavelet coherence of all these samples are shown in Fig. 6 for 19 prolonged VTs and Fig. 7 for 21 STVTs. In these figures, for clarity, all axes properties (that are similar to those in Fig. 2) are removed.

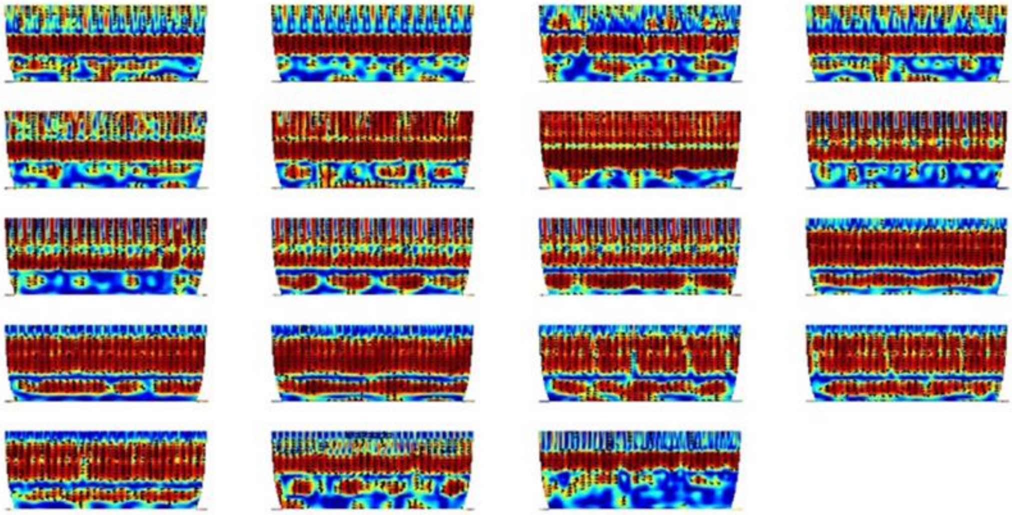

Figure 6. Wavelet coherence shown for all 19 episodes of prolonged VT. For each subfigure, axes and color properties are the same as in Fig. 2.

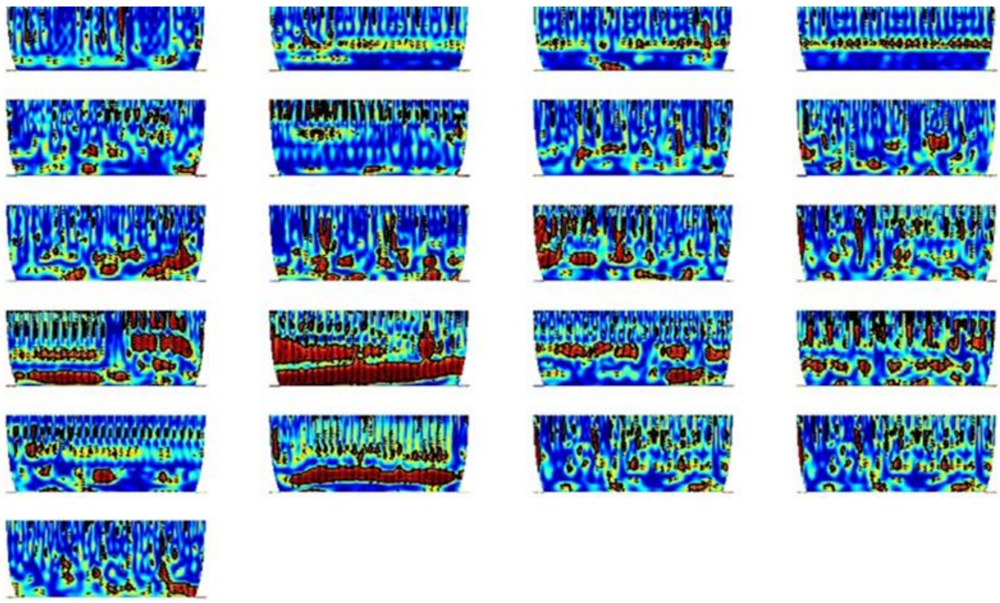

Figure 7. Wavelet coherence shown for all 21 episodes of STVT. For each subfigure, axes and color properties are the same as in Fig. 2.

The patterns in Figs. 4 to 7 are consistent with those in Figs. 2 and 3: prolonged VT exhibits strong correlation between signals, while STVT shows weak, dispersed correlation. Strong correlation and coherence are beneficial for normal sinus rhythms but can hinder the heart's ability to self-recover during arrhythmias like fibrillation and tachycardia. Table 1 summarizes the classifications and observed patterns of XWS and wavelet coherence. Strong XWS patterns were detected in 16 of 19 prolonged VT samples (84.2 %) but only 2 of 21 STVT samples. Conversely, weak and dispersed XWS patterns were predominant in 19 of 21 STVT samples (90.5 %) and matched only 3 of 19 prolonged VT cases. Similarly, wavelet coherence revealed strong correlation in all prolonged VT samples, while 19 of 21 STVT samples displayed weak, dispersed coherence. Thus, wavelet coherence achieves detection rates of 100% for prolonged VT and 90.5 % for STVT.

Table 1. Summary of classifications and observed patterns of XWS and wavelet coherence in all the VT samples studied.

Classification	XWS - Strong, localized power	XWS - Weak, dispersed power	Strong wavelet coherence	Weak wavelet coherence
Prolonged VT (19 samples)	16	3	19	0
STVT (21 samples)	2	19	2	19

3.2. Discussion

The statistical results confirm that both cross-wavelet power spectrum and wavelet coherence are effective indicators of STVT. These findings support our hypothesis that there is a relationship between ventricular activation (Vv) and atrial activation (Va) at VT frequencies. As shown in Fig. 1, ventricular signals are prominent in the right atrium (RA), while the sinus rhythm remains in control, suggesting that the sinoatrial (SA) node maintains RA dynamics during VT episodes, with rapid ventricular excitation unable to reach the RA.

Cardiac function is regulated by mechano-electrical coupling, which operates from cellular to whole-heart levels, providing feedback from the mechanical environment to electrical activity [22]. This coupling affects various cardiac components and can contribute to both arrhythmia initiation and termination [22]. Mechanically sensitive fibroblasts in cardiac tissue may play a key role in linking the ventricles and atria despite their electrical separation, potentially by sensing mechanical stress during prolonged VT [23].

In cases of prolonged VT, the SA node's proximity to the Va measurement site suggests it could be impacted by these mechanical stresses, potentially altering SA node dynamics and affecting recovery [23]. Unlike normal states where the SA node drives ventricular contraction, prolonged VT may shift the dynamics such that SA node function is only preserved when Va is minimally influenced by Vv.

Recent studies propose that dissipation of excitation wave fronts in cardiac tissues can lead to self-terminating arrhythmias by disrupting propagation [24, 25]. This model, which might also explain low-frequency planar wave fronts, could be relevant to STVT and suggests both self-terminating and spontaneous arrhythmia events are possible.

4. CONCLUSIONS

In the present study, the cross-wavelet technique is used to evaluate the correlation strength of bivariate timeseries of ventricular and atrial signals of rat heartbeats in the frequency range of

5 - 80 Hz. It is found that the cases of prolonged VT are predominantly associated with a significantly strong correlation between the two signals whereas the STVT ones show a low and disregarded correlation. Our results indicate that XWS and wavelet coherence may be utilized to predict self-terminated or prolonged ventricular tachycardia from ventricular and atrial signals with more than 84 % accuracy. The results are consistent with the hypothesis that a strong correlation between left ventricular and right atrial signals during tachycardia is not favorable for the heart to recover its sinus rhythm. This is named as the electrically reciprocal connection, which is induced by the mechanical coupling between the ventricle and the atrium. This effect may be explained by a mechanical-electrical interaction between the ventricle and the atrium. Further experiments and analyses need to be done to verify this finding. If this is confirmed, the results may lead to the development of new and more effective methods for the treatment of ventricular tachycardia.

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CRediT authorship contribution statement. Le Duy Manh, Bui Phuong Thuy, Bui Van Hai analyzed data and prepared the manuscript. C.K. Chan carried out the experiment. Le Duy Manh, Man Minh Tan, Trinh Xuan Hoang, C.K. Chan and Pik-Yin Lai discussed the results, writing & editing. Le Duy Manh and Trinh Xuan Hoang supervised the project. All authors reviewed the manuscript.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

The table displays the normal and ventricular tachycardia (VT) beating periods observed in seven rat hearts known to have VT.

Rat No. and label	Normal RR interval (ms)	VT RR interval (ms)
1-(110117)	182±1	52±1, 66±1
2-(110121)	202 ± 1	53 ± 1, 55 ± 1
3-(110209)	194 ± 1	51 ± 1, 53 ± 1
4-(110713)	184 ± 1	61 ± 1, 66 ± 1, 71 ± 1, 79 ± 2,
5-(110714)	210 ± 1	67 ± 1, 95 ± 1, 100 ± 2
6-(100723)	300 ± 3	146 ± 2
7-(110805)	150 ± 1	45 ± 1

Rat No. is just the order number of heart. Rat label (shown in bracket) is the label of the recorded file in experiments (or file name).

RR interval - the time between two successive R-waves of the QRS signal on the electrocardiogram.

The normal RR interval represents the beating period during a normal rhythm unaffected by arrhythmia.

In the case of ventricular tachycardia (VT), the RR interval reflects the beating period of the ventricles during this abnormal rhythm. Variations in VT RR intervals may occur among hearts due to different beating periods associated with multiple VT episodes. Notably, all VT periods are shorter than half of the normal beating period.