Dynamic assessment and overnight evaluation on autonomic imbalance in patients with sleep apnea via volatility clustering of descending (or ascending) heartbeat intervals

Yuo-Hsien Shiau [a,b,*], Jia-Hong Sie [c]

[a] Graduate Institute of Applied Physics, National Chengchi University, Taipei 11605, Taiwan, ROC
[b] Center for Computational Research and Applications, National Chengchi University, Taipei 11605, Taiwan, ROC
[c] Institute of Biomedical Engineering, National Yang-Ming University, Taipei 11221, Taiwan, ROC

ARTICLE INFO

Article history:
Received 6 May 2013
Accepted 30 June 2013
Available online 24 July 2013

Keywords:
Diagnosis
Heartbeat interval
Volatility clustering
Sleep apnea
Autonomic imbalance

It is known that sleep apnea (SA) constitutes a major social problem because of its emerging association with cardiovascular morbidity [1–3], where an estimated prevalence of 30% to 50% among patients with coronary heart disease and 50% among hypertensive patients. Although the pathogenic effects of SA on cardiovascular diseases are complex, it is believed that autonomic dysregulation should be involved [4]. Abundant evidences link the activation of sympathetic nervous system to cardiovascular outcomes of SA patients [5]. For example, obstructive SA with a continuous repetition of obstructive events during the night can lead to a permanent dysregulation of the autonomic cardiovascular control resulting in sympathetic overactivity. When the apnea is interrupted by arousal from sleep, concurrent sympathetic excess and parasympathetic withdrawal will appear [6], and a postapneic surge in both heart rate and blood pressure will be observed. Thus, autonomic imbalance can be expected in SA patients. In addition, an independent association between obstructive SA and atrial fibrillation (AF) has been shown in a cross sectional study [7]. Ghias et al. reported a series of experiments proposing an autonomic link between SA and AF inducibility. In particular, concurrent slowing of the heart rate and rise in systolic blood pressure after apnea were observed in most cases [8]. Kapa et al. also reported that simultaneous increases in cardiac parasympathetic and vasoconstricting sympathetic tone may be seen during obstructive SA [9]. Therefore, based upon mentioned above the origin of autonomic imbalance for SA patients is still debatable.

Spectral analysis on heart rate variability (HRV) is an attractive non-invasive tool that has been widely used to estimate sympathovagal modulation, where high-frequency (HF) power of HRV is synchronous to respiration and it is thought to represent parasympathetic (or vagal) activity. However, the respiratory cycle, including apnea and hyperpnea, of SA frequently falls in the low-frequency (LF) band, that is classically thought to be a non-respiratory marker of sympathetic modulation [10,11]. Therefore, SA patients with higher sympathovagal modulation (LF/HF) would be questionable via spectral analysis.

In this study, we introduced three new/robust indices to evaluate autonomic nervous system (ANS) for SA patients as well as for normal subjects, where R_+ and R_- indices were, respectively, to characterize overnight parasympathetic and sympathetic tone, and the R_-/R_+ index was for describing sympathovagal modulation during overnight sleep. R_- and R_+ indices were established on the concept of detecting sustained increases in autonomic tone. When sympathetic (parasympathetic) tone increases predominantly, descending (ascending) heartbeat intervals (HIs) would be expected. Moreover, the clustering degree of these descending (ascending) HIs indicates the activation degree of sympathetic (parasympathetic) tone. The calculations of R_+ and R_- indices are shown in Appendix A.

Besides, we also introduced three dynamic indices N_+, N_-, and S which would be helpful to realize dynamical changes in autonomic tone before and during SA (see Appendix A). N_+ and N_- were used for assessing parasympathetic and sympathetic activity, respectively. Frequently large volatility in N_+ or in N_- series indicates the sleep process is far from homeostasis, therefore, pathogenic causes due to autonomic dysregulation can be expected. The S index was for describing the activity of these two autonomic tone dynamically modulated in response to the epsiodes of SA as well as the periods of normal breathing. For example, we may say that parasympathetic (sympathetic) tone would be absolutely dominant if $S = 1$ (-1).

We used two open-access databases to explore the origin of autonomic imbalance for SA patients [12]. One was the Apnea-ECG database (http://www.physionet.org/physiobank/database/apnea-ecg/), in which apnea (class A), borderline apnea (class B), and control (normal, or class C) subjects were classified according to the total time duration of apnea and hypopnea happened during sleep. There were 40 recordings in class A, 10 recordings in class B, and 20 recordings in class C. The subjects were 57 men and 13 women between 27 and 63 years of age. In order to test the robustness of the proposed indices, the additional database is necessary to be included. Therefore, the other database for the cross analysis was the MIT-BIH polysomnographic database (http://www.physionet.org/physiobank/database/slpdb/), in which there were 18 recordings from 16 male SA patients, aged 32 to 56 (mean age 43) and apnea-hypopnea index was used to diagnose these subjects.

Fig. 1 illustrates HI, N_+, N_-, and S of a normal subject. No large volatility in N_+, N_-, and S series was observed. On the contrary, SA patients displayed large volatility in N_+, N_-, and S series during apnoeic episodes (shown in Fig. 2), where S frequently switched from 1 to -1, and vice versa. Fig. 2 also illustrates the autonomic dynamics before apnea, where S frequently reached to -1. Thus, sympathetic overactivity can be found for SA patients even under the period of normal breathing.

Fig. 3 demonstrates statistical characteristics of R_+, R_-, and R_-/R_+ for apnea, borderline apnea, and control subjects from the Apnea-ECG database. In Fig. 3(a) the R_+ index provided a significant differentiation for apnea and control groups ($^{***}P < 0.001$), however, no significant differences in between apnea and borderline apnea groups as well as in between borderline apnea and control groups. In Fig. 3(b) significant differentiations for apnea and control groups ($^{***}P < 0.001$) as well as for apnea and borderline apnea groups ($^{*}P < 0.05$) were observed through the R_- index. In Fig. 3(c) the R_-/R_+ index had no statistical

* Corresponding author at: Graduate Institute of Applied Physics, National Chengchi University, Taipei 11605, Taiwan, ROC. Tel.: +886 2 29393091x62987; fax: +886 2 29360360.
E-mail address: yhshiau@nccu.edu.tw (Y.-H. Shiau).

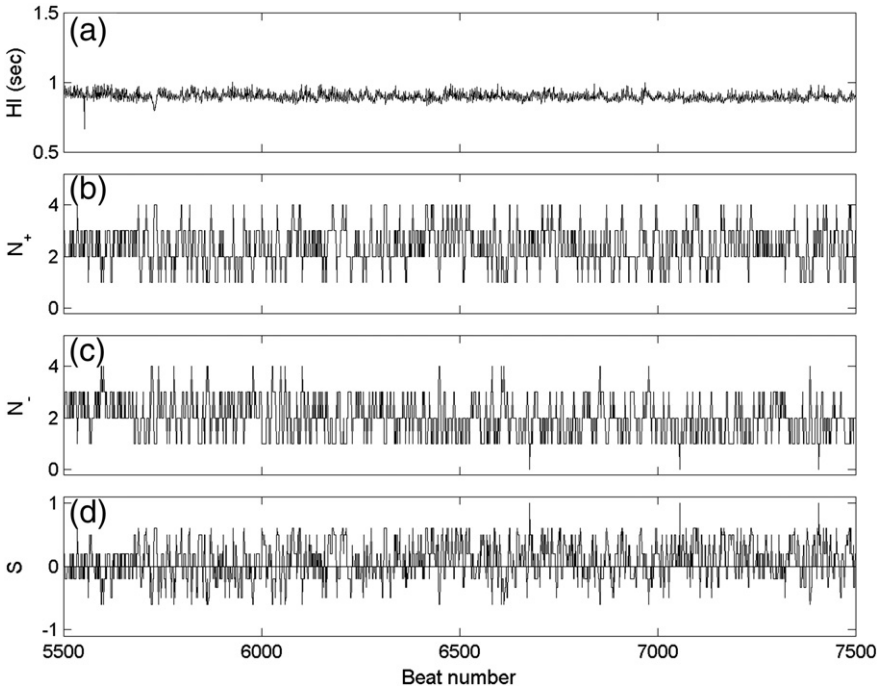

Fig. 1. Illustrations of HI (a), N_+ (b), N_- (c), and S (d) for a normal subject (label c02 in Apnea-ECG database), respectively.

differences for these three groups. Based up results of the R_+ and R_- indices the receiver operating characteristic (ROC) curves shown in Fig. 3(d) reflected both high sensitivity and specificity for apnea and control groups, where the AUC value for the R_+ and R_- indices can be up to 0.930 and 0.875, respectively. As expected, the ROC curve for the R_-/R_+ index was almost below than the diagonal and the AUC value was only 0.395.

Fig. 4 illustrates statistical characteristics of R_+, R_-, and R_-/R_+ for SA patients from the MIT-BIH polysomnographic database as well as for control subjects from the Apnea-ECG database. In Fig. 4(a)–(b) the R_+ and R_- indices provided significant differentiations for apnea and control groups, where $^{***}P < 0.001$ for R_+ and $^{**}P < 0.01$ for R_-. In Fig. 4(c) the R_-/R_+ index had no statistical differences for these two groups. The ROC curves shown in Fig. 4(d) displayed both high sensitivity and specificity for the R_+ and R_- indices, where the AUC value for the R_+ and R_- indices can be up to 0.925 and 0.803, respectively. As for the R_-/R_+ index, the AUC value was just 0.339.

It is well accepted that bradycardia (tachycardia) is resulted from the overexcited parasympathetic (sympathetic) tone. In addition, it is also known that episodes of SA are accompanied by a characteristic heart rate

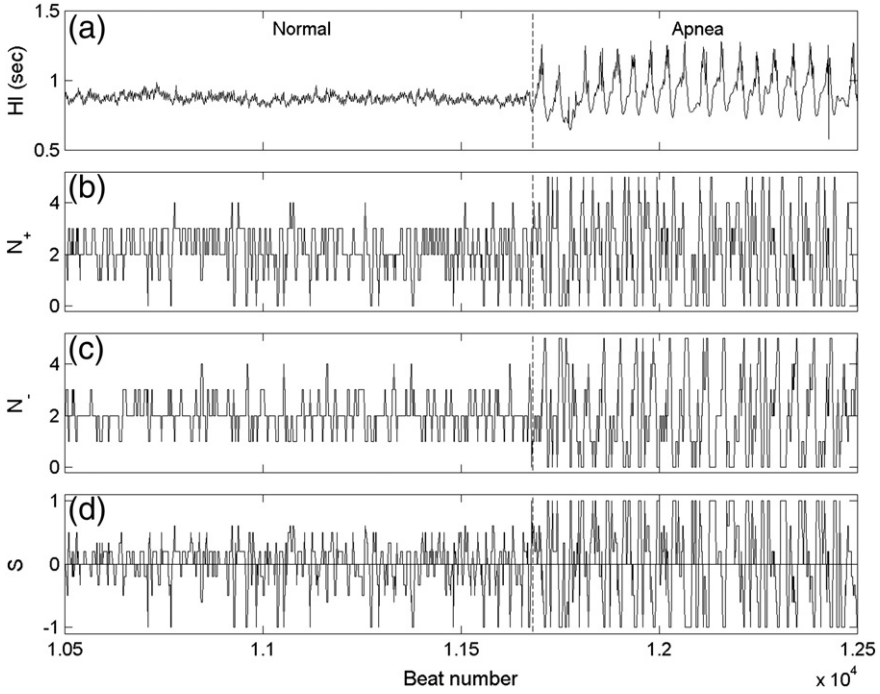

Fig. 2. Illustrations of HI (a), N_+ (b), N_- (c), and S (d) for an SA patient (label a03 in Apnea-ECG database), respectively. The dashed line represents the onset of SA.

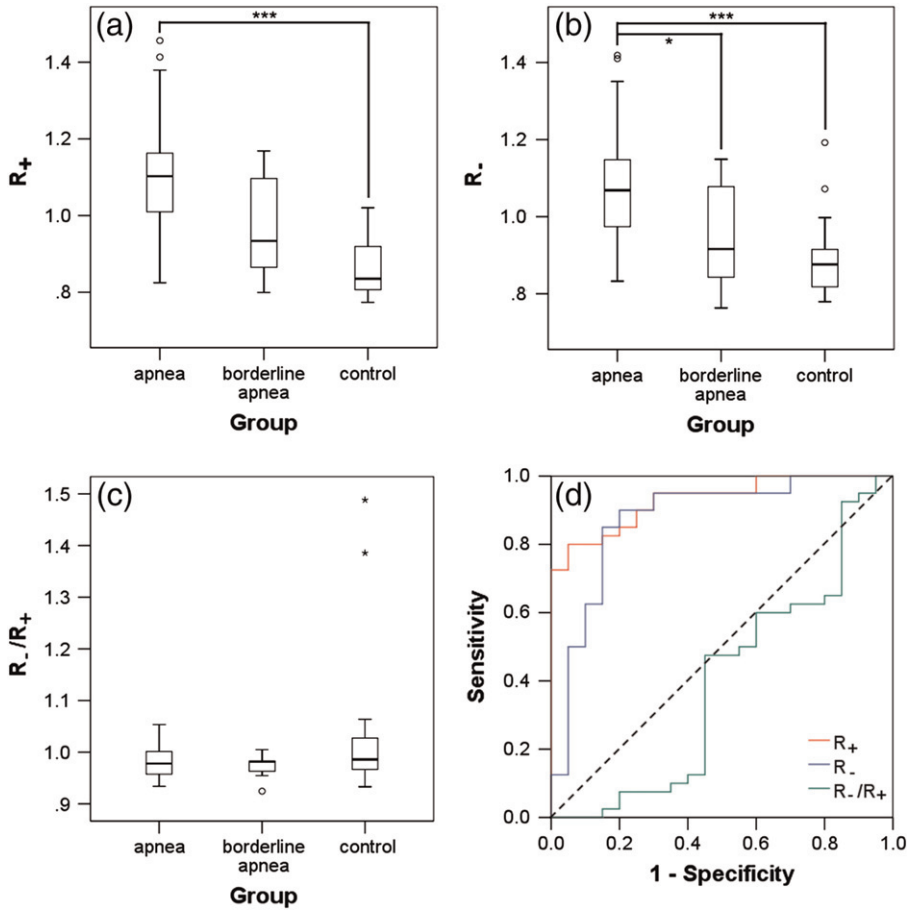

Fig. 3. Boxplots for comparisons of R_+ (a), R_- (b), and R_-/R_+ (c) in between apnea, borderline apnea, and control subjects, where all analyzed subjects were from the Apnea-ECG database. Boxes represent the 75th percentile, median, and 25th percentile. Whiskers show the largest and the smallest observed values. Difference was assessed by Scheffe post hoc test ($^{***}P < 0.001$, $^{**}P < 0.01$, and $^{*}P < 0.05$). The ROC curves between apnea and control groups shown in (d), in which red, blue, and green curves are corresponding to R_+, R_-, and R_-/R_+, respectively. The diagonal (dashed) represents as a reference line.

pattern, which consists of bradycardia during apnea followed by abrupt tachycardia on its cessation [13]. The *S* pattern shown in Fig. 2(d) displays acute sympathovagal modulations during apnoeic episodes, therefore, autonomic imbalance and non-homeostatic sleep can be well characterized.

The interplay between the sympathetic and parasympathetic regulation of heartbeat is usually organized in a reciprocal fashion, i.e., increased activity in one system is accompanied by decreased activity in the other [14]. The cold face test and diving reflex, analogous situations as SA, are unique noninvasive maneuvers to challenge ANS that simultaneously increases both sympathetic and parasympathetic activities [15,16]. In this study, both sympathetic and parasympathetic excesses were characterized in SA patients, therefore, SA patients with cardiovascular morbidity would be expected [3,17]. Besides, these results provided the possible pathogenic mechanism between SA and AF. A very recent clinical study reported that patients with untreated obstructive SA have a higher recurrence of AF even after radio-frequency catheter ablation [18]. It has been suggested that parasympathetic activation which causes action potential shortening, and sympathetic activation which enhances the calcium transient are important and necessary components for the onset of paroxysmal AF [19]. Owing to those, electrical atrial remodeling due to autonomic dysregulation might be considered in SA patients. Therefore, our proposed time-domain indices can well reflect the activity of ANS in SA.

It is known that SA patients exhibit daytime sleepiness and fatigue [4]. What factors determine sleep quality? It is believed that the total duration of deep sleep would play a crucial role. Penzel et al. showed that the heartbeat on larger time scales statistically exhibited uncorrelated white noise for normal and SA subjects during deep sleep [20], thus volatility clustering of descending (or ascending) HIs would be not expected in deep sleep. In this study, no volatility clustering observed in most of normal subjects through R_+ and R_- overnight indices (smaller than 1) would raise an interesting concept about sleep quality. Activated autonomic tone usually responds to internal and/or external stimuli, which certainly induce volatility clustering of descending (or ascending) HIs and shorten the duration of deep sleep. Owing to that, we may say that R_+ and R_- indices could be potential indicators for assessing sleep quality.

To conclude, in this study we used three time-domain indices to evaluate ANS for SA patients as well as for normal subjects during overnight sleep. The robustness of the proposed indices was verified by two open-access databases, where R_+ and R_- indices provided significant differentiations for different groups. The possible pathogenic mechanism between SA and AF as well as relationship between sleep quality and volatility clustering of descending (or ascending) HIs were also discussed. We think nonlinear measures like the present proposed indices that resulted from sophisticated math would become powerful tools for clinical applications. However, the understanding of the physiological basis of nonlinear measures should be an important ingredient for future applications, rather than considering them as numerical indices supported by clinical studies in large-scale database. Therefore, the present nonlinear indices could make HRV measures to become the possibility for widespread clinical applications.

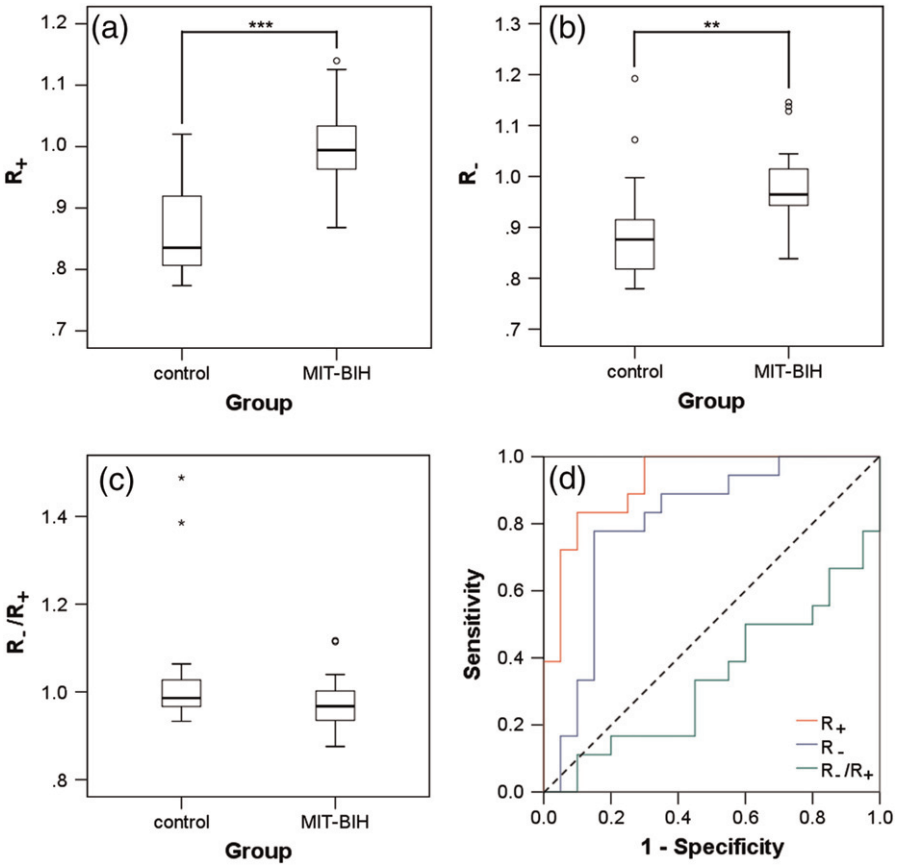

Fig. 4. Boxplots for comparisons of R_+ (a), R_- (b), and R_-/R_+ (c) in between apnea and control subjects, where apnea (label MIT-BIH) and control subjects, respectively, were from the MIT-BIH and Apnea-ECG database. Boxes represent the 75th percentile, median, and 25th percentile. Whiskers show the largest and the smallest observed values. Difference was assessed by Scheffe post hoc test (* * *$P < 0.001$, * *$P < 0.01$, and *$P < 0.05$). The ROC curves between apnea and control groups shown in (d), in which red, blue, and green curves are corresponding to R_+, R_-, and R_-/R_+, respectively. The diagonal (dashed) represents as a reference line.

This work was partially supported by the National Science Council of the Republic of China (Taiwan) under Contract Nos. NSC 101-2112-M-004-002-MY3.

The current authors previously proposed a time-domain apnea index which reflected the clustering degree of large volatility embedded in HRV [21]. Under sophisticated modifications, the previous index can be extended to evaluate sympathetic and parasympathetic tone for analyzed subjects. The detailed mathematical procedure is given in the following.

In order to characterize the activation of parasympathetic tone in ANS, the logarithmic return of HIs *R(i)* is considered.

$$R(i) = \ln\left[\frac{RR(i)}{RR(i-1)}\right], \tag{1}$$

where *RR(i)* is the HI at the beat number *i*. Moreover, the normalized return $R_{nor}(i)$ is defined as

$$R_{nor}(i) \equiv \frac{R(i)-\mu}{\sigma}. \tag{2}$$

where μ and σ are the mean and standard deviation of *R(i)* series, respectively. The positive $R_{nor}(i)$ sequence, corresponding to the difference of consecutive ascending HIs, are first sorted and in which the largest *p*% fluctuations are identified. We would want to see if these large and positive fluctuations will have clustering behaviour in the $R_{nor}(i)$ sequence. To do so, the simplest way is to replace these large and positive fluctuations by 1, and the rest of the $R_{nor}(i)$ sequence by 0. Therefore, the $R_{nor}(i)$ sequence will be translated into a binary series, which only contains 0 and 1. We use the so called moving window method to measure the clustering behaviour of the binary-type $R_{nor}(i)$ series. A moving window with fixed size n-beat is first chosen. We put the window on the first event of the binary series and count the number of events with values equal to 1 within the window. We then move the window to the second event and again do the counting. We repeat the same procedure until we finish scanning through the whole binary sequence, and finally get the sequence of the number of events, denoted as $N_+(i)$. We will then calculate the standard deviation σ_+ of the overnight $N_+(i)$ sequence and compare with that of the white noise σ_W, where $\sigma_W = \sqrt{nP(1-P)}$ and $P = p/100$. Owing to that, a clustering index R_+ for characterizing the overnight activity of parasympathetic tone can be defined as

$$R_+ \equiv \frac{\sigma_+}{\sigma_W}. \tag{3}$$

If R_+ is much larger than one, it denotes that the clustering behaviour of ascending HIs is much stronger and the activation of parasympathetic tone can be expected. On the contrary, bluntly parasympathetic tone will show up if R_+ is smaller than one.

Concerning on sympathetic tone, the logarithmic return of HIs *R(i)* is defined as a different way,

$$R(i) = \ln\left[\frac{RR(i-1)}{RR(i)}\right]. \tag{4}$$

Follow the similar procedure as mentioned above, $N_-(i)$, σ_-, and R_- can be obtained. Therefore, the methodology for evaluation of parasympathetic and sympathetic tone is established. In order to describe the activity of these two autonomic tone rapidly modulated in response to the epsiodes of SA as well as the periods of normal

breathing, the dynamic index S is introduced as

$$S(i) \equiv \frac{N_+(i) - N_-(i)}{N_+(i) + N_-(i)}. \quad (5)$$

where the maximum and minimum value of S is 1 and -1, respectively. If S fluctuates without large volatility, it means that both parasympathetic and sympathetic activities are comparable in the n-beat window. On the contrary, parasympathetic (sympathetic) tone would be absolutely dominant if S can be up to 1 (-1).

Finally, it shall be noted that the 5-beat window size as well as largest 40% fluctuations were considered in this study. The detailed explanations can be referred to Ref. [21].

References

[1] Andreas S, Schultz R, Werner GS, Kreuzer H. Prevalence of obstructive sleep apnea in patients with coronary disease. Coron Artery Dis 1996;7:541–5.
[2] Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease. J Am Coll Cardiol 2008;52:686–717.
[3] Kasai T, Flores JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. Circulation 2012;126:1495–510.
[4] Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004;79:1036–46.
[5] Jaffe LM, Kjekshus J, Gottlieb SS. Importance and management of chronic sleep apnoea in cardiology. Eur Heart J 2013;34:809–15.
[6] Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol 2009;54:375–85.
[7] Gami AS, Pressman G, Caples SM, et al. Association between atrial fibrillation and obstructive sleep apnea. Circulation 2004;110:364–7.
[8] Ghias M, Scherlag BJ, Lu Z, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. J Am Coll Cardiol 2009;54:2075–83.
[9] Kapa S, Javaheri S, Somers VK. Obstructive sleep apnea and arrhythmias. Sleep Med Clin 2007;2:575–81.
[10] Leung RS, Floras JS, Lorenzl-Filho G, et al. Influence of Cheyne–Stokes respiration on cardiovascular oscillations in heart failure. Am J Respir Crit Care Med 2003;167:1534–9.
[11] Shiau YH. Nonlinear measures on heart rate variability: a clinical tool or not? Auton Neurosci Basic Clin 2010;152:119–20.
[12] Goldberger AL, Amaral LAN, Glass L, et al. PhysioBank, PhysioToolkit, and PhysioNet : components of a new research resource for complex physiologic signals. Circulation 2000;101:e215–20.
[13] Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome: mechanisms, and usefulness of 24 h electrocardiography as a screening technique. Lancet 1984;1:126–31.
[14] Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 1994;90:1826–31.
[15] Stemper B, Hilz MJ, Rauhut U, Neundorfer B. Evaluation of cold face test bradycardia by means of spectral analysis. Clin Auton Res 2002;12:78–83.
[16] Ishikawa H, Matsuhima M, Nagashima M, Osuga A. Screening of children with arrhythmias for arrhythmia development during diving and swimming: face immersion as a substitute for diving and exercise stress testing as a substitute for swimming. Jpn Circ J 1992;56:881–90.
[17] Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. Circulation 2008;118:863–71.
[18] Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm 2013;10:331–7.
[19] Chen PS, Tan AY. Autonomic nerve activity and atrial fibrillation. Heart Rhythm 2007;4:S61–4.
[20] Penzel T, Kantelhardt JW, Grote L, Peter JH, Bunde A. Comparison of detrended fluctuation analysis and spectral analysis for heart rate variability in sleep and sleep apnea. IEEE Trans Biomed Eng 2003;50:1143–51.
[21] Shiau YH, Sie JH, Li SP. Detecting sleep apnea by volatility clustering of heart rate variability. Int J Cardiol 2013;168(2):1638–40.

0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2013.06.115

Circulating microRNAs as potential biomarkers for the early diagnosis of acute myocardial infarction: Promises and challenges

Feng Huang [a], Jian-Ping Huang [b], Rui-Xing Yin [a,*], Jin-Zhen Wu [a]

[a] Department of Cardiology, Institute of Cardiovascular Diseases, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi, China
[b] Alibaba Business College, Hangzhou Normal University, Hangzhou 310036, China

ARTICLE INFO

Article history:
Received 24 May 2013
Accepted 30 June 2013
Available online 17 July 2013

Keywords:
Acute myocardial infarction
Circulating microRNAs
Biomarkers
Early diagnosis

We read with great interest the letter of Lippi et al., who recently performed a meta-analysis of different circulating microRNAs (miRs), e.g. miR-1, -133, -208, -499 and -663b, describing their sensitivity and specificity in diagnosis of acute myocardial infarction (AMI) [1]. In fact, the increased cell-free miRs may not only be a product of plasma membrane disruption following cell death, but also a consequence of an active release from living cells exposed to ischemic condition [2], thereby it can be hypothesized that circulating cardiac miRs may be earlier biomarkers of myocardial necrosis.

A rapid and efficient assessment of AMI is essential because of the reduced mortality rate and prognostic benefit following timely interventions. Nevertheless, early diagnostic evaluation of patients suspected of having AMI remains a challenge, especially when electrocardiogram (ECG) is nondiagnostic. Currently, definitive diagnosis of AMI is mainly based on the elevated biomarkers of damaged cardiomyocytes, cardiac troponin T and I (cTnT and cTnI) or creatinine kinase-MB isoenzyme (CK-MB) if cTn is unavailable, in the context of clinical and ECG findings [3]. A new generation of more sensitive troponin assays with improved accuracy in the early diagnosis of AMI is also now available [4,5]. Unfortunately, these circulating biomarkers would not increase to a detectable level until 2 h after acute coronary occlusion [5,6]; moreover, their sensitivity were far from sufficient in the early hours, which makes them less suitable for the rapid and accurate evaluation of AMI. Subsequently, several biomarkers for quick detection of myocardial injury have been proposed, among which myoglobin, heart-type fatty acid-binding protein and ischemia modified albumin are the most promising candidates [6,7]. But they have limitation in clinical practice, because these biomarkers require supplementation with some other analyses such as troponins to support their value. Similarly, a significant release of mitochondrial DNA can be observed in plasma within 1 h after AMI both in human and

* Corresponding author. Tel.: +86 771 5326125; fax: +86 771 5353342.
E-mail address: yinruixing@163.com (R.-X. Yin).