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Neuromodulation for Atrial Fibrillation Control

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Conflict of Interest
Dr. Oh is a co-holder of patents for an arrhythmia treatment device using auditory stimulation and electrode design for auditory nerve stimulation with rights assigned to Seoul National University.

AUTHOR'S SUMMARY

Trigger and functional substrate are related to the tone of autonomic nervous system, and the role of the autonomic nerve is more significant in paroxysmal atrial fibrillation (AF) compared to non-paroxysmal AF. Neuromodulation targets can be divided into efferent and afferent pathways. Various approaches are currently under investigation. If a technique is less invasive and has an acceptable level of efficacy, it may be widely utilized.

ABSTRACT

Trigger and functional substrate are related to the tone of autonomic nervous system, and the role of the autonomic nerve is more significant in paroxysmal atrial fibrillation (AF) compared to non-paroxysmal AF. We have several options for neuromodulation to help to manage patients with AF. Neuromodulation targets can be divided into efferent and afferent pathways. On the efferent side, block would be an intuitive approach. However, permanent block is hard to achieve due to completeness of the procedure and reinnervation issues. Temporary block such as botulinum toxin injection into ganglionated plexi would be a possible option for post-cardiac surgery AF. Low-level subthreshold stimulation could also prevent AF, but the invasiveness of the procedure is the barrier for the general use. On the afferent side, block is also an option. Various renal denervation approaches are currently under investigation. Auditory vagus nerve stimulation is one of the representative low-level afferent stimulation methods. This technique is noninvasive and easy to apply, so it has the potential to be widely utilized if its efficacy is confirmed.

Keywords: Autonomic nerves; Atrial fibrillation; Denervation; Stimulation; Ganglionated plexus

INTRODUCTION

Atrial fibrillation (AF) is a complex arrhythmia because the mechanism of AF has not been elucidated completely. The current treatment standards highlight the significance of the rhythm control strategy for AF.[1)2)] Trigger and substrate are main components of

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Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

pathophysiology of arrhythmia including AF, and these can be influenced by the autonomic nerve system. Hence, the autonomic nerve control could be a possible tool for managing AF.

ANATOMICAL CONSIDERATION

Sympathetic and parasympathetic innervations of the heart are very rich and asymmetric. The atria are innervated by parasympathetic and sympathetic nerves, whereas the ventricles are predominantly innervated by sympathetic nerves. The postganglionic parasympathetic neurons are primarily located in epicardial fat pads. The postganglionic sympathetic nerves originate from the extracardiac sites, the stellate ganglia and the sympathetic trunks (**Figure 1**), and they travel along the great arteries.

Interestingly, parasympathetic and sympathetic nerve fibers are not completely separated from each other but are commonly mixed and have interconnections between them.[3] In the mediastinum, the cardiac branch of the vagus nerves is located in front of the trachea and the primary bronchus, posterior to the superior vena cava. The main branch of the vagus nerve goes to the abdomen along with the esophagus. Mediastinal nerves cannot penetrate the pericardium directly, but they go into the heart along with great vessels. That is the so-called heart hilum, the main port of entry: space between the aorta and the pulmonary artery, and space between the left superior pulmonary vein (PV) and the right superior PV or the superior vena cava.[4]

Cardiac ganglionated plexus (GPs) in the epicardial fat pads have sympathetic nerve fibers as well as parasympathetic nerves; therefore, the fat pads play a role as an autonomic nerve station. Canine hearts have well-known 3 epicardial fat pads: the right PV fat pad (so-called sinus nodal fat pad), the inferior vena cava-left atrium fat pad (so-called atrioventricular nodal fat pad) and the third fat pad (superior vena cava-aorta fat pad).[5] In the human heart, the

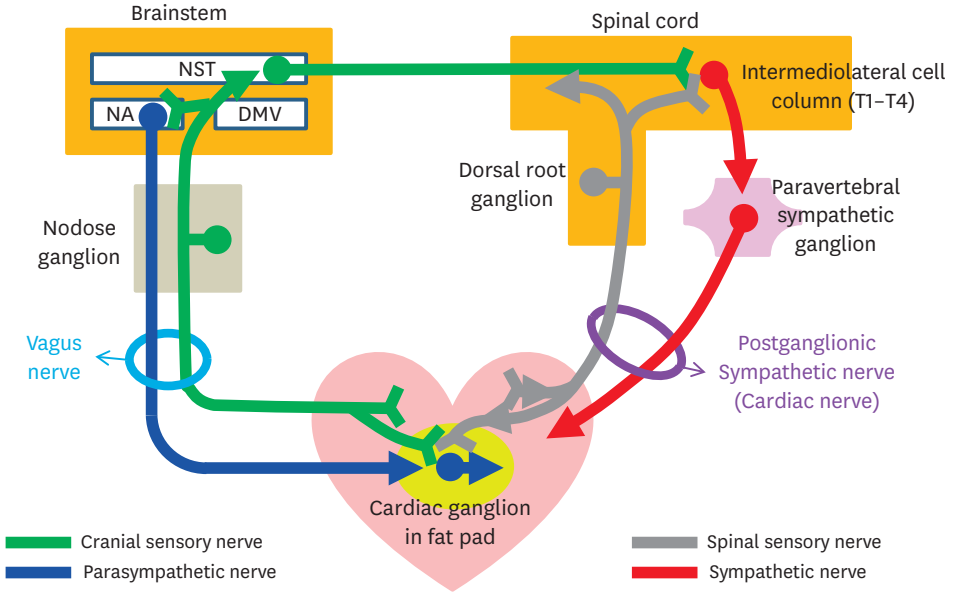

Figure 1. Autonomic innervation of the heart.
DMV = dorsal motor nucleus of the vagus; NA = nucleus ambiguus; NST = nucleus of the solitary tract.

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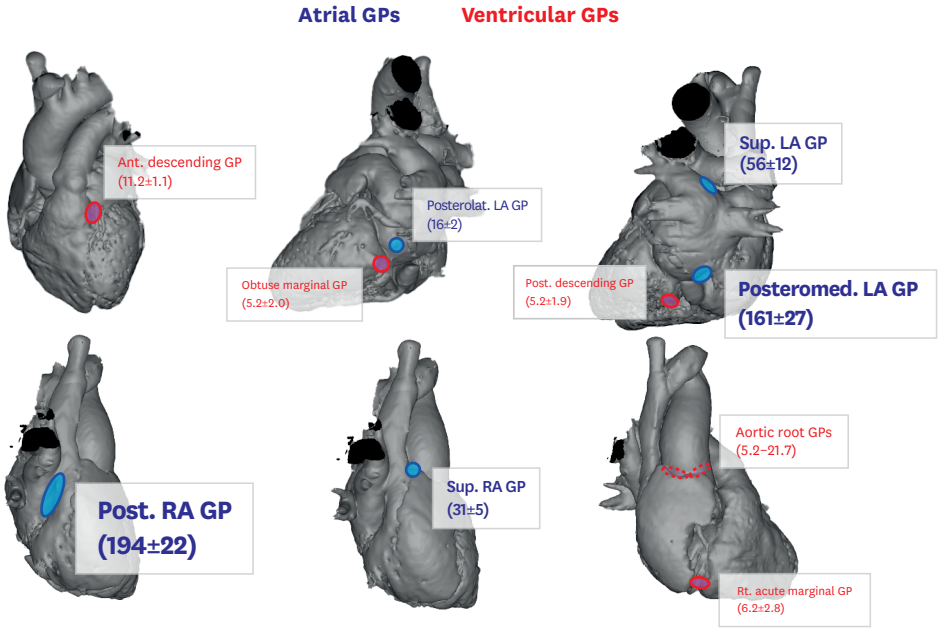

Figure 2. Major human cardiac ganglionated plexi: locations and number of ganglia. Numbers indicate number of ganglia per heart based on Armour's work.[6] Blue and red color indicates atrial and ventricular GPs, respectively. Ganglionated plexus with large number of ganglia is expressed with large font size.
GP = ganglionated plexi; LA = left atrium; RA = right atrium.

existence and location of the epicardial fat pads also seem to be similar to those in the canine heart. This has been demonstrated in several anatomical studies.[4][6] **Figure 2** shows major human cardiac GPs based on Armour's work.[6] The most prominent GPs are the posterior right atrial GP (also known as anterior right GP) and posteromedial left atrial GP (also known as inferior right GP), as in canine hearts. Autonomic nerve terminals are distributed widely in both the atria and ventricles, but the atria are much innervated than the ventricles.[7]

Acetylcholine is the main neurotransmitter in the efferent system, but glutamate is important in the afferent system.[8] In addition to these, neurons using several types of possible neurotransmitters such as nitric oxide, vasoactive intestinal peptide, calcitonin gene-related peptide, substance P, and so on, were found in atrial cardiac GPs.[9]

ELECTROPHYSIOLOGICAL CONSIDERATION

Both sympathetic and parasympathetic stimulation can shorten the atrial effective refractory period, action potential duration, and reentrant wavelength.[10] In addition, parasympathetic activation also affects refractory period duration and refractoriness heterogeneity, that are not much affected by sympathetic activation.[10] The initiation and maintenance of AF are highly dependent on these electrophysiological characteristics based on arrhythmia mechanisms. Sympathetic stimulation affects automaticity, early and late afterdepolarization, and reentry. Parasympathetic activation affects early afterdepolarization and reentry (**Figure 3**). Conclusively, trigger and functional substrate are related to the tone of the autonomic nervous system, and they play a major role in paroxysmal AF (PAF); therefore, the autonomic nerve is more important in the pathophysiology of PAF than non-PAF.

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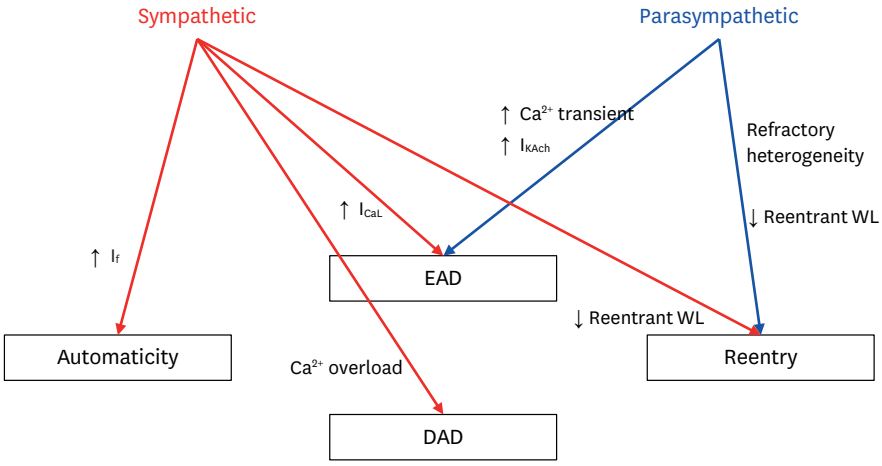

Figure 3. Autonomic contribution to arrhythmia mechanisms.
DAD = delayed afterdepolarization; EAD = early afterdepolarization; WL = wavelength.

The importance of autonomic nerves had been demonstrated in the transplanted heart. Heart transplantation procedures involve anastomosis of great vessels and the posterior wall of the left atrium. These are ports of the autonomic nerve, the so-called heart hilum as previously mentioned in the Anatomical Consideration section. Therefore, transplanted heart is a totally denervated heart. The Cleveland Clinic researchers analyzed the incidence of AF in patients who underwent heart transplantation vs. coronary artery bypass grafting (CABG). The CABG group was age- and sex-matched low-risk patients. They found that no heart transplantation was the most powerful predictor of post-cardiac surgery AF.[11] These results may be associated with total denervation as well as the complete isolation of PVs, that is the key procedure of AF ablation. The Texas Heart Institute also published data on the incidence of post-cardiac surgery AF after heart transplantation, that was only 5.4%.[12] That is quite a low level because the general incidence of post-cardiac surgery AF is known to be around 30%.

EVALUATION OF AUTONOMIC NERVE ACTIVITY

Then, how can we evaluate the nerve activity? One of the most widely used methods is heart rate variability (HRV) analysis that is an indirect measurement and noninvasive method. A representative study on autonomic tone and AF occurrence was investigated by Bettoni and Zimmermann[13] In the frequency-domain analyses, a significant increase in high-frequency components, an indicator of parasympathetic activation, was observed before PAF, together with a progressive decrease in low-frequency components, an indicator of sympathetic activation. The low-to-high frequency ratio thus showed a linear increase until 10 minutes before PAF, followed by a sharp decrease immediately before PAF. This suggests a primary increase in sympathetic tone followed by a marked modulation toward vagal predominance.[13] HRV is a convenient tool, but it can only provide indirect information. The gold standard of evaluation of autonomic tone must be nerve activity recording using electrodes, although this is an invasive method. It is also technically challenging because of the low signal-to-noise ratio. This limitation can be resolved by various signal processing methods such as cubic smoothing spline.[14]

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The arrhythmogenicity of intrinsic cardiac nerve activity (ICNA) was demonstrated in animal models.[15] The investigators recorded nerve activity in the superior left GP, left stellate ganglion, left vagus nerve, and ligament of Marshall in a chronic rapid pacing model for creating persistent AF, and they found an association between ICNA and atrial tachyarrhythmias.[15]

NERVE ACTIVITY CONTROL FOR ATRIAL FIBRILLATION: NEUROMODULATION

We can modulate autonomic nerve activity at several levels in the efferent and afferent pathways (**Figure 4**).

Efferent block

Among several targets for neuromodulation, efferent nerve block is an intuitive approach. The key component is denervation that is possible at many levels of the autonomic nervous system, but the higher the target level we block, the bigger the side effects are. Therefore, the most peripheral part, the cardiac GP, would be the most suitable target for denervation. The acute effects of GP ablation on AF inducibility were demonstrated by Professor Zipes' lab and the Oklahoma group.[5][16] They found that AF was not inducible after ablation of both the right PV fat pad and the inferior vena cava-left atrium fat pad. Then, one of the main questions is which GPs would be the appropriate targets for AF control. Cardiac surgeons evaluated surgical fat pad excision and post-cardiac surgery AF to determine which mechanism would be more complicated than simple PAF. Reported outcomes were variable. During the cardiac surgery, ventral cardiac denervation was performed by excising the fat pads around the superior vena cava, the aorta, and the main pulmonary artery. Melo et al.[17] reported that ventral cardiac denervation could reduce AF, but Alex and Guvendik[18] reported no effect. On the contrary, Cummings et al.[19] showed fat pad elimination paradoxically increased postop AF although their fat pad elimination was less invasive than ventral cardiac denervation. The problem with this approach is that the ventral fat pads have GPs for mainly ventricular innervation.

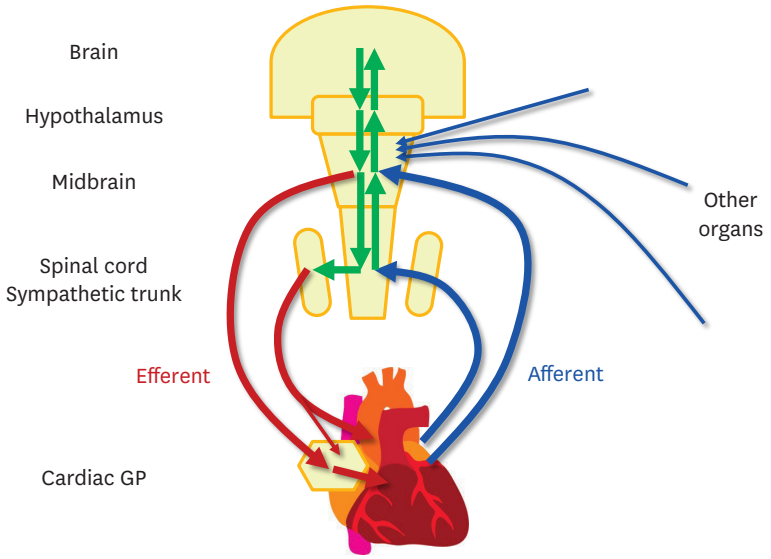

Figure 4. Targets of neuromodulation.
GP = ganglionated plexi.

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Then, the next question must be how atrial GPs innervate the atria. My lab used the retrograde neuronal tracer, cholera toxin subunit B (CTB), to evaluate the atrial innervation pattern of each GP. CTB has been used for neuroanatomical mapping, binds to GM1 ganglioside which is concentrated on the synaptic membrane of nerve cells, is transported along axonal pathways with a velocity of 102 mm/d, and cannot be transported trans-synaptically.[20)21)] In Experiment 1, CTB was injected into the atria to evaluate the GP-to-atrial connection. In Experiment 2, CTB was injected into the major GPs, including the ligament of Marshall, to evaluate the inter-GP connection. This study demonstrated that GPs project axons widely to both the same and opposite sides of the atria, and furthermore, there were numerous neuroanatomical interconnections among GPs.[22)] Therefore, we cannot achieve a complete efferent block by removing a number of GPs. Removal of all cardiac GPs should be performed for this goal, but it is technically difficult.

Next question: can we achieve permanent block by ablation? The answer seems to be "no." The long-term effects of fat pad ablation were investigated in an animal model.[23)] In this study, major epicardial GPs were ablated, but all denervation effects disappeared 4 weeks after the ablation. GP ablation has been adopted in the catheter ablation procedure for AF. However, GP ablation alone showed poor outcomes. GP ablation combined with PV isolation may be a possible therapeutic option. The possible mechanism would be reinnervation.[24-28)] In the case of heart transplantation, which results in total denervation of the heart, reinnervation of the sympathetic nerves occurs after one year.[29)] In addition, parasympathetic reinnervation seems to begin in the early period, less than one year, according to HRV data.[30)] The other mechanism would be increased end-organ sensitivity due to muscarinic receptor remodeling.[31-33)]

Furthermore, there is synaptic plasticity, which is the ability of neurons to alter their strength of communication at the synapse level. In the brain, the induction of long-term potentiation and long-term depression is dependent on the activation of N-methyl-D-aspartate (NMDA) type glutamate receptors.[34)] In the heart, synaptic plasticity within GP could contribute to the pathophysiology of arrhythmias such as AF.[35)] Shi et al.[36)] evaluated the effect of NMDA on AF in a rat model and found that NMDA treatment induced AF and increased atrial fibrosis, while the antagonist reduced its effect.

Therefore, a permanent efferent block seems impossible to achieve. Instead, a temporary block could be useful in some clinical situations such as post-cardiac surgery AF. Botulinum toxin blocks the exocytotic release of acetylcholine stored in synaptic vesicles and, as a result, blocks cholinergic neurotransmission temporarily. The effects of botulinum toxin injection in epicardial GP on AF were investigated in an animal model.[37)] Temporary suppression of vagally mediated AF for at least 1 week was achieved with botulinum toxin injection, and this effect might be associated with reduced dispersion of the effective refractory period. Based on the findings of this experiment, randomized clinical trials were performed and demonstrated that botulinum toxin injection suppressed post-cardiac surgery AF.[38-40)] However, Waldron et al.[41)] failed to detect significant effects.

Low level efferent stimulation

High-level efferent stimulation induces AF, but low-level, subthreshold stimulation can prevent AF. It was demonstrated by subthreshold stimulation of the cervical vagus nerve[42)] and the preganglionic branch of the vagus nerve[43)] in animal models. In humans, a randomized trial demonstrated the effect of subthreshold stimulation of the cardiac branch of the vagus nerve on postop AF.[44)] Low-level GP stimulation was also investigated

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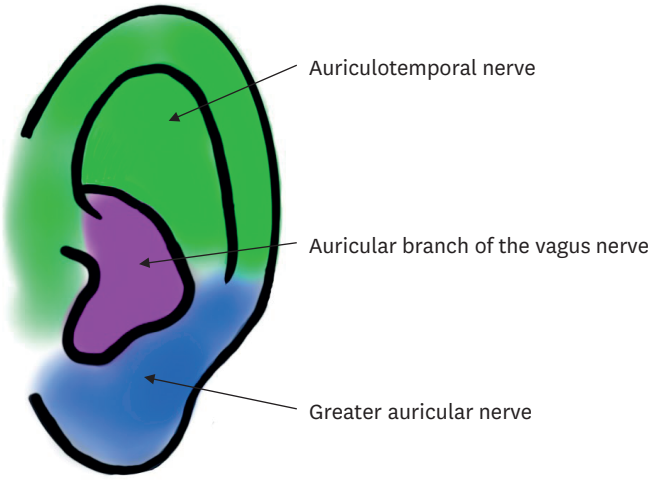

Figure 5. Cutaneous innervation of the ear. The distribution of these cutaneous nerves exhibits varying degrees of overlap.

and showed prevention of shortening of the effective refractory period in the rapid pacing model.[45] The major limitation of this approach is that it requires invasive procedures.

Afferent block

The most widely known method is catheter-based renal denervation which was originally developed for medically-intractable hypertension. The basic mechanism for AF can be explained by cardiorenal-neuraxial pathways.[46] Increased renal sympathetic tone may give an increased signal of autonomic tone to the heart, and as a result it may induce AF and even sudden death in high-risk patients. Therefore, renal denervation might inhibit them. One of the representative trials is ERADICATE-AF trial, in which patients were randomized into 2 groups: PV isolation with cryoballoon ablation vs. PV isolation with cryoballoon ablation plus renal denervation.[47] The renal denervation group showed a better outcome in this trial. One of the issues with catheter-based renal denervation would be incomplete denervation or reinnervation, as in GP ablation. Anatomically, overall 16% of nerve fibers were located at distances greater than 3 mm from the endoluminal surface of the renal artery.[48] These findings indicate that a substantial proportion of the sympathetic nerve fibers were located deeper in the peri-arterial soft tissue than in the depth of the lesion created by the conventional catheter-based renal sympathetic denervation system. A laparoscopic approach could overcome this barrier, and a pilot study has proven the anti-arrhythmic effect in a swine model.[49]

Low level afferent stimulation

Afferent nerve stimulation also has effects on autonomic control. Acupuncture may be a kind of afferent nerve stimulation. Lomuscio et al.[50] demonstrated that the acupuncture group showed a similar rate of AF recurrence to the amiodarone group after direct current cardioversion. Another representative example is auricular vagus nerve stimulation (AVNS). The auricular branch of the vagus nerve innervates the conchal bowl of the ear and external auditory canal (**Figure 5**). Arnold's reflex is a coughing reflex observed in many individuals when the external auditory canal is touched. Given the heterogeneity in the results of studies using functional magnetic resonance imaging, there is currently no clear consensus on the auricular sites, but it is reasonable to surmise that the concha and inner tragus are suitable locations for vagal modulation.[51]

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The Oklahoma group conducted a human pilot trial of transcutaneous AVNS using clip electrodes applied to tragus (cathode) and lobule (anode) to evaluate the acute effect on AF inducibility.[52] The investigators also conducted a chronic study, a randomized clinical trial called the TREAT-AF trial, in which they used tragus stimulation for 1 hour daily for 6 months and found that there was a significant 85% reduction in the median AF burden in the AVNS group relative to the sham group.[53]

CONCLUSION

We have several options for neuromodulation to help to manage patients with AF. Targets of neuromodulation are classified into the efferent and the afferent systems. On the efferent side, a block would be an intuitive approach. However, permanent block is hard to achieve due to the completeness of the procedure and reinnervation issues. A temporary block, such as botulinum toxin injection into the GP, would be a possible option for post-cardiac surgery AF. Low-level subthreshold stimulation could prevent AF, but the invasiveness of the procedure is a barrier to its general use. On the afferent side, block would also be considered. Currently, various renal denervation approaches are being investigated. Auditory vagus nerve stimulation is one of the representative low-level afferent stimulation methods. This is noninvasive and easy to apply, so it will have a chance to be utilized widely if its efficacy is proven. This type of treatment can be delivered by a wearable device that will be able to have an electrocardiogram (ECG) recording function. The recurrence of AF after treatment has been investigated using cardiac implantable electronic devices[54] and artificial-intelligence-driven ECG[55] as well as conventional ECG monitoring.[56] Furthermore, many types of wearable devices can take over the role of AF management and monitoring in the future.[57]

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