Preventive and Personalized Strategies in Ambulatory and Clinical Cardiac Electrophysiology

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Abbreviations

3PM	Predictive, preventive, and personalized medicine
AI	Artificial intelligence

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AS	Aortic stenosis
AV node	Atrioventricular node
AVB	Atrioventricular block
BIS	Bispectral index scale
BMI	Body mass index
CAN	Cardioneuroablation
CDRIE	Device-related infective endocarditis
CIED	Cardiac implantable electronic devices
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
ECVS	Extracardiac vagal nerve stimulation
EP	Electrophysiology
EPS	Electrophysiological study
ESC	European Society of Cardiology
IDE	Investigational Device Exemption
ILR	Implantable loop recorder
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left bundle branch block
LP	Leadless pacemaker
MAV	Micra AV (atrioventricular)
MPC	Model predictive control
MVR	Micra VR (one chamber/ventricular)
PM	Pacemaker
PONV	Postoperative nausea and vomiting
PPIPS	Permanent pacemaker implantation preventive strategy
PPM	Permanent pacemaker
PR, QRS	Parts of ECG decryption
PVI	Pulmonary vein isolation
RBBB	Right bundle branch block
RFA	Radiofrequency ablation
SAVR	Surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement
TIVA	Total intravenous anesthesia
TLE	Transvenous lead extraction
TV-PM	Transvenous pacemaker
VVI, VDD	Stimulation modes of pacemaker

1 Electrophysiology as a Success Story of the Intersection of Biomedicine and Engineering

Contemporary electrophysiology encompasses two main fields. One uses the electrical activity of living cells to evaluate biological signaling processes for medical diagnosis; the other exploits various types of currents for treating numerous lesions, both in destructive and non-destructive manners. Both of these two aspects of

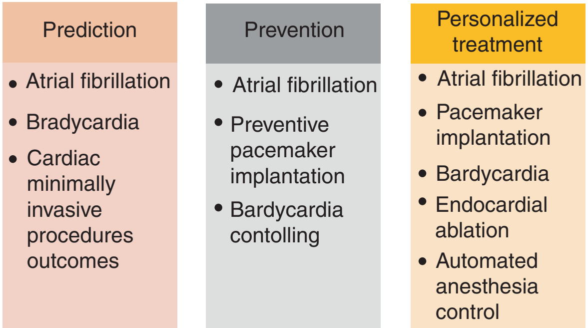

Fig. 1 3P Medicine principia in some aspects of cardiac electrophysiology

contemporary Electrophysiology require advanced technology equipment. That is why Electrophysiology is in the focus of many Biomedical Engineering education curricula worldwide (e.g. [1–4]).

Electrophysiology in medicine relates mostly to two main areas: neurology and cardiology. In neurology, it is focused on an examination of brain signals, neuroimaging and neurostimulation. There are a plethora of reports describing the diagnostic and therapeutic potential of neurologic electrophysiology [5–7].

In modern cardiology, both diagnostics and therapeutic procedures benefit from the electrophysiology approach. In this chapter, we will discuss some of them in view of 3P Medicine.

The main idea is illustrated in Fig. 1.

2 Preventive and Personalized Aspects of Atrial Fibrillation Diagnostic and Treatment Strategies

Atrial fibrillation (AF) is the most common type of heart-treated arrhythmia. It presents a completely irregular heart rate and is accompanied by an increased risk of thromboembolic and cardiovascular complications, hospitalizations, and deaths. A few percent of patients in the course of AF suffer from a stroke, apart from approx. 20% mortality rate carries complications in the form of chronic paresis, speech problems, and cognitive disorders. The above factors result in dramatic social consequences related to the costs of treatments burdening health care systems, leaving the labor market, and is a huge load for the economic systems of individual countries and societies. According to the official data, approx. 50–60 million people worldwide experience AF in its paroxysmal, persistent or permanent form [8, 9]. There are many serious scientific reasons to talk about the plague of AF, and the total number of patients is repeatedly greater [10]. The need for developing rational **predictive** and **prevention** strategies are of paramount importance. Only in the US annual treatment costs of atrial fibrillation are nearing $26 billion [11].

Several modern monitoring technologies aim to diagnose various cardiac arrhythmias as standard ECG and prolonged 24–48 h ECG Holter monitoring. Due to the fact that some episodes of AF appear relatively seldom (e.g., a few times a year), the critical issue is the recording duration. The application of a monitoring framework based on the concept of chronic registration 24 h/365 days is a gold standard of

ECG registration in the shape of the implantable loop recorder (ILR) technique [12]. Unfortunately, this is an invasive procedure with obvious limitations. Numerous efforts have been taken to develop a system for continuous non-invasive long-term ECG monitoring [13, 14]. The projects concerning a variety of hardware, software, and algorithms as a part of artificial intelligence and machine learning processes are still under development. The continuous ECG monitoring is becoming not only a modern technological solution but also constitutes a necessity to broaden **preventive** actions aiming to limit the enormous impact of AF on health, social, and economic aspects of our life globally.

There are two main strategies to treat AF episodes, i.e., rate or rhythm control therapy [15]. With growing evidence supporting early rhythm control also for asymptomatic and new-onset AF patients, we observe a change in the paradigm of AF treatment. Nevertheless, many factors influence the final decision to undertake invasive activities, such as age, comorbidities, echocardiographic parameters, potential success rate, patient's understanding of the clinical situation, etc. Because many factors influence the decision to finally undertake invasive activities like catheter ablation technologies, the effectiveness of chosen treatment method, age and category of patients, special **personalized** AF Heart Teams are established to discuss and decide about the selection decision criteria for the patients [16]. Sometimes they may range from specialist cardiologists (electrophysiologist, heart failure specialist, echocardiographist, etc.) to multidisciplinary teams (cardiologist, cardiac surgeon, endocrinologist, hematologist, nephrologist, neurologist, and others) who plan AF treatments jointly depending on individual patient needs and availability of services. Considering the significant impact of AF on a variety of aspects of our health, social and economic milieu, there is substantial space for **predictive**, **preventive,** and **personalized** actions as described previously [17].

3 Preventive Leadless Pacemaker Implantation in Patients After Tavr Procedure

Aortic stenosis (AS) is the most common valve lesion, often requiring transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) due to the increased risk of sudden cardiac death [18]. The AS prevalence increases with the aging of the population. Till the TAVR era, the interventional approach of the elderly and frail patients was associated with high operational risk. It changed in 2002, with the proof-of-concept first TAVR procedure performed by Cribier, which created a new treatment approach for the highest-risk patients [19]. The indisputable safety profile of the procedure mentioned above led to creating TAVR strong recommendation (IA) in ESC/EACTS Guidelines for the management of valvular heart disease from 2021 for all patients above 75 years or those with high operational risk (STS-PROM/EuroSCORE II > 8%) [18]. Since the first case, TAVR use in the elderly population has only risen. Moreover, the procedure's indications are also spreading among the younger population. It results in increase by 2.7 times the number of TAVR procedures in patients <65 years old between 2015 and 2021. That said, the TAVR procedure count reached nearly equal volume as SAVR by 2021 [20].

The safety profile in patients with severe AS presenting low operation risk was recently evaluated in the PARTNER 3 trial. In the mentioned research, study participants were randomized into groups undergoing TAVR with SAPIEN 3 system and SAVR procedure. The primary composite endpoint was death, stroke or rehospitalization at 1 year. Both 30 days and 1 year after the procedure, SAPIEN 3 system proved the safety procedure profile and was superior to SAVR in the case of the primary endpoint. Moreover, the SAVR procedure was associated with a significantly higher rate of new-onset atrial fibrillation at 30 days, a more extended index hospitalization, and a higher risk of a poor treatment outcome (death or a low KCCQ score) at 30 days compared to TAVR [21]. Developing the newer TAVR systems significantly reduced complications, which may explain the eagerness to involve younger and lower-risk patients in the TAVR procedure.

Nevertheless, new-onset or worsening conduction disturbances remain one of the most common complications after TAVR. They are found in 34.8% of patients at hospital discharge, with the Left Bundle Branch Block (LBBB) as the most common conduction disorder [22]. Randomized trials and registries show that such complications require pacemaker (PM) implantation in up to 25.9% of patients with consequent conduction disorders [23]. However, what needs to be emphasized is that AS per se increases the risk of conduction disturbances.

For example, the stenotic process of aortic valve severe calcification may involve a near-located heart conduction system. Such situation is usually observed in patients with low-flow, low-gradient AS with preserved ejection fraction. This is because the atrioventricular (AV) node is located in the triangle of Koch's apex, near the aortic valve's non-coronary cusp. Three positions of the AV node can be listed with the most common right-sided. However, the left-sided AV node, especially superficial to the endocardium, seems to be particularly vulnerable to calcification and TAVR post-procedure-related conduction disturbances.

Another heart conduction structure—the left bundle branch of the AV node—is a superficial structure positioned on the crest of the interventricular septum. It is located at the base of the interleaflet triangle, separating the aortic valve's non-coronary and right-coronary leaflets, which the TAVR procedure can easily harm. Both situations can lead to PM implantation.

3.1 Permanent Pacemaker Implantation as a Preventive Strategy

ESC Guidelines on cardiac pacing and cardiac resynchronization therapy clearly recommend: asymptomatic patients or those who do not require pacemaker implantation due to standard indications do not need a permanent pacemaker implantation preventive strategy (PPIPS) before the TAVR procedure [23].

However, due to the post-TAVR risk of further conduction disturbances advancing in the future, early PPIPS after TAVR should be considered in several cases. With pre-existing right bundle branch block, developing any other conduction disturbances during or after TAVR, even transient high-degree atrioventricular block (AVB), PR prolongation, or QRS axis change, is a clear indication of a PPIPS. Another case when PPIPS should be implemented for patients >48 h after TAVI are:

- New LBBB with QRS > 150 ms.
- Pre-existing conduction abnormality who develops prolongation of QRS or PR > 20 ms.
- PR > 240 ms.

Yet, before the PM implantation decision, one should have an electrophysiological study (EPS) that measures the His bundle -Ventricular interval. The nominal value that justifies the implantation procedure should be at least 70 ms. Those who developed bifascicular block after TAVR and did not meet above mentioned criteria, yet have had syncope after the procedure, should also be considered for PPIPS. It has been proven that in elderly patients with unexplained, recurrent syncope and bifascicular block (for example, LBBB or RBBB with left anterior fascicular block), PPIPS significantly reduces the risk of symptoms recurrence [24]. However, one in eight patients with a transvenous pacemaker (TV-PM) may experience peri- and post-procedural complications [25]. The risk of complications rises with such burdens as age, BMI, and frailty syndrome, which are all often in the characteristic spectrum for a patient after the TAVR procedure.

3.2 Leadless Pacemakers in TAVR Population

The arrival of leadless pacemakers (LPs) (Fig. 2) in 2012 became a cornerstone in the treatment of bradycardia and atrioventricular (AV) conduction disorders as an alternative to TV-PMs. Currently, the only available LPs on the market are Micra VR (MVR) and the newly developed Micra AV (MAV), which allows AV synchronous ventricle pacing (VDD mode).

However, their external construction is similar. With a low mass of 1.75 g, dimensions of 25.9 mm × 6.7 mm, and volume of 0.8 cc Micra occupies around 1% of the hearts' right ventricle volume. MVR and MAV longevity is estimated between 8 and 13 years, which depends on the pacing mode, ventricle pacing percentage, and

Fig. 2 Leadless Pacemaker—Micra (own picture)

implanted place's electrical parameters. Even though Micra is considered an unremovable device after a couple of months since implantation due to encapsulation [26], another implantation of Micra in the same patient is feasible and safe. However, due to the expected limited lifespan in TAVR-related, elderly and frail populations, it seems to be a relatively rare need.

The most common conduction disturbance after TAVR—the newly developed LBBB—has a relatively high long-term recovery rate to normal conductive function (26.2% at long-term follow-up [27]). Thus, such situation allows LP to work often as a backup mode extending battery life.

One of the reasons behind LP technology development was the improvement of the safety profile in cardiac pacing. The pocket and leads account for two-thirds of transvenous PM complications, and their lack in LP technology is one of their most significant advantages. Reducing the risk of infective endocarditis is essential from the point of view of a person with an artificial aortic valve.

The first study exploring the MVR safety profile was Investigational Device Exemption (IDE). The IDE study showed 48% (HR 0.52; 95% CI 0.35–0.77;) fewer complications compared to TV-PMs, a high implant success rate (99.2%), and stable low pacing thresholds at 6 months in 98.3% of patients [28]. The second one—The Post-Approval Registry—proved a low rate of major complications throughout 12 months (2.7% CI:2.0–3.6%) with no device-related infections. Major complications were mainly reduced by a 47% relative risk reduction in hospitalizations and an 82% relative risk reduction in system revisions. The all-cause mortality does not differ at 2-year follow-up in groups of LPs and TV-PMs, even though patients obtaining LP are usually burdened with more comorbidities [29]. Micra's implantation safety, performance, and post-procedural complications were also evaluated in patients who underwent MAV implantation after the TAVR procedure between November 2020 and June 2021. The short-term safety and performance of the LP were once again proved with a 1-month follow-up [30]. Most of LP's indications are similar to the TAVR population. Thus, LP should be considered for patients with frailty syndrome and chronic kidney disease, especially those on dialysis, with less than 10 years of life span, hindered access to the TV-PM, but also with a history of cardiac device-related infective endocarditis (CDRIE). The MAV should be preferred over MVR in patients with AV block but without bradycardia or persistent supraventricular arrhythmia, due to the VDD pacing mode.

This demonstrates how important is a **personalized** approach before taking a decision about the procedure to be employed.

4 Prediction, Prevention, and Personalization: A Strategy for Managing Patients with Symptomatic Bradycardia

Management of sinus node dysfunction or atrioventricular conduction disorders leading to symptomatic bradycardia remains a diagnostic and therapeutic challenge. According to the guidelines of the European and American cardiological societies ESC/EHRA/ACC/AHA/HRS, if these disorders are of internal origin and are irreversible, the treatment of choice is PM implantation [23, 31]. The method has been proven and improved for many years. However, it is burdened with significant limitations and not without the risk of complications. The recent rapid development of technology has significantly increased diagnostic possibilities and expanded the number of therapeutic options, from optimizing the stimulation itself to techniques to avoid it. Such a variety of options create a possibility to **personalize** the therapy to reduce complication risk and improve the quality of life. Saving lives, although still a priority, is no longer the only goal, and a specific therapeutic option may be an optimal solution for one patient but a difficult or unacceptable compromise for others.

It becomes possible to:

- consider the patient's individual preferences, plans, and professional and private activities.
- anticipate what limitations of potential solutions will be relevant in individual cases.
- **prevent** or minimize cumulative risk throughout chronic therapy.

Developing an optimal therapeutic strategy often requires a multidisciplinary approach and the inclusion of the patient in the decision-making process [32]. Both to know their preferences and share responsibility for decisions made.

Until recently, the only therapeutic option for a patient with symptomatic bradycardia, if it was not reversible, was PM implantation, a prosthesis of the heart's physiological pacemaker/conduction system. This method has been successfully used for many years. Subsequent PM generations are becoming more reliable and their capabilities more excellent. With new implantation technics, cardiac pacing became more physiological, i.e., His-bundle pacing or its left branch [33, 34]. However, the main limitations of this method remain the same. The generator must be replaced every few years and systematically checked by professional medical personnel.

Moreover, one should remember the possible infectious complications of implanted PMs due to periprocedural and blood–borne origin or lead damage. The risk increases with the duration of therapy. No less crucial, the PM—by itself—limits the quality of everyday life and physical activity and sometimes can force one to change a professional life. The risk of complications from PPM significantly increases in young patients with a long-life expectancy. On the other hand, often, it is the only available therapy form. Implantation procedures last shorter and shorter, and consequently, the periprocedural risk is significantly reduced. New pacing options, such as resynchronization with a left ventricle electrode, physiological pacing in the region of the His-bundle or its left branch, or the recently introduced implantation of LP, enable an individualized approach to each patient.

Cardioneuroablation (CNA)—a new therapeutic option for patients with symptomatic bradycardia—has been available for several years [35, 36]. A procedure involves modifying the heart's parasympathetic part of the autonomic nervous system of the heart's physiological pacemaker/conducting system. The vagus nerve, which belongs to the parasympathetic nervous system, has an inhibitory effect on the sinus node responsible for generating the heart rhythm and the atrioventricular junction responsible for conduction. CNA is an invasive procedure involving damage through radiofrequency electric energy to the ends of the vagal nerve (post-ganglionic neurons and interneurons), located in the epicardium, in the left atrium in the vicinity of the pulmonary venous ostia, interatrial septum and the mitral annulus, also in the area of the roof of the right atrium and the coronary sinus ostium. CNA is a beneficial method of bradycardia treatment caused by excessive vagal nerve tension-functional bradycardia. The rising evidence suggests that it should be a first-choice treatment in such cases [37]. It can be used in particular cases of structural damage to the heart's physiological pacemaker/conduction system, releasing its functional reserves from the vagal nerve influence. This procedure is more complicated than the implantation of a PM and, unlike it, requires general anesthesia.

Moreover, the periprocedural risk is higher, and the qualification process for CNA is more complex and time-consuming. In the short term, it requires more significant commitment and acceptance of the risk of complications and possible failure of therapy by a patient. However, in many cases, it allows for avoiding or postponing the prosthesis of the heart's physiological pacemaker/conduction system, which is PM implantation, yet not excluding this option in the future [38, 39].

The abovementioned options allow physicians to offer a more **personalized** approach to bradycardia therapy. Knowing the advantages and limitations of individual therapeutic strategies—the patient's lifestyle and preferences, as well as the estimated lifespan—allows for risk complications **prediction** and estimation related to the considered therapies. Such awareness leads to preventing and minimizing adverse events. For example, the younger the patient, with a less incriminating medical history, the longer lifespan, which entails a significant increase in the cumulative risk of long-term complications of therapy with implantable devices. However, the increased short-term periprocedural risk is more acceptable. PM implantation at a young age presupposes more PM replacement procedures in the future. Each procedure is associated with an increased risk of infectious complications. Also, the lifetime of the electrodes in pacing systems is limited due to physical damage, which can come with patient activity. It is crucial to consider the patient's lifestyle and occupational activity, i.e., transvenous pacemaker precludes some activities, such as sports involving the shoulder girdle. It also excludes the possibility of working with an electric arc and forces the avoidance of strong electromagnetic fields. It binds the patient to the center controlling the implanted device and makes him strictly, chronically dependent on the healthcare system. For this, the acceptance of an individually increased risk associated with a more complicated and arduous CNA procedure and a more complicated procedure qualification process may be accepted. The number of variables necessary to consider in this case requires a more detailed analysis of individual therapy options, optimally with the participation of a multidisciplinary team: electrophysiologists, other specialists in the case of comorbidities, a psychologist, or a career counselor (EP Heart Team) (Fig. 3).

Most importantly—the patient needs to be actively involved in this decision-making process, understanding and accepting both the short-term risk associated with the PM implantation or CNA procedure itself and the cumulative long-term risk and possible limitations resulting from such a choice. Even within the same age group, optimal therapy strategies may vary depending on other factors. The patient

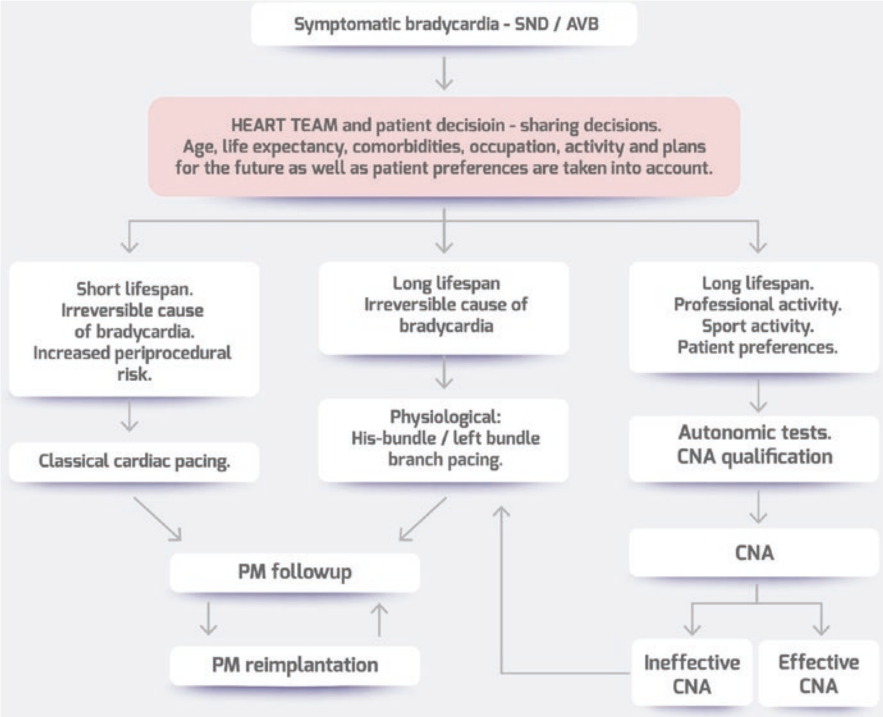

Fig. 3 The decision-making process and a strategy for personalized management of patients with symptomatic bradycardia (own scheme)

may ultimately prefer the well-established medical procedure – the PM, with all its limitations.

A more considerable challenge is the 3P Medicine approach to optimize the already implemented pacing system. An individual-**personalized** approach to each patient requires a reassessment of indications for permanent cardiac pacing. The guidelines of European and American cardiological societies ESC/EHRA/ACC/AHA/HRS [23, 31] reassures with such a procedure, requiring a reassessment of indications for continued PM therapy with PPM before each pacemaker replacement, electrode extraction and replacement and during the entire long-term follow-up.

Patients who had a conventional cardiac PM implanted a few years ago might now be qualified for physiological pacing or can avoid PPM by CNA procedure. In a study of a Danish population of patients who had a pacemaker implanted before the age of 50, it was shown that vasovagal syncope, resulting from an exaggerated reflex, the efferent arm of which is the vagus nerve, was in 5% of cases. If it is a cardioinhibitory type of reflex, i.e., when it results in bradycardia or even a pause in the heart rhythm, CNA would be a causal treatment and would avoid PM implantation. In the same population, it was shown that in 50% of patients qualified for PPM, the cause of atrioventricular node dysfunction could not be determined [40].

Continuous development of diagnostic tools, the autonomic nervous system tests improvement, or the use of implanted loop recorders undoubtedly expand the possible medical solutions for patients whose diagnostics were completed several years ago. This group would include patients who could benefit from a different therapy. Reassessment of indications for continuing PPM therapy or its possible optimization to physiological is not burdensome and should be performed in each case. However, changing the current therapy is a much more complex issue. There are various options: continuation of the current PPM, replacing it with more physiological pacing of the His-bundle or its left branch, or CNA, and discontinuation of PM therapy (Fig. 4).

Changing the current therapy, i.e., cardiac pacing to a different mode or stopping it, is not easy, even when the new method seems to be better. **Personalization** of the approach to this problem is inevitable in this case. The potential risk is no longer only due to implementing a new treatment method but also possible complications resulting from abandoning the current treatment method. Changing the pacing method to physiological or its complete cessation after a successful CNA procedure is associated with an additional risk of removal of the existing pacing system. Treatment by transvenous lead extraction (TLE) carries a 2–3% risk of severe periprocedural complications. This risk can be minimized by performing TLE in

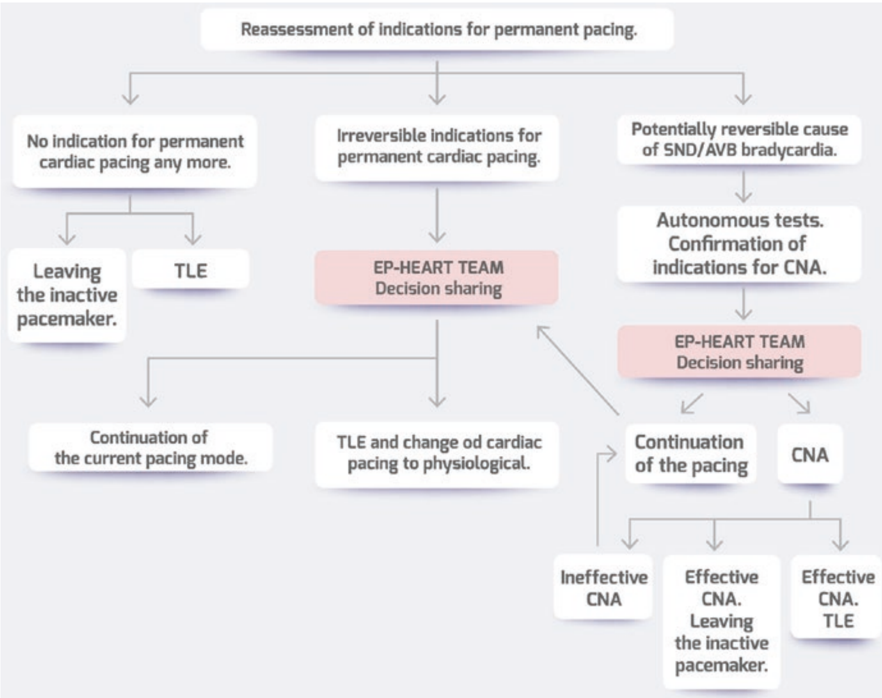

Fig. 4 Reassessment processes for permanent pacing, cardioneuroablation, and transvenous lead extraction (own scheme)

hi-volume centers [41, 42]. However, there are only a few, and they often require transporting a patient to a different center in another city for the procedure. It is an additional difficulty and stress during the treatment process. Abandonment of an inactive pacing system is not a good solution. It is associated with a long-term risk of infective endocarditis. Such a solution can be accepted only in the case of the patient's refusal to undergo the TLE procedure or a very high risk associated with this procedure.

The consideration of the potential benefits and risks of changing treatment should also be based on a multi-professional assessment by EP Heart Team and the patient. Patients who have already received PPM are more aware of its limitations and potential risks. Estimating and anticipating the risks resulting from individual options, **preventing**, and eliminating already existing limitations, such as impairment of physical activity, professional activity or social exclusion, is indispensable.

5 Automatic Control of Anesthesia for Pulmonary Vein Isolation and Cardioneuroablation Procedures

Pulmonary vein isolation (PVI) is a technique of catheter ablation of atrial fibrillation, the most often diagnosed arrhythmia worldwide and, as such, an important treatment option in modern cardiologist's armamentarium. The concept of PVI emerged after the publication of a landmark paper by Haïssaguerre et al. [43]. Nowadays, it is an established AF treatment modality, both as the first-line therapy and as a bail-out after failed drug therapy [16]. It can be performed using two energy sources: cryoballoon and catheter ablation with radiofrequency (RFA) current. The efficacy of both techniques is comparable, at least as a first procedure in the paroxysmal form of AF [44]. Cryoballoon PVI, compared to RFA, results in shorter procedure time and seems to be better tolerated by patients [45]. As a result, lower levels of anesthesia during cryoballoon PVI can be safely used. However, a few patient's and procedural characteristics, such as redo procedure or left atrial enlargement, favor RFA over cryoballoon [46, 47]. As RFA PVI results in longer procedural time, which is invariably associated with patient spending prolonged time motionless in a recumbent position, it is less well tolerated. Movement of patients during the procedure can result in disturbance of the electroanatomical mapping system and inadvertent damage of the cardiac tissue, even leading to cardiac tamponade. The aforementioned obstacles favor deeper levels of anesthesia during RFA PVI. Findings from 2010 randomized clinical trial support the use of general anesthesia over conscious sedation during RFA PVI [48]. Unfortunately, performing PVI under general anesthesia is more challenging regarding electrophysiology lab workflow and the availability of anesthesiologists. In Japan, only 0.5% of patients undergo general anesthesia during RFA PVI [49]. To address these logistic obstacles, a trial on total intravenous anesthesia (TIVA) provided by cardiologists with support from anesthesiologists was performed. TIVA using intravenous propofol and fentanyl was administered by cardiologists in the EP lab in 160 consecutive patients. Airway support was provided via i-gel, and all patients were ventilated in synchronized intermittent mandatory ventilation mode provided by a standard respirator. Doses of anesthetic were titrated to maintain a bispectral index (BIS) between 30 and 50. Only in 3% of cases the intervention of a supporting anesthesiologist was needed, and in 2%, TIVA was abandoned. There were no anesthesia-related complications [50]. This study supports the feasibility of TIVA administered by a cardiologist during RFA PVI, which is especially important in the face of an anesthesiologists' shortage.

In recent years, a novel therapy for bradyarrhythmias emerged – endocardial ablation of the vagal nerve postsynaptic neurons, i.e., CNA. During the procedure, monitoring of residual vagal innervation is essential. The monitoring can be performed by solely observing an increase in heart rate, evoking vagal reactions during high-frequency stimulation, or by direct transvenous stimulation of vagal nerve—extracardiac vagal nerve stimulation (ECVS) [51]. Due to the proximity of the accessory nerve, ECVS leads to head rotation while performed without a neuromuscular blocking agent. This unpredictable movement can result in loss of efficient vagal stimulation and even vascular damage by pacing electrode, so ECVS is generally performed after the neuromuscular blockade. However, it complicates further course of CNA, as neuromuscular blockade decreases the excitability of the diaphragm and monitoring of the phrenic nerve cannot be reliably performed so long as effect of the neuromuscular blocking agent is sustained. The remarks mentioned above makes anesthesia of patients undergoing CNA especially challenging. Method for simplified, more reliable and reproducible general anesthesia to prevent complications and ease management of patients in EP lab is sorely needed. Considering the introduced procedure, the use of the automated control system for anesthesia can be seen as the supplementary tool for support medical staff in this challenging intervention.

Recently we have witnessed an unprecedented international effort to improve the quality and availability of medical care. In this regard, researchers in clinical automation have focused on novel solutions in the field of physiological closed-loop control systems. This scientific area requires a multidisciplinary approach combining specialist knowledge to tackle the problem in a holistic manner. In this context, automated control **in personalized** therapies is one of the most promising research areas, where the application of new research techniques and cutting-edge technologies, such as artificial intelligence (AI), can expand the frontiers of this challenging field [52, 53]. Automatic control engineering has become an important enabling technology in many areas of medicine and biomedical technology. Prominent examples include the artificial pancreas, closed-loop anesthesia, and **personalized** drug-dosing strategies in neurology, oncology, endocrinology, and psychiatry [52]. It is a testament to the power of control systems that allow individualizing treatment by providing mechanisms for linking treatment goals to treatment regimens, thus achieving the desired therapeutic effect. Consequently, the arrival of control systems engineering in the clinic makes the visionary concept of "treat the patient, not the disease" technologically and economically feasible. In this regard, it is desirable to develop automated drug-dosing techniques to prevent under or overdosing issues and to provide a more personalized solution. Additionally, continuous advances in medical sensors, medical equipment and AI have created propitious conditions for incorporating closed-loop systems. For this, patient-dynamics models can be used to predict the patient's pharmacological/biological response to the drug/substance administered, which can be incorporated into the individualized control system design and tuning [52–54]. This issue is one of the open research questions that can be explored to personalize the control system in the context of model individualization.

In the setting of previously described interventions, an important aspect is related to an anesthesia process required for the proper execution of the surgery. The total intravenous anesthesia (TIVA) process generally refers to the loss of sensation. It can be described as the absence of recall and response to a noxious stimulus as the effect of the used drugs. Usually, the medications applied during intravenous anesthesia can be split into three groups: analgesic, hypnotic and those providing a neuromuscular blockade. Those drugs have a physiological effect on the loss of sensitivity to pain and loss of consciousness, interpreted as the depth of hypnosis and caused paralysis of affected skeletal muscles, respectively [52–54]. The anesthesia process is usually divided into three stages, induction, maintenance, and emergence. The simplest TIVA considers only one hypnotic drug, propofol, and its effect is measured by the depth of the hypnosis level. This scheme can be extended to a multivariable case, where more than one drug is infused, having mutual interaction between them. Nevertheless, here we will focus on the simplest case, where the potential benefits could be interpolated to even more complex control system configurations. Figure 5 shows the closed-loop control system where the main components of the analyzed scheme are indicated.

In the classical approach, the anesthesiologist observes the monitors representing patients' vital signs and manually regulates the infusion pump's rates based on their experience. While in automated control, the main idea consists of applying the control algorithm (designed software) that computes the required amount of the drug based on patient state measurements (obtained through clinical monitors equipped with specific sensors). Calculated infusion rates are applied using the computer-controlled infusion pump (actuator). Using an automated system can relieve a medical staff from continuously monitoring and modifying the drug dosage, which is a highly demanding task, especially during long interventions where

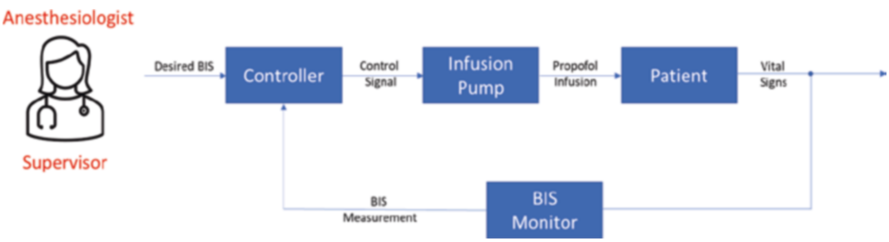

Fig. 5 Automated drug administration in anesthesia—schematic closed-control-loop for depth of hypnosis (own scheme)

it is challenging to maintain the necessary concentration for a long time. The purpose of such an automated control system is to support the anesthesiologist in this difficult process and not to replace them [53, 54]. In this way, the anesthesiologist becomes a supervisor of the process, acting only in critical situations, which permits them to focus on high-level tasks.

Nowadays, many control techniques that have been proposed for depth of hypnosis control in anesthesia process have been widely proven, e.g., A Proportional-Integrative-Derivative (PID) controllers, regulators based on fuzzy logic as well as model predictive control (MPC) techniques, to name a few [52, 55–60]. However, in the context of **personalized** medicine in anesthesia process, the MPC techniques have the greatest potential since they could use an individualized patient's model. As an example, a pharmacokinetic/pharmacodynamic (PK/PD) model for propofol could be indicated, which relates the drug infusing with its clinical effect represented by the bispectral index cale (BIS) [61]. This model is derived from the compartmental model, where some of its parameters are related to patients' physical characteristics (like; age, height, weight and gender). Finally, it should be highlighted that the **personalized** model can be exploited to predict the effect of the drug on each individual resulting in a powerful and flexible toll. When combined with an appropriate control technique, like the MPC, the resulting control action takes into account the specific patient's response to the infused drug provided by the personalized model [56–61]. The control algorithm uses this **predictive** feature to compute the optimal drug dosage, considering limitations and constraints indicated by the type of intervention and clinical practice. As a consequence, the control algorithm is able to provide the right value of the drug dosage. Simultaneously, it reduces the possibility of the drug's over/under dosage, where both could have a negative impact on the patient. The under dosage could result in the regaining consciousness and, consequently, provoking severe traumatic experiences. Whereas overdosage could result in postoperative complications such as postoperative nausea and vomiting (PONV), resulting in a longer recovery [62–65].

With these characteristics, a personalized control scheme assures the **preventive** measure to reduce postoperative complications and to limit the influence of a human factor [66–69]. Moreover, automated anesthesia is able to provide a more unified procedure due to the limited role of the subjective decision of the anesthesiologist [57–59].

6 Conclusions

Continuous ECG monitoring based on the 24 h/365 days concept could be extremely effective in clinical practice for diagnosing atrial fibrillation episodes and other arrhythmias. This might change the paradigm of recognizing not only supraventricular arrhythmias but also brain infarcts sources, syncopal episodes and influence a strategy for anticoagulation therapy.

Dedicated **personalized** AF Heart Team is of crucial importance for decisions concerning diagnostic and therapeutic options in patients with AF and numerous other arrhythmias. Such attitude will presumably influence health, social and economic policies in different countries and systems. PPM implantation **preventive** strategy after transcatheter aortic valve replacement is emphasized by cardiology guidelines and should be widely used. Not yet registered device-related infective endocarditis in patients with leadless pacemakers, a significantly lower risk of peri-procedural and post-procedural complications in LPs compared to the transvenous pacemaker—also proved in a TAVR population—seems to favor the LP in frail and elderly patients. Proceeding according to the idea of **personalization**, **prediction,** and **prevention** in treating symptomatic bradycardia and its optimization should no longer be an option but a common practice. Routine application of the guidelines recommendations facilitates everyday practice but often leads to difficulty accepting and unnecessary compromises. The patient's age, occupation, plans for the future, the cumulative risk of long-term complications and difficulty in estimating other preferences cannot be easily summarized in recommendations IA or IIIA arbitrarily presented in the guidelines of cardiological societies. Each patient should be considered individually, and the decision as to the therapy method in seemingly similar cases may vary. Automatic control of anesthesia process, as described above, fits into paradigms of 3P Medicine addressing **personalized**, **predictive**, and **preventive** aspects. These properties can be of added value in the context of cardiologic surgeries, improving the overall patient state after the intervention and thus reducing their postoperative recovery time. However, it must be highlighted that significant effort must be dedicated to developing new technologies and techniques, making them reliable and widely accepted modalities that will be used in clinical practice.

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