



The history, hotspots, and trends of electrocardiogram

Xiang-Lin YANG^{1,2*}, Guo-Zhen LIU^{3*}, Yun-Hai TONG¹, Hong YAN², Zhi XU², Qi CHEN⁴,
Xiang LIU¹, Hong-Hao ZHANG³, Hong-Bo WANG⁵, Shao-Hua TAN¹

¹Key Laboratory of Machine Perception (Ministry of Education), School of Electronics Engineering and Computer Science, Peking University, Beijing, China

²State Key Laboratory of Space Medicine Fundamentals and Application, China Astronaut Research and Training Center, Beijing, China

³Institute for Medical Humanities, Peking University Health Science Center, Beijing, China

⁴Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China

⁵PKU Healthcare IT Co., Ltd., Beijing, China

Abstract

The electrocardiogram (ECG) has broad applications in clinical diagnosis and prognosis of cardiovascular disease. Many researchers have contributed to its progressive development. To commemorate those pioneers, and to better study and promote the use of ECG, we reviewed and present here a systematic introduction about the history, hotspots, and trends of ECG. In the historical part, information including the invention, improvement, and extensive applications of ECG, such as in long QT syndrome (LQTS), angina, and myocardial infarction (MI), are chronologically presented. New technologies and applications from the 1990s are also introduced. In the second part, we use the bibliometric analysis method to analyze the hotspots in the field of ECG-related research. By using total citations and year-specific total citations as our main criteria, four key hotspots in ECG-related research were identified from 11 articles, including atrial fibrillation, LQTS, angina and MI, and heart rate variability. Recent studies in those four areas are also reported. In the final part, we discuss the future trends concerning ECG-related research. The authors believe that improvement of the ECG instrumentation, big data mining for ECG, and the accuracy of diagnosis and application will be areas of continuous concern.

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1 Introduction

The electrocardiogram (ECG) has played an important role in the understanding of cardiovascular diseases. It has broad applications in the clinical diagnosis and prognosis of cardiovascular diseases, as well as in health assessment, biomedical recognition, fatigue study, and other areas.^[1–4] The extensive research on ECG has made a great contribution to the advancements in cardiology,^[5,6] and, consequently, many articles on ECG have been published. As the number and quality of these articles are increasing every

year,^[7] it is difficult to keep abreast of hotspots and trends of ECG. To address this issue, Yang, *et al.*^[8] in 2012 presented a systemic description and analysis of the characteristics and hotspots from highly cited ECG-related articles by using the bibliometric analysis method in searching the Science Citation Index Expanded database; unfortunately, few details were available then. To compensate for the lack of details in the article by Yang, *et al.*^[8] and the new hotspots appearing in 2013, we will recall, in this paper, the history of ECG development and give more details about the hotspots in 2013 by using the bibliometric method, as well as discuss the future trends.

2 History

With more than 100 years of development, the history of ECG has been complicated and unorganized. To better understand the development and application of ECG, we divided its history into three chronological periods: invention, extensive application, and further development.

*The first two authors contributed equally to this manuscript.

Correspondence to: Xiang-Lin YANG, PhD, School of Electronics Engineering and Computer Science, Peking University, Beijing, China; Yun-Hai TONG, School of Electronics Engineering and Computer Science, Peking University, Beijing, China. E-mails: yangxianglin@pku.edu.cn (YANG XL); yhtong@pku.edu.cn (TONG YH).

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2.1 The invention of ECG: from bioelectricity to electrophysiology

The observation of natural electrical phenomena, such as the electrical discharge of cramp fish and thunder, has a long history. In 1781, Galvani observed, while dissecting a frog, that electric stimulation of frog nerves could cause muscle contraction, which he called “animal electricity.” Galvani’s discovery for the first time revealed the biological basis of electrophysiology.^[9]

The history of ECG could be traced back from the discovery of the electric activity of heart muscle by Köllicker and Müller in 1856. Later, the first ECG of a human being was recorded in 1869 or 1870 with a siphon instrument by Muirhead in London.^[5] In 1901, Einthoven made a breakthrough in ECG technology with his invention of the string galvanometer, a device that could accurately measure ECG signals. In 1906, he proposed the clinical use of ECG and compiled a wealth of descriptive information about ECG patterns and arrhythmias.^[6] He also invented the three leads and thus established the uniformity of the recording process, for which he won the Nobel Prize in 1924.^[6]

2.2 Extensive application: ECG as an important tool for diagnosis

With the popularity of ECG in medical practice, a number of diseases, such as arrhythmia and ischemia, were subsequently recognized and understood, which greatly aided in the treatment of these conditions.

In 1930, Wolff, Parkinson, and White reported on 11 young patients with paroxysms of tachycardia, or atrial fibrillation (AF) that had a functional bundle branch block, and an abnormally short PR interval on ECG during sinus rhythm.^[10] This was subsequently described as Wolff-Parkinson-White syndrome, or pre-excitation syndrome.^[11,12] Although the possibility of the existence of atrioventricular accessory pathways was first raised by Stanley Kent in 1913,^[13] it was not until 1933 that the mechanism of Wolff-Parkinson-White syndrome was confirmed by Holzmänn and Scherf.^[14]

In 1948, Kalter and Schwartz reviewed clinical ECGs from 6,059 patients and found five cases of macroscopically visible T-wave alternans (TWA), a frequency of 0.08%.^[15,16] Probably because of the very low incidence of visible TWA, it remained nothing more than an ECG curiosity for many decades until microscopic TWA was first reported in 1982.^[15,17] However, TWA could be dated from the pioneering observations by Hering in 1908,^[15,18] and shortly thereafter, it was recognized that TWA could occur in normal hearts as a result of marked acceleration of heart rate, and also in the impaired or intoxicated myocardium as ob-

served by Thomas Lewis.^[15,19]

In 1955, AF was first proposed as a common arrhythmia by Fraser,^[20] and was confirmed to have implications in the management of future stroke risk.^[21] In 1957, long QT syndrome (LQTS) was first described by Jervell in four children with deafness who experienced sudden cardiac death and recurrent syncope, and were found to have QT prolongation on their ECGs,^[22] which was subsequently used as the criterion for the diagnosis of LQTS.^[23] In 1959, Prinzmetal first described a variant angina pectoris condition that manifested as ST segment elevation rather than typical angina with ST segment depression.^[24]

In 1960, Smirk and Palmer highlighted the risk of sudden death from ventricular fibrillation, particularly when a ventricular premature beat occurred at the same time as a T wave, which was called an R-on-T ventricular premature beat.^[25] In 1966, *torsades de pointes* (TdP) was first described by Dessertenne, which is a special type of ventricular tachycardia presenting as polymorphic ventricular tachycardia, with a characteristic illusion of the twisting of the QRS complex around the isoelectric baseline.^[26] In 1967, the ECG characteristics of a common disease of sick sinus syndrome (SSS), named sinus node dysfunction (SND), was first proposed by Lown.^[27]

2.3 Further development: new instruments and new applications

In 1957, Norman Holter invented the dynamic ECG (DCG), also named Holter ECG. This portable device enables the continuous monitoring of various electrical activities of the cardiovascular system for >24 h, contributing to the analysis of arrhythmias and the determination of the site of myocardial ischemia. In recent years, with the development of new technologies, innovations in ECG technology are continuously being made, such as the invention of the 4-dimensional (4-D) ECG and remote ECG monitor.

Besides ECG devices, new diagnostic theories on the basis of ECG have also been proposed. In 1989, Brugada syndrome was first observed in the ECG among survivors of cardiac arrest;^[28] yet, it was not until 1992 that it was recognized by the Brugada brothers as a distinct clinical entity characterized by abnormal ECG findings, causing sudden death due to idiopathic ventricular fibrillation in the heart.^[29] In 1996, resting ECG was first applied by Voukiklaris to examine coronary heart disease and cardiovascular diseases,^[30] although the first report of coronary thrombosis could be dated back to 1901 by Krehl.^[31] In 1999, short QT syndrome (SQTS) was discovered as an inheritable primary electrical disease of the heart that showed an unusually short QT interval (225 ms).^[32]

3 Review of the hotspots in the most highly cited articles

The highly cited articles may reveal the research hotspots and trends by themselves,^[8,33] yet bibliometric methods using total citations (TC-Year) and total citations of that year (C-Year) are more efficient in identifying the hotspots in ECG-related research. TC-Year represents the total count of citations since the article was published to the end of a specific year,^[2] reflecting the overall performance and future trends,^[8,33] whereas C-Year represents the total number of citations of the article in a specific year,^[2] describing the characteristics and hotspots during that year.^[34] As presented in the article of Yang,^[8] four subject categories were identified as hotspots by TC-2012 and C-2012: AF,^[35] LQTS,^[36-38] angina and MI,^[39,40] and risk factor analysis and health evaluation.^[41]

To keep up with the hotspots in 2013, we used TC-2013 and C-2013 to analyze the highly cited ECG publications in the Web of Science database from Thomson Reuters (updated on April 20, 2014). More details about the bibliometric analysis method can be found by referring to the article of Yang.^[8] By the end of 2013, some 36,562 articles with the keywords “electrocardiogram” or “electrocardiography”

or “electrocardiology” in document titles, abstracts, or article keywords were found in the database, and 935 articles were identified as highly cited articles (TC-2013 \geq 100). We separately chose the top 10 articles ranked by TC-2013 (TC-2013 $>$ 950) and top 11 articles ranked by C-2013 (C-2013 $>$ 100); thus, 16 articles were selected for the five articles recurring under both criteria.^[35,36,39] Five articles were excluded because of low citations by recent publications and the other 11 were reviewed for the analysis of hotspots.^[42] Details of the articles are shown in Table 1 and 2, and the citation trends of these articles are shown in Figure 1 to 3. Eventually, four hotspots were discovered: AF,^[35] LQTS,^[36-38] angina and MI,^[39,40] and heart rate variability (HRV).^[41]

The first hotspot is AF, discovered in the paper by Haissaguerre.^[35] By examining the relationship of pulmonary veins and AF, this article demonstrated the role of pulmonary veins as an important source of ectopic beats, which initiates frequent paroxysms of AF. Since AF includes a wide variety of atrial activity, the assessment of the characteristics of this arrhythmia with ECG is highly important. Many researchers are conducting studies on how to diagnose AF more accurately. Leva, *et al.*^[43] presented a new

Table 1. Characteristics of the top 11 highly cited ECG-related articles (TC-2013 > 950).

Rank (TC-2013)	Rank (C-2013)	Rank (TC/Y)	Article Title	First Author	Published year	Published Journal
1(3,033)	2(203)	2(178.41)	Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins	Haissaguerre	1998	New England Journal of Medicine
2(2,802)	20(80)	66(29.49)	An analysis of the time-relations of electrocardiograms.	Bazett	1920	Heart
3(2,766)	6(128)	1(212.77)	Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol	Dahlof	2002	Lancet
4(1,452)	19(81)	11(60.5)	Health inequalities among British civil-servants - the Whitehall-II study	Marmot	1991	Lancet
5(1,389)	18(82)	12(60.39)	Right bundle-branch block, persistent ST segment elevation and sudden cardiac death - a distinct clinical and electrocardiographic syndrome - a multicenter report	Brugada	1992	Journal of the American College of Cardiology
6(1,140)	9(123)	13(60)	Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.	No authors listed	1996	European Heart Journal
7(1,135)	11(103)	6(75.67)	The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making	Antman	2000	Journal of the American Medical Association
8(1,097)	111(24)	143(19.95)	The electrocardiogram in population studies - a classification system	Blackburn	1960	Circulation
9(1,058)	1(225)	3(132.25)	Universal definition of myocardial infarction	Thygesen	2007	Circulation
10(999)	61(35)	27(43.43)	Frequency-domain measures of heart period variability and mortality after myocardial-infarction	Bigger	1992	Circulation

C-2013: the total number of citations of the article in 2013; ECG: electrocardiogram; TC-2013: total count of citations since the article was published to the end of 2013; TC/Y: total count of citations since the article was published to the end of the specific year.

Table 2. Characteristics of the top 11 highly cited ECG-related articles (C-2013 > 100).

Rank (C-2013)	Rank (TC-2013)	Rank (TC/Y)	Article Title	Author	Published year	Published Journal
1(225)	9(1,058)	3(132.25)	Universal definition of myocardial infarction	Thygesen	2007	Circulation
2(203)	1(3,033)	2(178.41)	Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins	Haissaguerre	1998	New England Journal of Medicine
3(137)	14(823)	8(63.31)	Multi-ethnic study of atherosclerosis: objectives and design	Bild	2002	American Journal of Epidemiology
4(133)	419(159)	18(53)	Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease	De Bruyne	2012	New England Journal of Medicine
5(132)	11(977)	17(54.28)	Heart rate variability: origins, methods, and interpretive caveats	Berntson	1997	Psychophysiology
6(128)	3(2,766)	1(212.77)	Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol	Dahlof	2002	Lancet
6(128)	17(788)	4(98.5)	Universal definition of myocardial infarction	Thygesen	2007	European Heart Journal
8(125)	80(387)	7(64.5)	A randomized, double-Blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction	Hare	2009	Journal of the American College of Cardiology
9(123)	6(1,140)	13(60)	Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.	No authors listed	1996	European Heart Journal
10(119)	13(883)	15(58.87)	The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease	Hagan	2000	Journal of the American Medical Association
11(103)	7(1,135)	6(75.67)	The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making	Antman	2000	Journal of the American Medical Association

C-2013: the total number of citations of the article in 2013; ECG: electrocardiogram; TC-2013: total count of citations since the article was published to the end of 2013; TC/Y: total count of citations since the article was published to the end of the specific year.

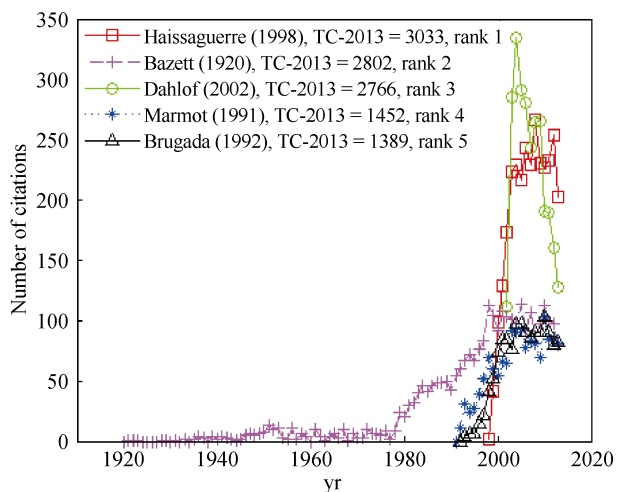


Figure 1. Citation life cycles of the top five highly cited ECG-related articles (TC-2013 > 950). TC-2013: total count of citations since the article was published to the end of 2013.

statistical method to deal with the identification of AF events based on the order identification of the ARIMA model. This model enables identifying the starting and end-

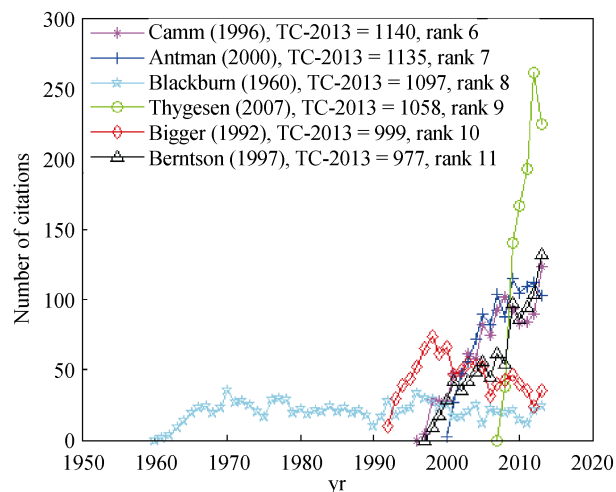


Figure 2. Citation life cycles of the top five highly cited ECG-related articles (TC-2013 > 950). TC-2013: total count of citations since the article was published to the end of 2013.

ing points of an AF event even when AF comes before, or after irregular heartbeat time slots.^[43] Gonna, *et al.*^[44] recorded the 12-lead ECG of 77 patients with AF and found that

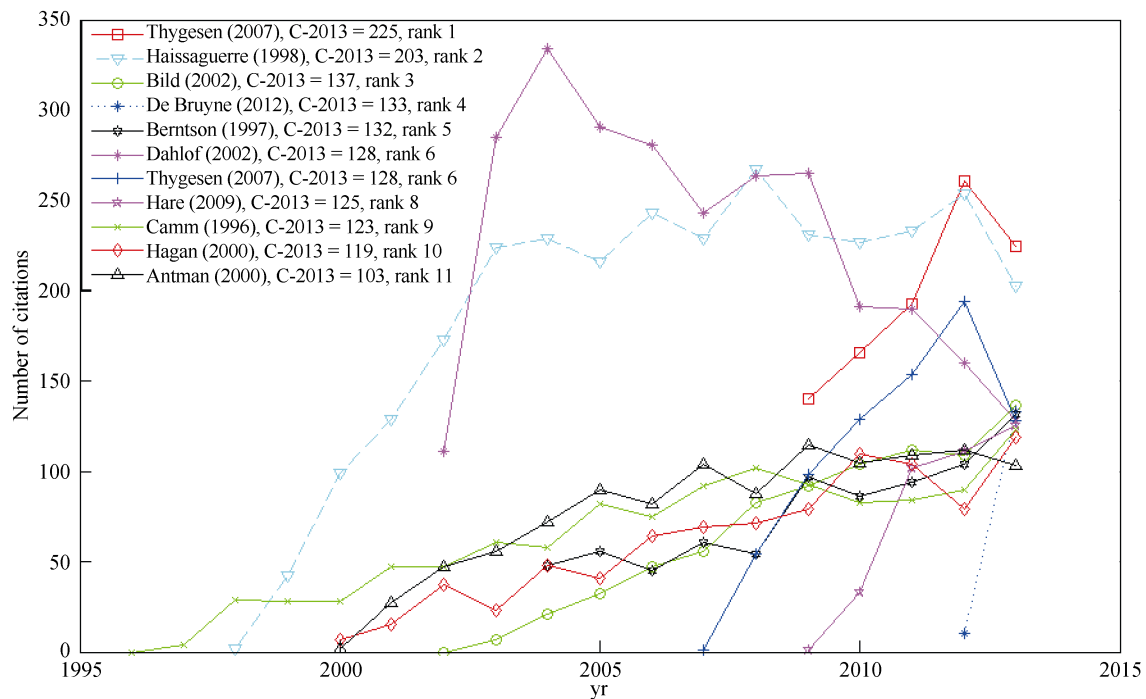


Figure 3. Citation life cycles of the top 11 highly cited ECG-related articles (C-2013 > 95). C-2013: total number of citations of the article in 2013.

prolonged P-wave duration measured by ECG predicts recurrent AF within one month.

The second hotspot is LQTS, discovered in the papers by Bazett^[36] and Moretti, *et al.*^[37] The QT interval corrected by Bazett's formula was highly cited by articles on the measurements of QT correction,^[45] SQTS, diagnosis of transient left ventricular apical ballooning with prolonged QTc interval,^[46] prevention of sudden cardiac death,^[47] assessment of the risk of arrhythmic events in patients with coronary artery disease by QT dispersion,^[48] and especially the LQTS, which received the most attention. Moretti differentiated induced pluripotent stem (iPS) cells from patients with Type 1 LQTS into cardiomyocytes, and observed prolonged action potentials in the ventricular and atrial cells. By using this model, they uncovered a dominant-negative trafficking defect associated with the particular mutation that causes this variant of LQTS. Further investigation of LQTS iPS cell-derived cardiomyocytes showed an increased susceptibility to catecholamine-induced tachyarrhythmia of these cells, and compounds that exacerbate the condition (including isoprenaline) were identified. Treatment of these cardiomyocytes with β -adrenergic receptor blockers attenuated the long QT phenotype.^[37,49] Besides Type 1 LQTS, Type 2 LQTS has also been modeled in cardiomyocytes by Itzhaki.^[50] In addition, unknown sex factors also modulate QT duration and arrhythmic events, with preliminary evidence of gene-specific differences in age-sex modulation. Re-

searchers found that among LQTS patients, the risk of cardiac events was higher in males until puberty and higher in females during adulthood. The same pattern was evident among LQT1 gene carriers.^[51]

The third hotspot is angina and MI discovered in the papers by Antman, *et al.*^[39] Hare, *et al.*^[40] and Hall, *et al.*^[52] In the article by Antman, the TIMI risk score was proposed as an effective grading system for risk factor analysis and risk evaluation in patients with unstable angina, or unstable angina/non-ST elevation MI (UA/NSTEMI).^[39] Hare's article demonstrates the safety provisional efficacy of intravenous allogeneic human mesenchymal stem cells through a double-blind, placebo-controlled, dose-ranging (0.5, 1.6, and 5 million cells/kg) trial.^[40] Hall & Barth investigated the definition of MI from aspects of ECG detection, diagnosis of imaging techniques, and clinical investigations.^[52] Apart from the frequently investigated biomarkers at the genetic level, ECG is also studied both in the clinical diagnosis and prevention of MI. In the field of diagnosis, Sarafoff made a comparison between ECG and magnetic resonance imaging (MRI), and found that electrocardiographic STEMI/NSTEMI classification characterizes the total size of MI more than the transmural extent, as assessed by cardiac magnetic resonance imaging (CMR).^[53] In the field of prevention, Naruse demonstrated that the presence of early repolarization increased the risk of ventricular fibrillation occurrences within 48 h after the AMI onset.^[54] The com-

bination of ECG with CMR, or biomarkers in diagnosis and prevention is also being widely investigated.^[55,56]

The fourth hotspot is HRV, reported in the papers by Berntson, *et al.*^[57] and Malik, *et al.*^[58]. Berntson examined the physiological origins and mechanisms of HRV, and provided guidelines, suggestions, and prospects for future research of HRV.^[57] Malik, *et al.*^[58] summarized the measurement, clinical application, and future possibilities of HRV, and suggested large prospective longitudinal studies to determine the sensitivity, specificity, and predictive value of HRV. As an important marker of autonomic nervous system activity, HRV has been proven to be predictive of future health-related events;^[59] thus, the investigation of the relation between HRV and disease prediction is also popular. Tang conducted a large-scale, population-based, cross-sectional study that proved the high sensitivity and specificity of short-term HRV to reflect typical HRV patterns for healthy subjects.^[59] In recent years, many studies were conducted to investigate the correlation of the changes in HRV and body conditions, such as in resting,^[60,61] depression,^[62] or even during the induction and decay of heat acclimation.^[63]

4 Future trends

The future trends of ECG-related research are mainly classified into three categories: improved ECG instrumentation, big data mining for ECG, and accuracy of ECG diagnosis and application.

The first trend of ECG-related research is the design and improvement of the ECG instrumentation. As an important indicator for health assessment and disease diagnosis, ECG is widely applied in the burgeoning market of telemedicine, e-healthcare, and home health delivery. This will provide new opportunities for ECG instrument machine development and research, and will change the model of health care. One focus of attention lies in the design and implementation of a wearable ECG monitor. The year 2013 witnessed the progress prosperity of wearable devices, and it is believed that smartphones have become a new tool for self-diagnosis and monitoring for outpatients, making it possible for real-time monitoring, self-diagnosis, and remote diagnosis.^[64] Many researchers are committed to the design of wearable, wireless ECG monitoring systems that integrate novel capacitive ECG sensors, some of which have demonstrated a 99% correlation with conventional electrodes.^[65] Meanwhile, the mobile ECG measurement and analysis system based on a mobile phone is being investigated, of which some researchers have given preliminary evidence of its capability and feasibility.^[66] As can be predicted, home ECG monitor equipment, or a remote diagnosis system with

the function of miniaturization, portability, security, wireless capability, and Web access to a qualified physician, will be the challenge and focus for subsequent investigations.^[66] Another example of a new device is 4-D ECG, consisting of a new display in which the vector loop is rotated and scanned along a timed axis to overcome the shortcomings of vectorcardiography (VCG).^[67] Furthermore, devices for comprehensive diagnosis combining ECG with other diagnostic indicators, such as MRI, functional MRI, ultrasound, CT scanner, oxygen saturation, blood pressure, EEG, pulse oximetry, and breathing and hemodynamic parameters, are currently being, or in the future will be, the subjects of more attention.

Another trend is big data mining for ECG. In an era of large amounts of big data, both the availability of large data and the computational power to handle them have increased tremendously; thus, big data mining of ECG for heart disease diagnosis and treatment shows strong promise and potential. Currently, besides the World's four authoritative ECG databases (international standard ECG databases)—the MIT-BIH Arrhythmia database, AHA (American Heart Association) ECG Arrhythmia Database, European Society of Cardiology Database, and European ST-T ECG Database, massive volumes of ECG data have also been recorded in hospitals, research institutions, and homes since the wide application of ECG. Therefore, ECG is generally considered an example of clinical "big data" characterized by volume, velocity, and variety, referred to as the "3Vs of big data."^[68] Jayapandian proposed a Web-based electrophysiological data management framework called Cloudwave to fill the gap between current approaches and the challenges in the growing volume of data, and the need for supporting multicenter collaborative studies with real-time and interactive access.^[68] Sahoo, *et al.*^[69] used the Cloudwave platform to analyze the large volume of ECG data for seizure detection and for correlating the effects of antiepileptic drugs on the autonomic nervous system.^[69] In addition, McGregor used the large volume of ECG data and derived signals, such as heart and other physiological data, to discover new patterns in neonatal intensive care, which has great potential to support a new wave of clinical discovery and identify trends or leads to earlier detection and prevention of a wide range of life-threatening medical conditions.^[70]

The third trend of ECG research is the accuracy of diagnosis and application in evidence-based medicine. As many miscellaneous and newly onset cardiovascular diseases lack a gold standard for diagnosis, new indicators, patterns, and methods, especially new algorithms, developed and verified by big data analysis and computer technology, will provide

great help in accurate and timely diagnosis and treatment. Song used the frequency features of RR interval series and the QRS barycenter sequence, both new indicators, to diagnosis myocardial ischemia.^[71] Li reported their preliminary studies on a novel navigation algorithm of ECG morphology for localizing the site of origin (SO) of ventricular arrhythmias (VA) and found some valuable discoveries, which offers a possibility for clinicians to localize the target area of SO of VA in real time with ECG.^[72] Another recent study focused on the origins of focal atrial tachycardias in adjacent structures, which is very difficult to differentiate by using ECG alone. The study found that clinical features and Holter monitoring can give additional information for accurately differentiating the focal atrial tachycardias originating from the adjacent structures.^[73]

5 Discussions

Thanks to the successive contributions from our predecessors, there has been a historic leap in ECG research. From Einthoven's invention of ECG to its extensive application and further development, ECG has gone through a long history. The highly cited articles can show the research hotspots by themselves,^[20] yet, bibliometric methods using TC-2013 and C-2013 were more efficient in identifying the hotspots in ECG-related research. In our review, four hotspots were discovered: AF^[35], LQTS,^[36–38] angina and MI,^[39,40] and HRV.^[41] For future prospects, three trends of ECG-related research are proposed and analyzed: improved ECG instrumentation, big data mining for ECG, and accuracy of ECG diagnosis and application. In retrospect, we can learn from the experience of our predecessors, and have a better understanding of the basic theories and methods of ECG. Looking forward, exploration in the field of ECG will hopefully never end, and ECG, as a classic and "old" technique, will continue to advance and to expand our understanding of cardiovascular diseases.

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