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Global Spotlights

Bioelectronic medicine and its applications in cardiology

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'When a man wanted to make a machine that would walk he created the wheel, which does not reflect a leg.' Guillame Apollinaire.

'Man has made many machines, complex and cunning, but which of them indeed rivals the workings of his heart?' Pablo Casals.

The history of bioelectronic medicine (BM) in cardiology is a tiara studded with emerald innovators, animated by impellent clinical needs. John 'Jack' Hopps, an electrical engineering working at the Radio and Electrical Engineering Division of the National Research Council in Ottawa, was recruited in 1949 by two cardiac surgeons in Toronto to make the heart beating again, while they were using hypothermia to make it stop during open-heart surgery.[1] By change, he discovered that this was indeed possible applying an electrical current to the heart by vacuum tubes and a small table radio powered by household current. Thanks to the advent of transistor circuitries allowing device miniaturization and to the development of transvenous catheter electrodes, the first pacemaker was implanted in 1958 to a Swedish engineer, Arne HW Larson at the age of 43 for complete heart block. He was then able to survive until the age of 86, though needing 26 pacemaker replacement procedures. This story perfectly summarizes the bright and dark sides of BM in cardiology, made of extraordinary advances, of electrical impulses, incessant research for device miniaturization, but also facing the drawbacks of intravenous catheters, limited battery duration, and unavoidable device replacement.

Thereafter, a similar experience was made by implantable cardioverted defibrillator (ICD) developer, Michel Mirowski,[2] who first tried to miniaturize and implant external defibrillator previously developed by Zoll, to minimize the risk of sudden cardiac death, as the one which killed his mentor and friend Henry Heller in Israel during a family dinner 2 weeks after the discovery that he was suffering from ventricular tachycardia. The idea of Mirowski was initially broadly rejected. Scepticism about the authenticity of data was spreading, up to propose that the dogs used in his experiments were trained to behave in a certain way using Pavlovian conditioning and leading authority on defibrillation, such as Bernard Lown and Paul Axelrod, to consider the development of ICD risky and potentially unethical due to the need of inducing ventricular fibrillation (VF) to test its efficacy.[3] They, notwithstanding, recognized that '*technological advance is so rapid that the man who says, it cannot be done, is frequently interrupted by someone who has done it*'.[3] Indeed, after 12 years from the original experiments, the first ICD was implanted in 1980 in three VF-related cardiac arrest patients. Since then, pacemakers and ICD technologies have met a continuous flow of innovation, up to the development and approval of either leadless or subcutaneous devices, limiting their complications and expanding therapeutic opportunities.[2] The discovery of these two devices has hence dramatically changed the face of cardiac care (*Figure 1*).

Another landmark step in the clinical implementation of BM in cardiology has been represented by the development of cardiac resynchronization therapy, using either a pacemaker (CRT-P) or a defibrillator (CRT-D), whose implantation is currently strongly recommended in patients with heart failure (HF) and ventricular dyssynchrony (mainly due to left bundle branch block), for their acknowledged effects on quality of life and mortality.[4] On the contrary, the potential usefulness of other devices such as cardiac contractility modulation, designed for HF patients unsuitable for CRT, and phrenic nerve stimulation, designed for patients with central apnoeas, is still matter of debate.[4]

In the eighties, following the propelling energy fostered by the study on the influences of the autonomic nervous system (ANS) on the heart, several other devices have been developed to act on the parasympathetic nervous system, either directly with vagal nerve stimulation (VNS) or interacting with the baroreflex, one of the autonomic reflex feedbacks. In facts, ANS being 'the wisdom of the body' plays

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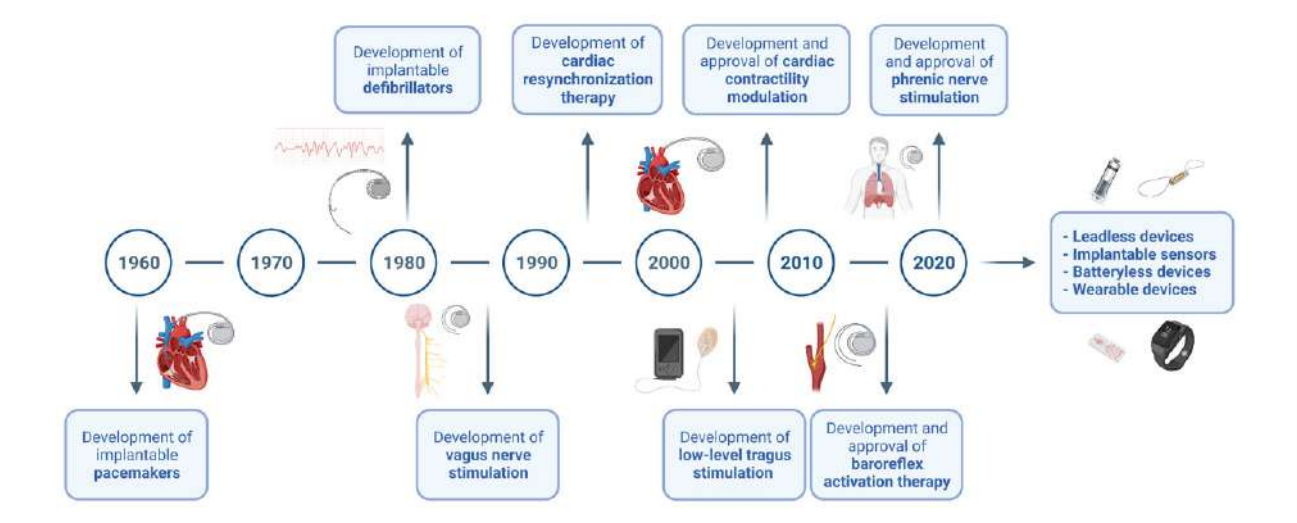

Figure 1 Bioelectronic medicine in cardiology: an endless tale. From the implantation of the first pacemaker in 1958, the last century has seen the development of various bioelectronic devices for patients with cardiovascular conditions. Most notably, implantable defibrillators and cardiac resynchronization therapy are nowadays broadly utilized, while vagus nerve stimulation has achieved less success in this field. In the last two decades, various devices have been developed and approved, while their clinical translation is still expected. Finally, the recently developed leadless and wearable devices, implantable sensors, and batteryless devices may change again the face of cardiovascular care in the next years. Created with BioRender.com.

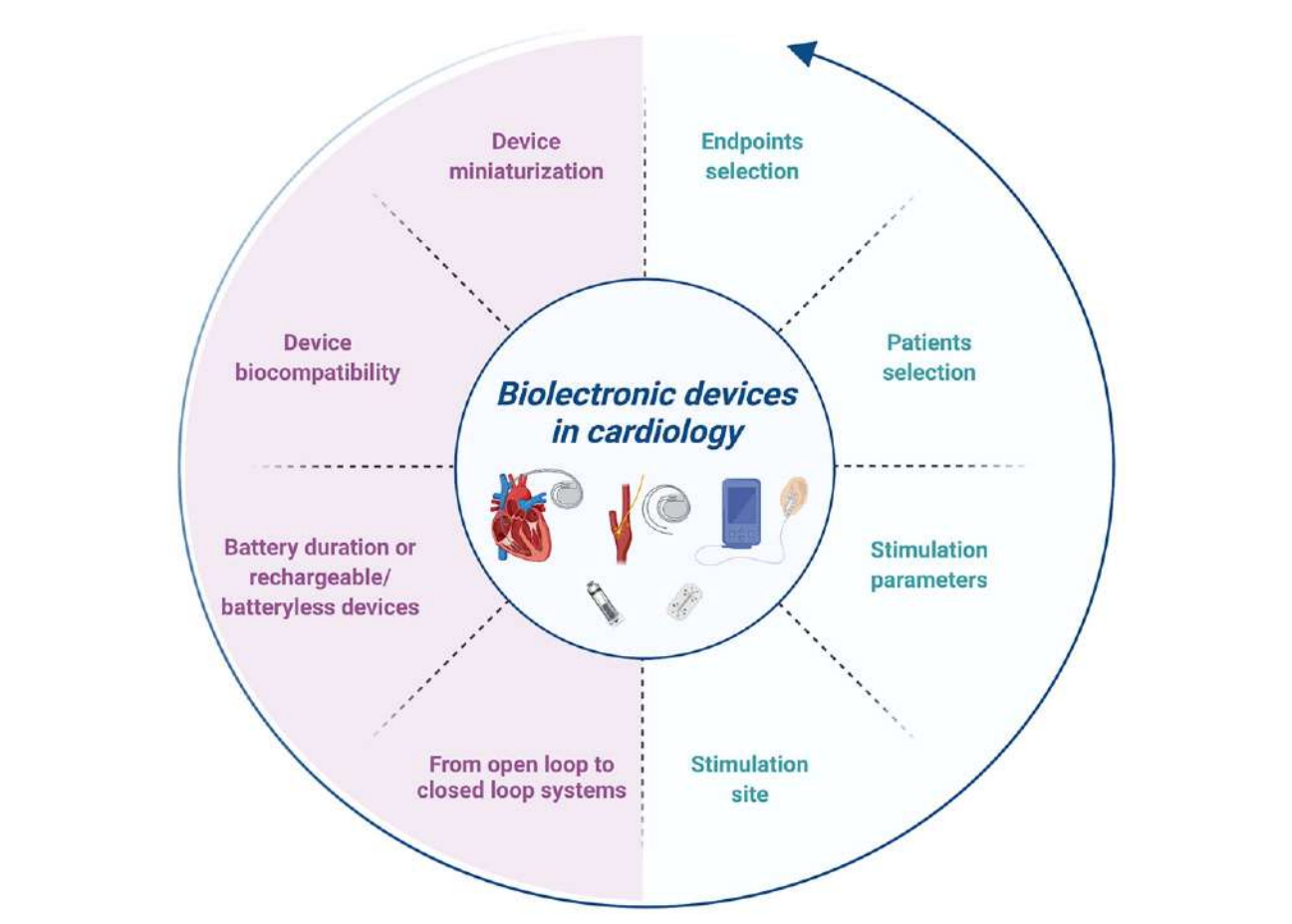

Figure 2 Paths of improvement for bioelectronic medicine in cardiology. Various open issues may be addressed to further optimize the implementation of bioelectronic devices in cardiology, either when projecting novel devices (left) or when designing clinical studies (right). Created with BioRender.com.

a key role in the control of homeostasis, while its imbalance underlies the development and the progression of several cardiovascular disease (e.g. hypertension, ischaemic heart disease, arrhythmias, HF). Therefore, BM devices have been envisioned as a valid alternative or complement to medications in such conditions, mostly to expand the therapeutic armamentarium in the most challenging patients, such as those with resistant hypertension or advanced HF.[5]

First developed to treat drug resistant epilepsy and depression, VNS was approved for clinical uses in 1997. In HF, despite the success of preclinical experiments, three trials (i.e. the CardioFit, the ANTHEM-HF, and the NECTAR-HF) confirmed the relative safety of VNS but demonstrated a variable and questionable success on subjective measures, apart from some effects on ventricular remodelling.[5] Subsequently, the phase-III INOVATE-HF trial was prematurely stopped for futility after the recruitment of 707 HF patients and a 16-month mean follow-up.[5] Although technological reasons (e.g. delivered currents, cycle length, stimulation frequency) may have contributed to such erratic results, the clinical efficacy of VNS in HF has hence been questionated.[5] More recently, the possibility to noninvasively stimulate the vagus nerve through its auricular branch (i.e. low-level tragus stimulation, LLTS) has emerged as an intriguing option. Indeed, various LLTS devices has been shown to be safe and effective on soft endpoints in small clinical trials in various cardiovascular conditions, including atrial fibrillation, myocardial infarction, and HF with either preserved or reduced ejection fraction.[6] Notably, beyond the expected cardiovascular effects, LLTS may also positively remodulate inflammatory and immune systems, in line with the autonomic inflammatory reflex hypothesis.[6,7]

As for BAT, after an initial attempt to work on the carotid sinus nerve, the system was then developed to be applied to the perivascular area around the carotid sinus.[5] A series of preliminary clinical studies have demonstrated the efficacy of BAT on patients with resistant hypertension, with some larger trials currently ongoing with a different design to test its long-term effects.[5] In HF patients, the HOPE4HF and the BeAT-HF have confirmed that BAT is safe, and may significantly improve functional status and exercise capacity, quality of life scores, and natriuretic peptides levels. However, the open label design and the lack of a sham-controlled arm remain major limitations.[5]

In the next future, several issues should be addressed to translate these advancements and the new BM devices constantly rising out of the water of preclinical models into clinical practice in the cardiovascular field.[8] First, while applying electrical impulses directly on the target organ as the heart (pacemakers, ICD, CRT devices) is easier and already a reality in cardiology, the stimulation of peripheral nerves and related circuits is still in his childhood. Some highly debated topics, such as the site and stimulation parameters (mostly frequency and amplitude) arise from the lack of knowledge around the physiology and pathophysiology in humans, easily recognizable by the fact that the first direct vagus nerve recording in healthy humans was only obtained in 2020.[9] This also implies the lack of procedures to adapt the neural stimulation to patients' specific features to maximize efficacy and minimize side effects. Further, this is tightly connected, on the one hand with the choice of the neural interfaces and electronics, and, on the other on the choice of the proper patient to be treated. As for the first issue, at the current stage of development most company use epineural electrodes, whose stimulation are far from being selective (especially when targeting large nerves) and mimicking physiological neural signalling (intraneural electrodes are a potential alternative on the ground). Furthermore, biocompatibility of neural interfaces, battery duration to face long-term stimulation, as well as device miniaturization, of utmost importance in case of multiple device implants, are other well-known hindrances to be surmounted. Another problem is that, commonly, open loop algorithms are used for nerve stimulation, without any self-adjustment of the system depending on the effect on the target organ, as it would be desirable in the attempt to mimic visceral homeostatic feedbacks. This would be greatly improved by using algorithms of stimulation exploiting closed loop approaches (*Figure 2*).

However, the most challenging topic is the proper selection of patients to be treated. In the main clinical trials conducted so far, some indirect clinical measures have been used to select patients to be implanted. The baseline condition of the target of treatment (i.e. vagal nerve activity or baroreflex sensitivity) is often overlooked due to the complexity of performing a neural recording or a physiological measure in a wide clinical scenario. This is partly driven by the market pressure to extend the treatment to as many patients as possible but may heavily dilute treatment effects involving also the wrong patient subset.[10] The proper selection of patients and the consequent increase of the size effect of treatment may allow to strongly decrease the number of patients to be recruited for phase-III trials, which are obviously incomparable with major pharmacological trials (hundreds vs. thousands of recruited patients), due to a higher biological and economical cost of BM device development and implantation. This, together with an early involvement of regulatory agencies in the study design, defining relevant outcomes, the need of sham procedures, and so on, will help in the future to dismiss the plethora of projects ending up in the quicksand of the so called 'valley of the death' opening to the new era of BM devices in cardiology.

Conflict of interest: none declared.

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