Review of Ex Vivo Cardiac Electrical Mapping and Intelligent Labeling of Atrial Fibrillation Substrates*

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Abstract: With the development of computer hardware and the growth of clinical database, tremendous progress has been made in the application of deep learning to electrocardiographic data, which provides new ideas for the ex vivo cardiac electrical mapping of atrial fibrillation (AF) substrates. The AF mechanism and current status of AF substrate research are first summarized. Then, the advantages and limitations of cardiac electrophysiological mapping techniques are analyzed. Finally, the application of deep learning to electrocardiogram (ECG) data is reviewed, the problems with the ex vivo intelligent labeling of an AF substrate and the possible solutions are discussed, an outlook on future development is provided.

Keywords: Catheter ablation, atrial fibrillation substrate, three-dimensional mapping, deep learning

1 Introduction

Atrial fibrillation (AF) is the most common persistent arrhythmia phenomenon, accounting for one-third of arrhythmia disorders, and is associated with stroke and heart failure [1]. According to the Framingham heart study, the prevalence of AF is approximately 25% in men and women aged 40 years and older, and the incidence of AF increases rapidly with age [2]. The risk of stroke is five times higher in those with AF compared to those without AF, and the one-year disability rate of stroke caused by AF is more than 50% [3].

AF ablation surgery is an important treatment for AF. It isolates the trigger and improves the atrial substrate, which requires three-dimensional (3D) atrial electro-anatomical information. Thus, 3D cardiac electrophysiological mapping is the first step in the current ablation procedures. The enhancement of cardiac electrophysiologic mapping technology has become the key to shortening the duration and improving the success rate of AF catheter ablation procedures [4]. Ex vivo cardiac 3D electrical mapping technology is non-invasive and simple, and also allows the simultaneous recording of atrial electrical signals. The key to improving the accuracy of the mapping is the extraction of more precise characteristics of the AF substrate.

In recent years, with the development of computer hardware and the growth of clinical databases, tremendous progress has been made in the application of deep learning to image recognition. When applied to clinical images, deep learning has even surpassed the accuracy of manually detecting cancer in cervical images [5]. Research on the processing of electrocardiogram (ECG) data using deep learning techniques has exploded [6] and has achieved comparable or even higher accuracy than traditional methods based on manually designed feature selection. For example, Avendi et al. [7] successfully segmented the left ventricle on a small magnetic resonance imaging (MRI) dataset of 45 patients using a combination of convolutional neural networks (CNNs), stacked encoders, and deformable models. Bai et al. [8] trained CNNs using a large MRI dataset provided by the UK Biobank database for ventricular assessment

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and atrial segmentation and achieved an accuracy comparable to that of manual methods. Ex vivo cardiac electrical mapping for AF is used to simultaneously record ECG activity with more than 200 electrodes, which requires the accurate identification of atrial electrical signals, and deep learning may be an effective tool [9].

This paper analyzes and reviews the development status of cardiac electrophysiological mapping technology based on the current status of AF mechanism and AF substrate research, summarizes the application of deep learning to ECG data, and discusses the problems with cardiac electrophysiological mapping and possible solutions for these. It also reviews the application of deep learning to extract AF substrate features, and provides an outlook on its application in AF ablation surgery and AF mechanism research.

2 Current research on atrial fibrillation

AF is characterized and defined by very rapid and uncoordinated atrial activity. Conceptually, the initiation and maintenance of AF are related to the trigger and AF substrate. The trigger is a rapidly firing lesion that serves as the initiator of the arrhythmia, and its maintenance generally requires the AF substrate, i.e., the electrophysiological, mechanical, and anatomical features of the atria that maintain AF. The mechanisms of AF induction and maintenance are complex and influenced by both the trigger and AF substrate [10]. The development of the substrate usually includes both electrical and structural elements of atrial remodeling [11]. The key conceptual framework for the induction and maintenance of AF is summarized in Fig. 1 [11].

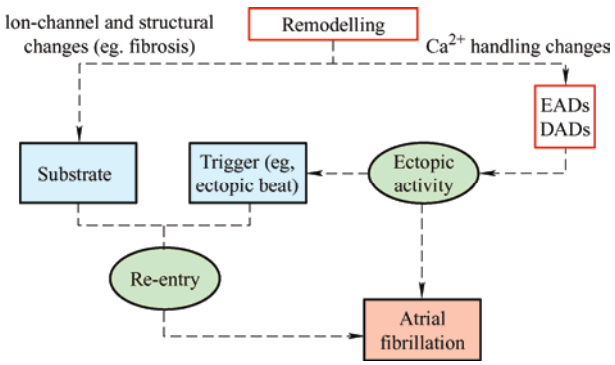

Fig. 1 Key concepts of AF induction and maintenance [11]

2.1 Atrial fibrillation mechanism

An ectopic lesion or excitation in the pulmonary vein (PV) and non-pulmonary vein region can produce a fast pulse and thus induce AF [12]. The trigger lesions predominantly occur in the PV, with 94% of AF trigger lesions located in the PV muscle sleeve [13].

The mechanisms of AF maintenance are extremely diverse, but there are three main widely accepted mechanistic hypotheses.

(1) Localized source excitation [14-15]: During AF triggering, some areas of abnormal excitation radiate high-frequency pulses in all directions, whereas the surrounding tissues cannot produce 1:1 conduction with the driving lesion because of the anisotropy and inhomogeneity of the conduction, which leads to AF.

(2) Multiple sub-wave reentry hypothesis [16]: When AF occurs, multiple sub-waves generated by high-frequency spiral waves in the atria collide, fuse, and annihilate each other to form new waves.

(3) Rotor theory [17-19]: In AF, there may be multiple spiral waves, but only one dominant reentry loop, which exists in the form of a rotor, and the dominant rotor and sub-rotors collide during propagation to form AF.

Among these, localized source excitation is the theoretical basis of the dominant AF treatment technique, radiofrequency ablation, which is currently one of the main strategies for the surgical treatment of AF.

2.2 Atrial fibrillation substrate

In a narrow sense, the AF substrate refers clinically to lesions located in the atria that are associated with the development and maintenance of AF [20]. Generally, the low-voltage area (LVA) and complex fractionated atrial electrogram (CFAE) are the predominant AF substrate.

Most studies define the cut-off value of the LVA of the left atrium (LA) as a bipolar voltage of 0.5 mV measured during sinus rhythm [21]. The LVA represents focal scarring of the atrial myocardium, and apoptosis

of cardiomyocytes, reflecting the heterogeneity of the intra-atrial structures. The CFAE is defined as an atrial intracardiac electrogram consisting of two or more transitions. In patients with AF combined with left atrial enlargement, the effective atrial expiration period becomes shorter, and the atrial wavelength is also shortened. To some extent, this affects the discrete and conduction velocity of atrial waves, which may be related to the presence of a wide range of CFAEs in the atria [22]. CFAE ablation in patients with persistent AF can improve the success rate of the ablation [23].

A wider definition of the AF substrate also includes the above-mentioned trigger lesions, which are subsequently referred to collectively as the AF substrate in this paper. The identification and localization of the AF substrate is an important step in understanding the mechanism of AF, which guides the development of surgical strategies and directly affects the duration and success rate of AF ablation.

3 Current research on cardiac mapping

From 1971, when Huang [24] combined the programmed electrical stimulation technique and intracavitary electrogram recording technique, the diagnosis of arrhythmia entered the era of cardiac electrophysiological detection from the era of electrocardiography. In 1976, Allessie proposed a 10-electrode unipolar labeling system, which successfully acquired the atrial velocity re-entry signal and was another breakthrough in cardiac electrophysiology. In 1980, Boinean developed a 72-electrode bipolar labeling system, which can use a computer to process and graph the ECG signal, and the accuracy and standardization of the labeling system has been further improved. The history of electrophysiological mapping technology is shown in Fig. 2.

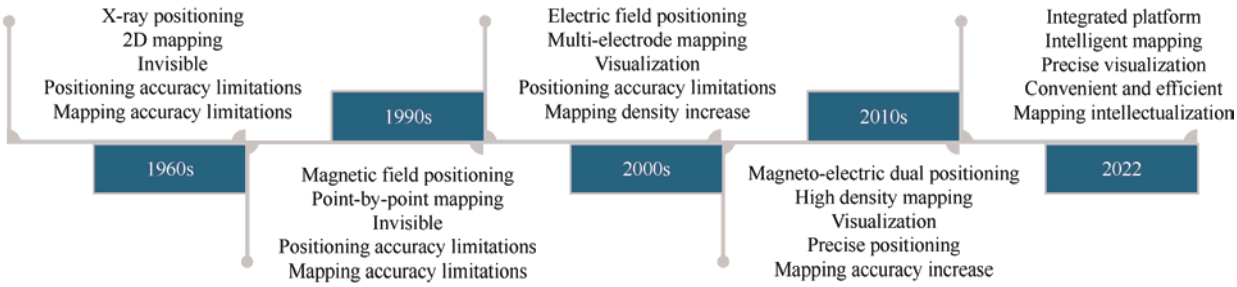

Fig. 2 History of the development of electrophysiological mapping technology

3.1 Three-dimensional mapping system

Currently, AF procedures are performed worldwide with 3D electrophysiological mapping systems. The most commonly used 3D mapping systems are the CARTO 3 (Biosense Webster) and EnSite Precision (Abbott) systems.

The EnSite Precision system provides a high degree of automation, flexibility, and accuracy to aid in the diagnosis of various cardiac arrhythmias. The CARTO 3 system is an advanced 3D cardiac mapping system that simultaneously acquires local anatomical locations and ECG signals. Cardiac mappings acquired with these systems are shown in Figs. 3 [25] and 4 [26], respectively.

Other systems include the HeartFlow Analysis system, which applies deep learning AI algorithms to standard coronary CT angiography, the CardioNXT 3D navigation system, which incorporates dynamic references, and Columbus, which is a domestic 3D mapping system.

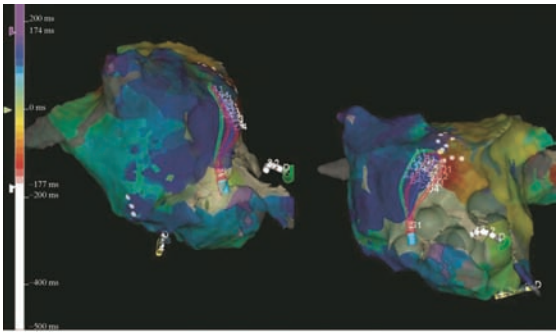

Fig. 3 Cardiac mapping with EnSite Precision system [25]

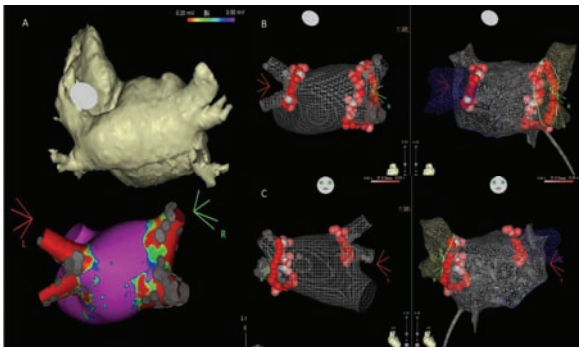

Fig. 4 Cardiac mapping with CARTO 3 system [26]

3.2 Cardiac mapping technology

Cardiac mapping technology has gradually been improved, mainly in the areas of endocardial mapping, epicardial mapping, optical mapping, and body surface mapping.

Endocardial mapping records the endocardial excitation at each site through a multi-stage catheter, analyzes the sequence of excitations, precisely locates the origin of abnormal electrophysiological activity, and allows radiofrequency ablation to be performed based on the navigation system. Epicardial mapping is an important technique to study the electrophysiological mechanisms of AF. It covers the entire external surface of the heart with a high density of detection electrodes, simultaneously detecting and recording the electrical activity, and producing data analysis maps through a computerized signal processing system. Endocardial and epicardial mapping are both invasive examinations and cannot be used for the long-term and continuous measurement of atrial electrical signals. They have limitations such as multiple blind areas, poor measurement accuracy, and a lack of intra-chamber electrogram information.

Optical mapping combines voltage-sensitive dyes with digital imaging techniques to convert the acquired optical signal into a data signal, along with signal processing to record the cellular membrane potential. Hansen et al. [27] observed rotors during AF with optical mapping, confirming that reentry is an important mechanism of AF maintenance. Zhao et al. [28] conducted high-resolution panoramic epicardial optical mapping of an explanted human atria combined with contrast-enhancement MRI images to analyze the cardiac wall thickness, myofiber orientations, and transmural fibrosis. The 3D human heart-specific atrial computer model that was constructed could be used to study the induction and maintenance mechanism of AF and guide ablation strategies. Optical mapping can only be conducted in explanted hearts because of the phototoxicity of the dye and mechanical motion of the heart. Therefore, it is limited to animal experiments.

Body surface potential mapping is based on the different potential distributions formed on the surface of the human body by the electrical activity of cardiomyocytes. It is a non-invasive method to visually reflect the internal electrophysiological condition of the heart. The development of electrocardiographic imaging (ECGI) [29] has led to further improvements in the accuracy and synchronization of the ECG signal measured by body surface mapping. Ehrlich et al. [30] used the CardioInsight ECVUETM system, applied a 252 electrode vest to a patient's torso, and obtained high-resolution images of the heart and vest electrodes using chest computed tomography (CT) with the mapping system shown in Fig. 5 [30]. Ramanathan et al. [31] used a multi-electrode vest to record ECG signals at 224 body sites and then reconstructed the potential, electrograms, and isochronous maps of the heart surface using geometric information obtained by CT and mathematical algorithms, the process of which is shown in Fig. 6 [31]. Although body surface mapping has limitations such as the reliance on CT to construct electro-anatomical maps, inability to guide ablation in real time (only preoperative labeling can be performed), and decrease in accuracy under far-field wave interference, it truly achieves non-invasive long-term continuous labeling of atrial electrical signals in patients with AF. Thus, it has received increasing attention from practitioners and has promise for clinical applications.

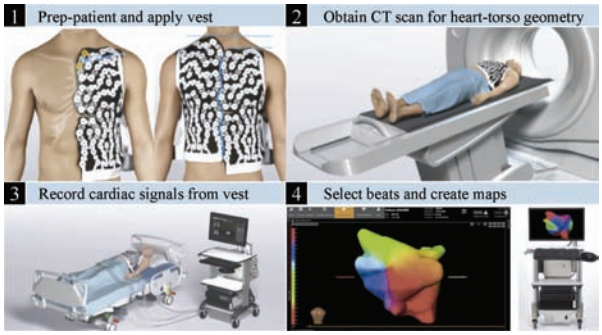

Fig. 5 CardioInsight mapping system [30]

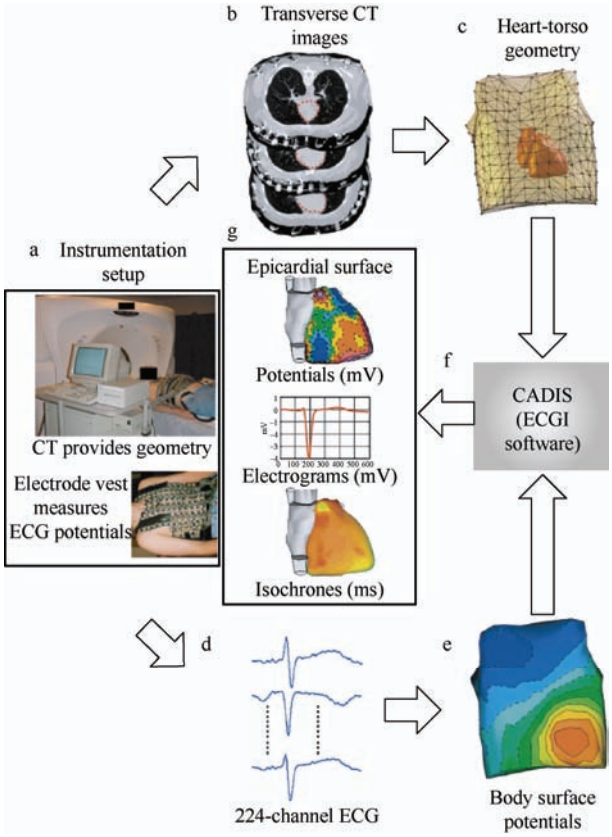

Fig. 6 Block diagram of the ECG imaging [31]

4 Deep learning in ECG data analysis

Cardiac electrical mapping techniques for AF are achieved by recognizing the typical pathological electrical activity of the AF substrate. Thus, the key to improving the mapping accuracy is a more accurate extraction of the characteristics of the AF substrate.

Deep learning methods focus on learning the internal structure of the data. With the progressive research on the use of deep learning techniques for diagnosing atrial electrophysiology and the development of image recognition techniques, the automatic learning of features and classification models based on deep learning has become a research hotspot [32]. The current applications of deep learning in ECG data analysis mainly include AF detection, atrial segmentation, and in vivo AF labeling map analysis. Deep learning may be an effective tool for the ex vivo cardiac electrical mapping of AF, but its application in this field has not previously been reported.

4.1 Deep learning in atrial fibrillation detection

The theoretical basis of the intelligent AF detection algorithm is the absence of P-waves and absolute irregularity of the RR interval [33] in the AF rhythm ECG compared to the sinus rhythm ECG.

The most commonly used deep learning models mainly include the convolutional deep neural network (DNN), convolutional neural network (CNN), residual neural network (ResNet), support vector machines (SVM), recurrent neural network (RNN), densely connected convolutional recurrent neural network (DBRNN), bidirectional long-short term memory network (BLSTM), visual geometric group network (VGGNet), generative adversarial network (GAN), and bidirectional RNN with dilated CNN (BRDC). Tab. 1 summarizes the relevant information of some AF detection algorithms.

Tab. 1 Summary of research information related to AF detection algorithms

Authors	Database	Feature engineering	Model	Sensitivity (%)	Specificity (%)	Accuracy (%)
Hannun et al. [34]	91 232 single-lead ECGs from 53 549 patients	—[a]	DNN	86.10	94.10	—
Bao et al. [35]	Physinet/Cin C Challenges 2017 Database	Butterworth bandpass filters	CNN-BLSTM	—	—	86.00
Zhao et al. [36]	MIT-BIH AF Database	Series of f-waves instead of normal P-waves	ResNet	99.26	99.42	99.47
Wen et al. [37]	Database of physiological signals collected from 37 subjects by non-contact sensors	Wavelet transform and root mean square (RMS) filter	SVM	96.80	—	94.50
Dang et al. [38]	MIT-BIH AF Database	RR interval and heartbeat sequence	CNN-BLSTM	99.93	97.03	96.59
Deng et al. [39]	MIT-BIH AF Database	Time-domain features of ECG sequences, one-hot label	CNN	99.07	97.05	98.03
Limam et al. [40]	Physinet/Cin C Challenges 2017 Database	R-peak position in the signal and heart rate	CRNN-SVM	72.30	98.70	—
Liu et al. [41]	Physinet/Cin C Challenges 2017 Database	Short-term Fourier transform (STFT), Bayesian optimization	CNN-LSTM	84.00	91.00	90.00
Islam et al. [42]	Physinet/Cin C Challenges 2017 Database	Chebyshev type II filter, Pan-Tompkins normalization technique	GAN-BRDC	99.90	—	99.90

Note: [a] Unpublished.

Deep learning algorithms have shown excellent detection performance in AF detection. However, some studies have not fully escaped the limitations of feature extraction. For example, although Liu et al. [41] used a CNN as a classifier in their study, the short-time Fourier transform (STFT) and Bayesian optimization were still required to process ECG signals.

4.2 Deep learning in atrial segmentation

Gadolinium-enhanced magnetic resonance imaging (GE-MRI) has been widely used to study the extent of atrial fibrosis [43]. Recent studies suggest that the fingerprints of the atrial structure may be the key to studying the mechanisms of AF [27, 44].

Intelligent algorithms for fully automated atrial segmentation of the left atrium (LA) facilitate the accurate reconstruction and visualization of the atrial structures for clinical use. Some of the deep learning algorithms from the 2018 Atrial Segmentation Challenge are summarized in Tab. 2.

Tab. 2 Summary of the deep learning algorithm used in the 2018 atrial segmentation challenge

Authors	Summary	DC[a]	Model	Advantages/Limitations
Xia et al. [44]	2 networks (LA localization, LA segmentation), dice loss	93.2	2×3D U-Net	Good class imbalance management with best performance/high computational cost
Bian et al. [45]	ResNet101, dilated convolutional layers, pyramidal pooling, online hard example mining	92.6	2D Pyramid Network	Multi-scale representation/overfitting may be augmented by competitive training
Vesal et al. [46]	U-Net, dilated convolution, dice loss, cross-entropy loss	92.6	3D U-Net	Class imbalance management, cross-entropy loss/information loss of center cropping
Li et al. [47]	2 networks (3D U-Net for detection, HAANet for LA segmentation), dice loss	92.3	3D U-Net, HAANet[b]	Class imbalance management/Hierarchical mechanism for small gains
Puybareau et al. [48]	RGB 2D color images, VGG, multinomial loss function	92.3	VGG-Net	Short training time, pseudo-spatial representation/not multi-view or 3D view
Chen et al. [49]	Cross-entropy loss and sigmoid loss	92.1	2D U-Net	Short training time (2D), novel data augmentation
Jia et al. [50]	2 networks (LA localization, LA segmentation), contour loss	90.7	3D U-Net	Contour loss/high computational cost
Liu et al. [51]	2 networks (U-Net and FCN for LA segmentation, dice loss	90.3	2D U-Net, FCN	Short training time (2D)/native U-Net
Borra et al. [52]	Ostu algorithm, adding LA and PV segmentation, dice loss	89.8	3D U-Net	Ostu algorithm/high computational cost

Note: [a] Dice coefficient; [b] Hierarchical aggregation network.

The dual cascade U-Net model proposed by Xia et al. [44] achieved the highest performance in the challenge. Its entire framework consisted of two networks, the first network roughly located the atrial center based on a low-resolution down-sampled version of the input and divided a fixed-size region covering the atrial cavity, ignoring other irrelevant pixels to reduce the memory consumption. Then, the second network precisely segmented the atrial cavity from the cropped subregion obtained in the previous step. The algorithm was simple and clean, proving that classical networks such as U-Net are still very competitive in the field of image segmentation. Moreover, the results of the above algorithm showed that for 3D medical images, if the anisotropy differences in the three dimensions are not very large, a 3D input is better than a 2D input.

4.3 Deep learning in labeling map analysis

Recent studies have applied deep learning to in vivo AF 3D labeling map analysis. McGillivray et al. [53] used machine learning for a single-cell model of AF to localize local re-entrant drivers based on directly recorded ECGs. Zolotarev et al. [54] trained a deep learning model that could effectively classify the ECG image features of re-entrant drivers measured in vivo with an accuracy of 80%-90%, depending on the size of the multi-electrode mapping array. Alhusseini et al. [55] trained a CNN model with an accuracy of 95% for re-entrant driver detection. Ríos-Muñoz et al. [56] automatically identified rotors in an endocardial electrogram (EGM) using a CRNN with an accuracy of 80.04%. Liao et al. [57] applied a deep learning model to an original EGM signal and detected the

focal source as a potential ablation target with sensitivity, specificity, and accuracy values of 90%, 81.9%, and 82.5%, respectively. As shown, deep learning has decent performance in in vivo labeling map analysis, and its accuracy depends on the resolution of the labeling map and precision of the labeling electrodes.

5 Discussion of application problems

5.1 ECG signal noise artifact reduction

Acquiring atrial electrophysiological activity through ex vivo measurements and reducing the interference during measurements are central to improving the recognition of AF substrate dynamics. There are many sources of interference in an ECG signal, which are mainly divided into four categories: power frequency interference, baseline drift, electromyogram (EMG) interference, and motion artifacts. Noise artifacts during ECG signal measurement can greatly affect the quality of the measured signal and even make it impossible to assess cardiac activity. The typical frequencies and amplitudes of noise artifacts are shown in Tab. 3.

Tab. 3 Typical frequencies and amplitudes of noise artifacts

Noise artifact	Frequency/Hz	Amplitude ratio(%)
Power frequency interference	50	50-200
Baseline drift	0.05-2	15
EMG interference	5-1 000	10
Motion artifact	1-10	100-500

Power frequency interference is generated by the electromagnetic field formed by conventional AC currents of 50-60 Hz. Infinite impulse response (IIR) filters, finite impulse response (FIR) filters, and their variants such as high-Q comb filters are commonly used to remove power frequency interference from ECG signals [58].

Baseline drift is low-frequency noise caused mainly by breathing, body movements, scars on the skin, depletion of the electrode conducting gel, or poor contact between the electrodes and skin due to sweating. Baseline drift is usually removed using high-pass filters, band-pass filters, digital filters (IIR, FIR), adaptive filters, blind source separation (BSS) [59], and wavelet transforms.

Electromyographic interference is electrical activity generated by skeletal muscles and is sensitive to frequencies similar to the signal to be measured, making it difficult to avoid signal contamination during ECG recording. Dynamic filters [60] and threshold-based wavelet transforms [61] are usually used to suppress or remove EMG interference on the basis of maintaining the original geometric characteristics of the ECG signal.

Compared to the other three noise artifacts, motion artifacts have larger variability in their waveform characteristics and cannot be filtered out using simple low-pass, high-pass, and other band filters. Some researchers [62] have proposed a solution to discriminate the type of motion based on acceleration signals and eliminate noise in the time period of the motion artifacts, which can effectively improve the quality of ECG signals.

5.2 Other problems

At present, an ex vivo cardiac mapping system seems to be effective for cardiac mapping in patients with a short history (within 1 year) of paroxysmal AF, but its application in other challenging cases, such as patients with a long history of persistent AF and patients with short AF cycles, remains to be explored. The validation of ex vivo labeling results using the in vivo electrical labeling techniques that are currently applied in a clinical setting, and a comparison of the two images to analyze the correlation between the signals, are the keys to optimizing the deep learning model and improving the accuracy of AF substrate labeling, which is also an urgent problem in the current research on the ex vivo labeling of AF.

In addition, because of the individual variability of ECG signals, the apparently anonymous ECG data may be a threat to the personal privacy of users [63]. The privacy and security issues with the database are also aspects that need to be improved, such as by the use of differentiated privacy protection schemes [64].

6 Conclusions

AF ablation surgery is the most effective treatment for AF rhythm, but there are currently problems with the

long duration of the procedure and its low success rate, which could be overcome by ex vivo electrophysiological labeling technology. Cardiac 3D electrophysiological labeling is the basis of AF ablation surgery and currently the first step in such surgery. Although the key technology is well established, it still has some limitations.

(1) Invasive catheter operation of the mapping electrode increases the total procedure time (average mapping time is approximately 40 minutes), X-ray exposure, and procedural complications.

(2) The operation of the mapping electrode requires experience in catheterization.

(3) The limited density of electro-anatomical information obtained by point-by-point mapping results in incomplete information collection and affects the surgical strategy.

With the progressive research on the diagnosis of atrial electrophysiological diseases using deep learning technology and the combination of big data mining and computer model optimization, the ability to automatically diagnose cardiac diseases and intelligently label the AF substrate will continue to improve.

This paper summarized the development mechanism of AF and the electrophysiological characteristics of typical AF substrates such as the trigger, low-voltage area, and complex fractionated atrial electrogram. In addition, the advantages and limitations of cardiac electrophysiological mapping techniques were discussed. A comprehensive review of the current status of domestic and international research in the fields of ECG-based AF detection, MRI-based atrial segmentation, and in vivo AF 3D mapping analysis was presented, and the key problems that need to be explored in the future were summarized. Further research on ex vivo cardiac labeling technology and algorithms for the intelligent detection of the AF substrate, along with their application, will promote the improvement and development of AF ablation surgery and research on the AF mechanism and other related subjects.

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