Cross-Fourier analysis for differentiating prolonged and self-terminating ventricular tachycardia in isolated rat hearts

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Received 15 Jan. 2023; Revised 13 Mar. 2023; Accepted 10 May 2023; Published 25 May 2023.
DOI: https://doi.org/10.54939/1859-1043.j.mst.87.2023.85-93

ABSTRACT

The interaction between the ventricles and atria in the heart is an important aspect of cardiac function. During ventricular arrhythmias, such as ventricular tachycardia and ventricular fibrillation, the atrial interbeat interval appears different from that of normal sinus rhythm, even though there is no direct electrical connection between the ventricles and atria. To understand this phenomenon, bivariate time-series Fourier analysis was performed on ventricular and atrial signals. The results showed different levels of correlation from the ventricles to the atria during ventricular arrhythmias. We found that low interaction was associated with self-terminating ventricular arrhythmias, while strong connections were mostly seen in sustained ventricular arrhythmias. These findings suggest that the underlying mechanism behind this interaction may be due to the presence of mechano-electrical coupling, which serves as a bridge from the ventricles to the atria (reciprocal connections).

Keywords: Ventricular tachycardia; Arrhythmia; Bivariate time-series; Mechano-electrical coupling.

1. INTRODUCTION

Arrhythmia is a severe health issue nowadays. The ventricles, the body's primary blood-pumping unit, might malfunction, causing heart failure. The illness kills most people with cardiovascular disease [1]. One of the most common causes of sudden cardiac mortality is the development of ventricular fibrillation (VF) or ventricular tachycardia (VT) [2-4]. The difference between VT and VF is that VT is a quick but well-organized process, while VF is characterized by chaotic electrocardiographic activity that comes from the random and acyclic propagation of several separate wavelets throughout the heart. Clinical studies have indicated that VF nearly always occurs after VT and may last from a few beats to hundreds of beats or more, depending on the study's sample size and methodology [5-8]. Ventricular tachycardia is one of the most dangerous cardiovascular symptoms. It has the potential to progress to more severe conditions such as arrhythmia or cardiac failure [7, 9, 10]. Both rhythms may benefit from electroconvulsive treatment, and high-energy shock therapy is suggested in the case of a prolonged VF episode. Contrarily, VT rhythm must be treated with a low-energy bradycardia that is coordinated with the heart rate. It is possible for patients suffering from VF and/or VT to heal without the need for any external intervention, a condition known as self-terminating VF and/or VT [9, 10]. Understanding the underlying causes of these tachycardias will allow us to differentiate between the two aberrant cardiac rhythms and improve therapeutic strategies. Both types of arrhythmias may be studied

using a variety of methods [6-11]. Some of the methods that have been studied include the threshold intersection interval [11-13], complexity measurements for identifying VF/VT, peak function analysis cross-correlation, and regression tests applied to the peak value of the autocorrelation function. However, these methods have limitations: they need long time series for analysis (up to hours), also these methods just deal with single timeseries. The cross-wavelet power and cross-Fourier power spectra of the VF rhythms may be exploited using the approach proposed in our prior studies. The wavelet analysis function that provides the best results is chosen in the early stages of the process. Our prediction criteria have an overall success rate of 85 - 90% [13]. Sinus rhythm can only be recovered in the heart under VF if the heart's sino-atrial node is not being influenced by the VF from the ventricle. In reality, the wavelet transform is a powerful tool for analyzing a signal's time-frequency representation. Excellent frequency and temporal resolution can be achieved at all frequencies. Use the wavelet transform to look at high-resolution ECG data that was taken during both sinus rhythm and VT. This will help you better understand how long things take and how often they happen.

In this paper, ventricular tachycardia was performed in Langendorff isolated rat hearts to determine how to discriminate between self-terminating ventricular tachycardia (STVT) and prolonged/sustained ventricular tachycardia (prolonged-VT). Our findings support the concept that STVT is only achievable when the signals from the Sino-atrial node are not significantly impacted by the ventricular signals. The cross-Fourier power spectrum is used in the study. A new algorithm based on these quantities for classifying STVT and prolonged VT has been developed.

2. EXPERIMENTAL DETAILS AND ANALYSIS METHODS

The study was conducted on a sample of isolated hearts with ventricular arrhythmia who underwent Fourier analysis of their bivariate time series of ventricular and atrial signals. The data was collected and analyzed using appropriate electronic devices and software. The following steps were followed in the analysis:

Data Collection: Electrocardiogram (ECG) signals were collected from each isolated heart during a ventricular arrhythmia episode. The ECG signals were digitized at 4k sampling rate and stored for further analysis. The collected ECG signals were pre-processed to remove any noise and artifacts and were normalized to have a unit standard deviation.

Bivariate Timeseries Analysis: To discover commonalities in the recorded signal (sinusoidal functions), Cross-Fourier spectrum (XFS) methods may be used to find the common spectral power of a specific frequency. The dominating frequency of XFS between the RA and the ventricle was generally near the ventricular signal in our investigation. The spectrum power was computed for frequencies ranging from 0.0 to 60 Hz. This frequency range includes the normal frequency rank and also the tachycardia frequency rank up to ten times normal beating.

Experimental details: to ensure the heart can survive for 6 - 10 hours, the rat heart is taken from the body and placed in a solution of nutrition and artificial oxygen at 37 ^{o}C (Langendorff system, using Krebs-Henseleit solution). The rat heart was studied for 3 - 4 hours while it was still active (in healthy condition). The normal heart rate of these hearts is about 3 - 6 Hz and depends on their body weight. It is used to create tachycardia by introducing a fast, weak electrical stimulation between 20 - 62.5 Hz. Inserting electrodes

into the heart tissue monitors two bipolar pseudo-ECGs, one from the right atrium RA (Va) that is close to the sinoatrial node and the other from the apex. The other electrical signal is recorded from the right ventricle (Vv). The goal is to utilize these two signals to differentiate between STVT and prolonged VT. In the case where the VT is not dominating the complete heart, the RA signal is employed to describe its dynamics, whereas Vv represents the ventricle's signal. The heart is stimulated by a pacing electrode inserted into the septum between the two ventricles. A water-filled balloon linked to a pressure transducer is introduced into the left ventricle through the left atrium. This signal is called left ventricular pressure (LVP) and is used to classify an arrhythmia as fibrillation, tachycardia, or other abnormal activities. Fast pacing (20 - 62.5 Hz) may elicit VT in isolated hearts perfused with KH buffer [14, 15]. It was authorized by Academia Sinica's Board of Ethics [16, 17]. Both STVT and prolonged VT can be measured simultaneously. Statistical analysis can be done on these kinds of signals by taking the last five seconds of the heart signals.

3. RESULTS AND DISCUSSION

3.1. Results

The results of the Fourier analysis and bivariate time-series analysis were then analyzed to determine the pattern of interference between the ventricle and atria during VT or VF. The degree of interaction was classified as low or strong based on the results of the analysis.

Normally, in the absence of the autonomic nervous system (in isolated rat hearts, it is removed), it is well known that the atrial rhythm is quite regular, with little variation in the interbeat interval (IBI), as shown in Fig. 1 (two top sub-graphs). That is because the beating is controlled by a unit called Sinoatral node that regularly sends the control signal to the atrial. However, as we can see in the middle and bottom graphs for both STVT and prolonged VT, the variation of atrial rhythms is quite high. Despite the absence of reciprocal electrical connections from the ventricles and atria, there is still a significant difference in IBI patterns in patients with ventricular arrhythmia. The mechanism behind this difference in IBI patterns remains unclear, but it is believed to be related to the interaction between the ventricle and atria. This interaction is thought to play a critical role in the development and maintenance of ventricular arrhythmia, but the exact mechanism is not well understood.

The ECG signals used in this study are shown in Fig. 2. These signals contain both STVT and prolonged VT of ventricular tachycardia episodes. The signals were digitized at a sampling rate of 4000 Hz. As indicated in Fig. 2(a), STVT is defined as tachycardia that returns to normal within three minutes without any medical intervention; (b) shows a typical scenario of induced VT by fast pacing, the VT lasting for a long time (VT that is sustained for more than 3 minutes) and was regarded as prolonged-VT. It was decided to use intracoronary lidocaine injection (0.2 ml, 10 mM) to prevent heart damage from prolonged VTs. More specifically, we collected a total of 41 VT episodes from 7 isolated rat hearts; 22 of these were STVTs, whereas the other 19 were prolonged VTs. We used KH buffer with high calcium content (HCB) to assess the validity of our study of the dynamical signatures of STVT and prolonged VT. These HCB tests yielded 9 VT episodes. This HCB data shows that our research is accurate regardless of how STVTs

are produced. We utilized just the final 5 seconds of data before sinus rhythm recovery for STVT and the last 5 seconds of 3-minute selected data for prolonged VT. Due to the XFS method's limitations, we assume the signals are quasi-stationary in this short time window, that also is the reason why we used only 5 seconds for analysis.

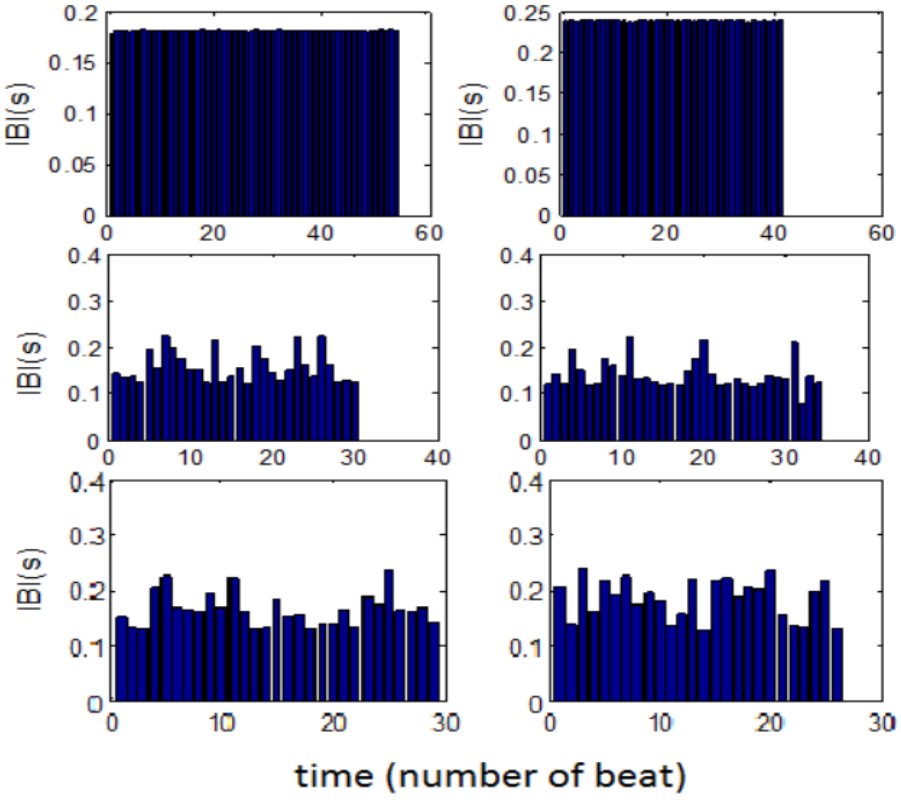

Figure 1. *Atrial Interbeat interval (IBI) estimated from experimental data. Two top sub-graphs are shown for two normal sinus rhythm samples (of different hearts). Two middle sub-graphs are shown for two STVT samples. Two bottom sub-graphs are shown for two prolonged VT samples.*

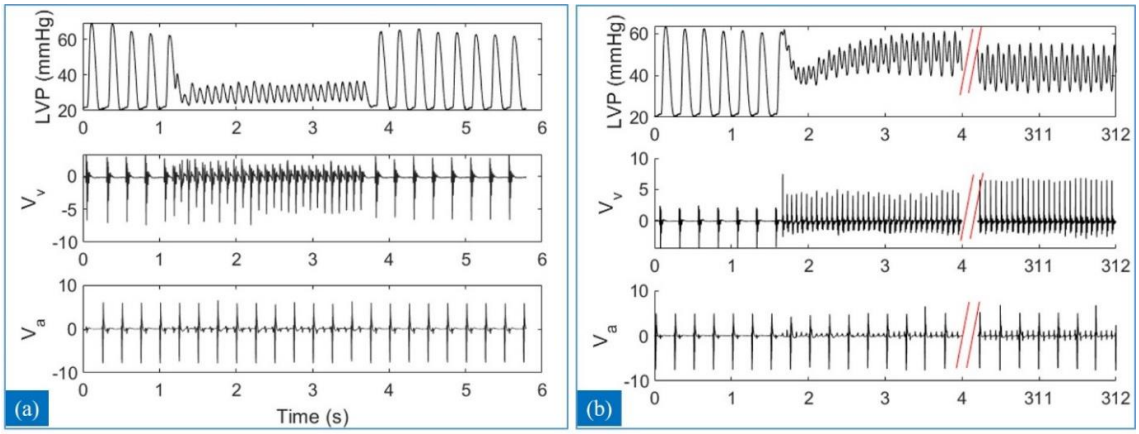

Figure 2. *For showing (a) a typical STVT, and (b) a typical prolonged VT: the signs to recognize it is VT or VF are the shape of Vv signals and the fluctuation of left ventricular pressure (LVP).*

Fourier spectral analysis of STVT and prolonged-VT episodes. Fig. 3 (a) and (b) show the Fourier power spectrum (FPS) and cross-Fourier spectrum (XFS) of Va and Vv of a typical prolonged VT and STVT, respectively. The top, middle, and bottom panels correspond to the XFS of Va and Vv, the FPS of Vv, and the FPS of Va. The dominant frequency is defined as the frequency with the highest power spectrum. Prolonged VT spectra often have confined frequency bands, while STVT spectra are more continuous and have magnitudes an order of magnitude less. The strength of the FPS of Va from prolonged VT episodes is more concentrated around the frequency of tachycardia (middle panel of Fig. 3 a)) than that of Vv from STVT episodes (bottom panel of Fig. 3 (a)), of course, there are some harmonic terms that appear as a consequence of the Fourier transform. In this case, the dominant frequencies of both Vv and Va are about 19 Hz, resulting in the same dominant frequency of the XFS with a high dominant power. As a consequence, prolonged STVT episodes' XFS dominating strength surpasses STVT's.

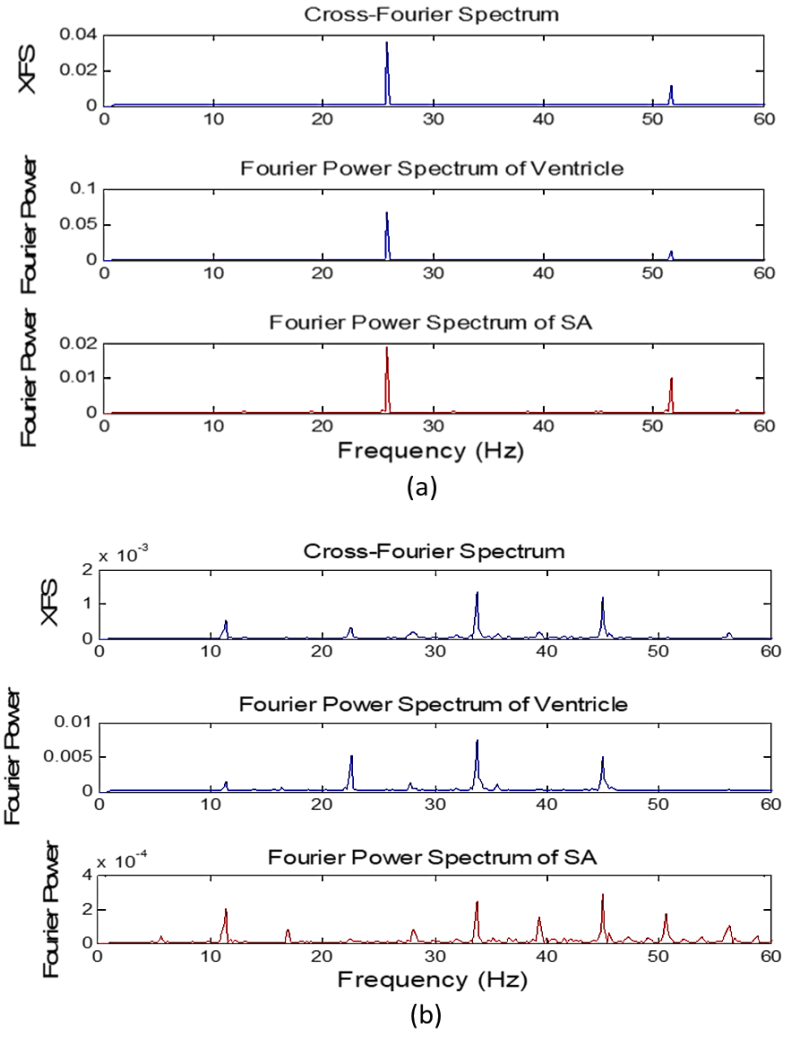

Figure 3. *(a) prolonged-VT. The top, middle, and bottom panels correspond to the XFS of Va and Vv, the FPS of Vv, and the FPS of Va, respectively. The dominant frequency of the XFS is about 26 Hz, corresponding to the third strongest components of both FPSs of Vv and Va. (b) A typical STVT. The arrangement of each panel is similar to that of (a).*

The Va of STVTs has a broad FPS distribution (Fig. 3 (b)). Due to the wide frequency range, the power is modest. The FPS of Vv is frequently close to that of tachycardia (Fig. 3 (b), center panel). This contributes to the XFS's limited dominating power (Fig. 3 (b), top panel).

Fig. 4 illustrates the XFS's dominating power for all VT episodes. The STVT group is denoted by black stars; the prolonged STVT group is red circles. The 24 STVTs have small dominating XFS values in a typical KH buffer (say lower than 0.005). Prolonged VTs have significant dominating XFS values (> 0.005) (17 out of 19). VTs with high dominant XFS power are unlikely to self-destruct, but VTs with low dominant power are likely to reestablish their normal rhythm. The horizontally green line of the value of 0.005 in Fig. 5 clearly illustrates two distinct groupings. The first group has minimal dominating power (0.005).

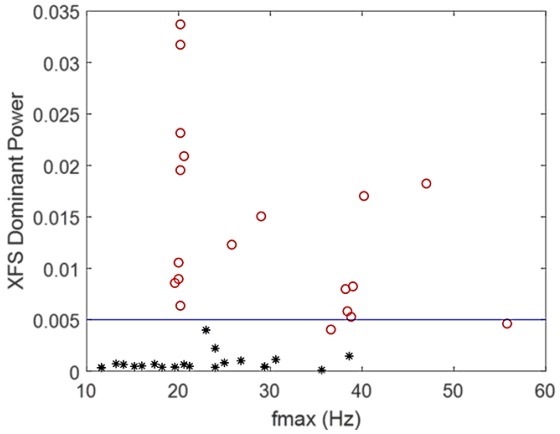

Figure 4. *Summary of the dynamical signatures of STVTs and prolonged VTs using XFS (cross Fourier Power spectrum) analysis. X-axis is the dominant frequency at which the highest power of XFS is obtained. Y-axis is the dominant power of XFS. The black stars indicate the STVT samples and the red circles for prolonged VTs.*

In Fig. 4, the group of small dominant powers (XFS < 0.005) has 24 VT episodes, 22 of which are STVT. Thus, VT episodes with low dominant XFS strength have a better probability of survival (~ 91.6%). The second group has considerable dominating power (> 0.005). It has seventy prolonged VT episodes (100%). Under HCB circumstances, all 14 VT episodes validate this dynamical signature: all 12 STVTs have tiny dominating XFS power, whereas the prolonged VTs have big. According to the XFS study, VT has minimal or no likelihood of self-termination when the dominating power of XFS is strong. All 41 episodes and the line that separates high and low XFS dominating power are used to figure out whether or not there will be a STVT or a prolonged VT.

Finally, data for these analyses is available, readers who are concerned may download from: *https://drive.google.com/drive/folders/1Un3DUh3iuvewYWal9rbHISZ2OhRZgSQe?usp=sharing*.

3.2. Discussion

The above statistical results from Fourier analysis show that cross-Fourier power spectrum (XFS) dominant powers are valid STVT indicators. This data analysis corroborates our hypothesis that there are relationships between Va and Vv around VT frequencies. As seen in Fig. 2, the ventricle mode was prevalent in the RA (middle and

bottom panels). A sinus rhythmic RA pounding while the ventricle beats more quickly during VT episodes means the SA node still controls the RA dynamics. In other words, rapid ventricular electrical excitation cannot reach the RA. The Vv component in Va must be coupled in some way. Many essential controls of cardiac function occur at different levels of cardiac muscle cells, tissues, and the whole heart, including acute beat-by-beat feedback from the local mechanical environment to electrical activity. This process is known as mechano-electrical coupling [7]. There are various types of mechano-electrical coupling effects in different units of the heart, such as the atria, sino atrial node, ventricle, and electro-mechanical auto-regulatory loop (feedback, feed forward). In relation to arrhythmia, this coupling has been shown to be one of the arrhythmia generators, also for arrhythmia termination [7]. There is a silent cell in cardiac tissue called fibroblast that is mechanically sensitive and may have an important role in establishing the connections between the ventricles and atria, which are well known to be electrically separated.

Mechanical coupling through mechanically sensitive cardiac fibroblasts [18] is one probable basis for this interaction. Since Vv exists in Va for prolonged VT, the RA fibroblasts may be feeling the mechanical stresses created by VT. Because Va's measurement point is near the SA node, the SA node should feel the impact stress. Mechanical couplings impact SA node dynamics [18]. In contrast to the normal state when the SA node transmits data to regulate ventricular contraction, intraventricular VT may change SA node dynamics. Therefore the SA node can only function when measured Va has no substantial amount of Vv. To recuperate, a person requires a regular SA node function. It was recently postulated [19-21] that the dissipation of excitation wavefronts in cardiac tissues might cause self-terminating arrhythmia. In this model, dissipation breaks the wave fronts of the excitations, preventing them from propagating. The dynamics of these non-propagating wavefronts stop the tachycardia and fibrillation. It would be fascinating to see whether our findings could be duplicated in their model when the SA node dynamics are introduced. Low-frequency planar fronts may be another way that STVT could happen [22].

Finally, their model allows for both self-terminating and spontaneous arrhythmia episodes. This is pretty similar to what we saw in certain VT incidents with HCB. Local wavefront dissipation is linked to current sodium inactivation [22]. The capacity of HCB to induce spontaneous transient VTs may be connected to calcium's ability to inhibit and modify sodium channel closure [23]. Even though there were only 9 VT episodes under HCB, 1 of them had STVT, which shows that the calcium channel plays a role in STVT.

4. CONCLUSIONS

Our analysis in isolated rat hearts discovers a good way to distinguish between STVT and prolonged or sustained ventricular tachycardia. The Fourier technique is used to evaluate the frequency range of 5–60 Hz for the correlation strength of bivariate time-series of ventricular and atrium signals. Prolonged-VT has the greatest significant association (high dominant power). STVT cases show a low and disregarded correlation. The dominant power of XFS may be utilized to predict STVT or prolonged VT ventricular tachycardia with more than 91% accuracy. This is a pretty good indicator in complex biological systems. This relationship may be explained by a mechanical-

electrical interaction between the ventricle and atrium. The results of this study are important for a better understanding of the underlying mechanism of ventricular arrhythmia that can help to improve diagnostic methods and may lead to the development of new and more effective treatments. However, more experimental and analytic researches need to be done before that goal.

Acknowledgement: *This research is funded by Graduate University of Science and Technology, Vietnam Academy of Science and Technology, under grant code number: GUST.STS.ĐT2020-VL04.*

REFERENCES

[1]. R. J. Myerburg, A. Castellanos, *"Cardiac arrest and cardiac death, in: E. Braunwald (Eds), Heart Disease: A Textbook of Cardiovascular Medicine"*. Philadelphia,PA, Saunders, p. 742, (1997).

[2]. E. Sandoe, B. Sigurd, *"Arrhythmia—A Guide to Clinical Electrocardiology"*, chapter 3, Verlags GmbH, Bingen am Rhein, Germany, (1991).

[3]. A. Karma, R.F. Gilmore Jr, *"Nonlinear dynamics of heart rhythm disorders"*. Physics Today, 60(3), 51-57, (2007).

[4]. Z. Qu, J.N. Weiss, *"Dynamics and cardiac arrhythmias"*. J. Cardiovasc Electrophysiol 17 1042–1049, (2006).

[5]. R. K. Thakur, G. J. Klein, C. A. Sivaram, M .Zardini, D. E. Schleinkofer, H. Nakagawa, R. Yee, W.M. Jackman, *"Anatomic substrate for idiopathic left ventricular tachycardia"*, Circulation 93, 497–501, (1996).

[6]. B. Befeler, *"Mechanical stimulation of the heart: its therapeutic value in tachyarrhythmia"*. Chest 73, 832–838, (1978).

[7]. T.A. Quinn, P. Kohl, *"Cardiac Mechano-Electric Coupling: Acute Effects of Mechanical Stimulation on Heart Rate and Rhythm"*, Physiol. Rev. 101(10), 37-92, (2021).

[8]. K. Daqrouq, A. Alkhateeb, M.N. Ajour, A. Morfeq, *"Neural network and wavelet average framing percentage energy for atrial fibrillation classification"*, Comput. Methods Prog. Biomed., 113 (3) 919-926, (2014).

[9]. P. D. Arini, F. H. Baglivo, J. P. Mart´ınez, and P. Laguna, "*Evaluation of ventricular repolarization dispersion during acute myocardial ischemia: spatial and temporal ECG indices"*, Med. Biol. Eng. Comput., 52, 375–391, (2014).

[10].P.C. Ivanov et al., *"Scaling behaviour of heartbeat intervals obtained by wavelet-based time-series analysis"*, Nature, 383, 323–327, (1996).

[11].R.J. Martis, U.R. Acharya, H. Adeli, *"Current methods in electrocardiogram characterization"*, Comput. Biol. Med. 48, 133–149, (2014).

[12].Ö. Yıldırım, P. Pławiak, R.-S. Tan, U.R. Acharya, *"Arrhythmia Detection Using Deep Convolutional Neural Network with Long Duration ECG Signals"*. Comput. Biol. Med. 102, 411–420, (2018).

[13].D. M. Le, A. V. Dvornikov, P. Y. Lai and C. K. Chan, *"Predicting Self-terminating Ventricular Fibrillation in an Isolated Heart, Europhys"*. Lett., 104, 48002, (2013).

[14].A.V. Dvornikov, Y.C. Mi, C.K. Chan, *"Transient analysis of force–frequency relationships in rat hearts perfused by Krebs-Henseleit and Tyrode solutions with different [Ca2+]o. Cardiovasc"*. Eng. Technol., 3, 203–210, (2012).

[15].S. Sridhar, D.M. Le, Y.C. Mi, S. Sinha, P.Y. Lai, C.K. Chan, *"Suppression of cardiac alternans by alternating period feedback stimulations"*, Phys. Rev. E 87, 042712, (2013).

[16].National Research Council, *"Guide for the Care and Use of Laboratory Animals"*, National Academy Press, Washington DC, (2011).

[17].R. N. Bracewell, *"The Fourier Transform and its Applications"*, 3rd edition, McGraw Hill, Boston, (2000).

[18].A Kamkin, I Kiseleva, G Isenberg, K.D Wagner, J Günther, H Theres, H Scholz, *"Cardiac fibroblasts and the mechanoelectric feedback mechanism in healthy and diseased hearts"*, Prog. Biophys. Mol. Biol., 82, 111-120, (2003).

[19].V. N. Biktashev, *"Dissipation of the Excitation Wave Fronts"*, Physics Review Letter 89, 168102, (2002).

[20].O. V. Aslanidi, A. Bailey, V. N. Biktashev, R. H. Clayton, and A. V. Holden, *"Enhanced self-termination of re-entrant arrhythmias as a pharmacological strategy for antiarrhythmic action"*, Chaos 12, 843–851, (2002).

[21].I. Biktasheva, V. Biktashev, W. Dawes, A. Holden, R. Saumarez, A.M. Savill, *"Dissipation of the excitation front as a mechanism of self-terminating arrhythmias"*. Int. J. Bifurc. Chaos 13, 3645–3656, (2003).

[22].M.A. de la Casa, F.J. de la Rubia, P.C. Ivanov, *"Patterns of spiral wave attenuation by low-frequency periodic planar fronts"*, Chaos 17, 015109, (2007).

[23].C. M. Armstrong and G. Cota, *"Calcium block of Na+ channels and its effect on closing rate"*, Proc. Natl. Acad. Sci. U.S.A., 96, 4154-4157, (1999).

TÓM TẮT

Phân tích phổ chéo Fourier trong phân loại nhịp nhanh thất kéo dài và tự hồi phục trong thí nghiệm với tim chuột cô lập

Sự tương tác giữa tâm thất và tâm nhĩ trong hoạt động tim là một yếu tố rất quan trọng của chức năng tim. Trong các rối loạn nhịp thất, chẳng hạn như nhịp nhanh thất và rối loạn tâm thất, chu kỳ nhịp tâm nhĩ xuất hiện khác với nhịp xoang bình thường, mặc dù không có kết nối điện trực tiếp giữa tâm thất tới tâm nhĩ. Để hiểu hiện tượng này, phân tích Fourier cặp dữ liệu đo đồng thời được thực hiện trên tín hiệu tâm thất và tâm nhĩ. Kết quả cho thấy mức độ tương quan khác nhau từ tâm thất đến tâm nhĩ trong các rối loạn nhịp thất. Chúng tôi thấy rằng, tương tác thấp có liên quan đến rối loạn nhịp thất tự tự hồi phục, trong khi các kết nối mạnh mẽ chủ yếu được thấy trong rối loạn nhịp thất kéo dài. Những phát hiện này cho thấy rằng, cơ chế cơ bản đằng sau sự tương tác này có thể là do sự hiện diện tương tác điện cơ, đóng vai trò là cầu nối từ tâm thất đến tâm nhĩ (kết nối ngược).

Từ khóa: Nhịp nhanh thất; Rối loạn nhịp tim; Cặp dữ liệu đồng thời; Tương tác điện cơ.