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REVIEW

Pacemaker dependency after implantation of electrophysiological devices

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Pacemaker dependency is observed in an appreciable number of chronically paced patients. Although there is no standard definition, pacemaker dependency has a significant impact on the management of patients in several clinical settings. In this review, we provide a comprehensive overview of the available data regarding definition, testing, clinical significance, epidemiology, and mechanisms of pacemaker dependency. Several issues regarding the underlying pathophysiology remain obscure and the potential value of interventions that may alter its incidence, clinical course, and consequences remains to be elucidated.

Keywords Pacing • Permanent pacemakers • Pacemaker dependency • Pacing dependent • Complications • AV junction ablation

Introduction

Fifty years after the first permanent pacemaker (PPM) implantation, we witness the continuous development and growing clinical application of implantable devices in a wide range of heart rhythm disorders.[1–3] Data on temporal trends of implantation rates are sparse, but there have clearly been considerable increases over past decades. A recent population-based study showed that the adjusted implantation incidence rates of PPMs increased 2.7-fold over 30 years.[4] Despite significant heterogeneity between different European countries, the implantation of electrophysiological devices (EPDs), and especially implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) systems, has substantially increased in the last few years.[5] Potential factors that possibly contribute to the increase in implantation rates of EPDs include an ageing population, advances in device technology, and the growing number of evidence-based indications.[4,5] In this context, and despite the clear clinical benefits, an increasing number of patients are exposed to risks and hazards associated with device implantation and therapy.[2,3,6–8] Pacemaker dependency is not an uncommon phenomenon in paced patients and, as will be discussed later, has significant implications in patient management and outcome.

Definition

In general, pacemaker-dependent patients have inadequate or even absent intrinsic rhythm and therefore can suffer significant symptoms or cardiac arrest after cessation of pacing.[9,10] The issue of pacemaker dependency is complex and actually there is a great diversity of definitions in the available literature. The need for a widely acceptable, clinically applicable, and practical definition has been recently underlined.[9,10] Some physicians consider the patient to be pacemaker-dependent if the ventricular rhythm is totally paced whenever seen in the pacemaker clinic or if the interrogation of the device shows that most of the time there is ventricular pacing according to the stored percentage of paced ventricular events.[9,10] However, this practice does not take into account several potential settings such as dual-chamber pacing with short atrioventricular (AV) delay, ventricular pacing with high base rate, no programming of features that promote intrinsic ventricular rhythm, biventricular pacing where the AV delay is usually short, or no programming of specific features that promote biventricular pacing in CRT systems (algorithms that promote continuous tracking and manage the premature ventricular beats).[2,3] The classical definition of pacemaker dependency includes the occurrence of asystole after cessation of ventricular

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pacing, namely the absence of an underlying escape rhythm.[9–17] It should be acknowledged that there is no agreement in the literature regarding the duration of asystole that characterizes the dependency.[9–17] There are also different protocols for testing the existence of underlying ventricular rhythm that apply gradual or abrupt cessation of pacing at different levels of low base rate.[9–17] Apart from the absence of intrinsic ventricular rhythm, it is clinically meaningful to consider as 'pacemaker-dependent' patients who develop symptoms even if they have an underlying escape rhythm since they may suffer serious complications after abrupt failure of the pacing system. This assumption has been adopted by several investigators.[10,13,14,17] In addition, it has been proposed that patients who receive a PPM for syncope due to intermittent asystole should be treated as pacemaker-dependent, even if they have seemingly a reliable underlying heart rhythm during the regular follow-up, given that in the case of pacing system failure, they would not be protected from recurrent spells.[9,10]

Pacemaker dependency testing is routinely performed during the regular follow-up of patients with EPDs. In most of the reported tests, a decrease in the base paced rate to 30–40 bpm is performed and then a close observation for an underlying intrinsic ventricular rhythm as well as recording of patients' symptoms.[13,15–17] Although some investigators proceed to complete cessation of back-up pacing after pacing at a low rate,[14,17] this practice does not seem to have significant advantage and may carry additional risks for the patient. Older protocols, when programmability of the devices via telemetry was unavailable, were employing complete overdrive inhibition of the pacemaker by chest wall stimulation (external overdrive suppression).[11,12] The decrease in the base paced rate may be abrupt or gradual. Although the abrupt lowering may increase the incidence of pacemaker dependency, it closely resembles the clinical scenario of abrupt pacing system failure.[10]

It could be proposed that there are different types of pacemaker dependency according to the underlying clinical situation. For example, after AV junction ablation, the dependency is certain. In paced patients with advanced heart block or documented syncope due to prolonged asystole pre-implant, the pacemaker dependency could be characterized as probable. Finally, if there is no intrinsic rhythm at a low pacing rate or the patient is symptomatic at this rate, the pacemaker dependency could be labelled as possible. It should be acknowledged that the clinical significance of this classification is questionable since the specific type of pacemaker dependency does not have a different impact on the management of the patient. In other words, regardless of the type, the patient should be treated as pacemaker-dependent.

Another issue that needs further discussion is the phenomenon of intermittent pacemaker dependency. Staessen *et al.*[11] demonstrated that among 142 patients who had a PPM for AV block, 20 showed improvement in the AV conduction during the follow-up. Moreover, Rosenheck *et al.*,[14] in a study of 74 patients with complete AV block who had a PPM, showed that 13% of them had different results at different tests of pacemaker dependency, namely the escape rhythm was unstable. In another study, fluctuations in pacemaker dependency during the follow-up were much more frequently observed in 83% of sinus node disease (SND) patients and in 27% of patients with AV block.[16] It is therefore evident that there is 'permanent' and 'intermittent' pacemaker dependency. However, it is recommended that even with one identification of dependency, the patient should be considered pacemaker-dependent, and this diagnosis should not be changed even if escape rhythm is detected on a future evaluation.[10,14] In other words, patients with intermittent recovery of intrinsic rhythm should be considered pacemaker-dependent since the moment of loss of intrinsic rhythm cannot be predicted.

Clinical significance

Knowledge of the status of the patient who has been implanted an EPD, in terms of pacemaker dependency, is very important. There are several clinical settings where pacemaker dependency has an impact on the patient management and outcome. The following situations are worth mentioning:

(i) *Electromagnetic interference*. Inappropriate inhibition of pacemaker output may be a response to external interference.[2,3] Therefore, particular attention should be paid on patients who are pacemaker-dependent. When these patients are exposed to sources of electromagnetic interference under controlled procedures in the hospital (electrocautery, magnetic resonance imaging, lithotripsy, radiofrequency ablation, etc.), the device should be programmed to an asynchronous mode with high ventricular output while close observation with a back-up of resuscitation and external pacing equipment during the procedure is needed. Moreover, in pacemaker-dependent patients, the treating physician should be stricter regarding precautions against exposure to sources of interference at home or at work. In this setting, programming of bipolar sensing is strongly recommended.

(ii) *Lead dysfunction*. Mechanical problems in implanted pacemaker leads are not uncommon, despite the fact that some contemporary models have a 10-year survival rate >97%.[3,18] However, this problem is much more significant in ICD leads. Although the reported survival of ICD leads varies between studies, it has been shown that the failure at 8 years is 28–40%.[19,20] Also, we recently witnessed some catastrophic complications related with failure of the Sprint Fidelis ICD leads. Conductor coil fractures may result in failure of stimulation or failure to capture or inappropriate inhibition due to oversensing of false signals. Insulation defects can also cause loss of capture, oversensing of false signals, and premature battery depletion. Therefore, a closer follow-up should be applied in pacemaker patients with signs of lead problems together with an early decision in favour of lead replacement. Furthermore, in these patients, some special safety features such as daily measurements of lead parameters, sound alerts for lead integrity such as high or low impedances, noise reversion mode should be programmed appropriately.

(iii) *Generator malfunctions*. Despite technological advances, the reliability of EPDs is not perfect. Several device malfunctions affecting PPM and ICDs have been reported.[21] An analysis of the FDA annual reports for the years 1990–2002 showed

that the annual malfunction replacement rate for PPMs and ICDs was 20.7 and 4.6 per 1000 implants, respectively.[22] Interestingly, during the study period, 2.25 million PPMs and 415 780 ICDs were implanted in the USA and 61 deaths were attributed to device malfunction.[22] A more recent study demonstrated that severe and accelerated battery depletion, manufacturer's advisories, and electronic or connector defects accounted for 13% of pulse generator removals.[18] It would be recommended that alerts regarding generator malfunctions should direct the treating physician to prompt replacement in pacemaker-dependent patients.

(iv) *Pacing system extraction*. Electrophysiological device-related infection represents a devastating complication with a challenging and often difficult management.[2,3,6] Notably, two recent reports indicate a disproportionate increase in EPD infections compared with implantation rates.[7,23] Current recommendations advocate a therapeutic approach of complete removal of the system (generator and leads) and antimicrobial therapy followed, in the majority of cases, by re-implantation at a remote site after some time period.[2,3,6,24] This practice has special difficulties in pacemaker-dependent patients since there is a need for temporary pacing before the implantation of the new system. It should be borne in mind that there are also some other rare conditions that necessitate the extraction of the leads.[25] Interestingly, a novel temporary pacing technique has been proposed for the treatment of EPD infection in pacemaker-dependent patients using transvenous active fixation leads and external re-sterilized pulse generators.[26]

(v) *Atrioventricular junction ablation*. The ablation of the AV junction can render a significant proportion of patients pacemaker-dependent in the long term.[27,28] Atrioventricular junction ablation represents an effective and still valid therapeutic option for patients with drug-refractory atrial fibrillation having a poor rate control.[29] In addition, AV junction ablation is increasingly performed in CRT patients with rapidly conducted atrial fibrillation and insufficient rates of biventricular pacing.[29,30] It is currently appreciated that heart failure patients with atrial fibrillation have significant improvement after CRT and therefore they are increasingly considered for biventricular pacing.[31]

(vi) *Permanent pacing after cardiac surgery*. It has been reported that 1–3% of patients undergoing major cardiac operations need permanent pacing for bradyarrhythmias.[32–34] This rate may reach the level of 5–6% in patients who have aortic valve replacement surgery. Of note, many of these subjects have long-term pacemaker dependency after the cardiac surgery, and consequently, they are exposed to the related risks.

(vii) *Elective generator change*. Although elective generator change of EPDs is considered a routine procedure for experienced implanters, the presence of pacemaker dependency makes the process more challenging and demanding. There are no reported recommendations about the mode of generator change in these patients. Some physicians prefer to do the replacement of the generator quickly without having a temporary pacemaker as a back-up. In this instance, programming of bipolar sensing in both the old and the new device is recommended. The major advantage of this option is that there is reduced risk of infection, given that generator change operations carry almost a double risk for infection compared with initial implantations, whereas the use of a temporary wire increases the infection risk significantly.[2,35] However, the safety is not optimal since an inadvertent damage of the lead or a sudden failure of the analyser may have devastating consequences.

(viii) *Selection of pacing mode*. The mode of pacing may have particular impact in pacemaker-dependent patients. The CTOPP trial showed that the yearly event rate of cardiovascular death or stroke steadily increased with decreasing unpaced heart rate (assessed at the first follow-up visit) in the ventricular pacing group, but it remained constant in the physiological pacing group.[15] Further analysis showed a physiological pacing advantage only in the subgroup of patients having an unpaced heart rate of $\leq$60 bpm. It was therefore concluded that pacemaker-dependent patients with low unpaced heart rate probably are paced frequently and will likely benefit from physiological pacing.[15]

Epidemiology: prognostic factors

The incidence of pacemaker dependency is variable and depends on the definition and testing technique. As mentioned before, there are differences in the protocols in terms of the lower basic pacing rate during the test, the gradual or not reduction of the rate of ventricular pacing, the duration of the test, and the evaluation of symptoms apart from the presence or absence of an escape rhythm. Of note, current protocols do not usually apply a complete cessation of back-up pacing for some time period. The latter process was very common in the past when external programmability by telemetry was unavailable. Moreover, the particular practice of each country regarding EPD implantation indications significantly affects the incidence of pacemaker dependency. For example, in poor countries with very poor resources and no cover of the costs by a national insurance, the pacemaker dependency incidence would be very high since only very symptomatic patients with advanced bradyarrhythmic disorders would have been implanted a PPM.[10]

The incidence of long-term pacemaker dependency depends mainly on the underlying bradyarrhythmic abnormality. It is well known that patients with high-grade AV block become pacemaker-dependent more frequently than those with SND.[11,13,16,17] In older studies, the incidence of pacemaker dependency in patients with high-grade AV block was reported to be 24–50%,[11–14] whereas in those with SND 6–12%.[11,13] However, in more contemporary studies that used different protocols, the incidence was much smaller. Nagatomo *et al.*[16] considered as pacemaker dependency the absence of escape or intrinsic rhythm for at least 30 s after gradual slowing of the pacing rate to 30 bpm, whereas they did not take into account the development of clinical symptoms. After a mean follow-up of 3.1 years, 2.2% of SND patients and 7.2% of AV block patients were pacemaker-dependent.[16] In a more recent retrospective study of 3638 patients, pacemaker

dependency was defined as the absence of an intrinsic rhythm producing a ventricular asystole longer than 5 s or occurrence of bradycardia symptoms during a back-up pacing of 30 bpm (gradual decrease) and subsequent complete cessation of pacing.[17] Pacemaker dependency was observed in 0.6 and in 3.5% of patients with SND and AV block, respectively.[17] In the setting of AV junction ablation, the reported long-term dependency is 30–42%[27,28] whereas in patients who have a PPM after cardiac operations, the long-term dependency is 40–63%.[32–34]

Several factors have been associated with the development of pacemaker dependency after permanent pacing for standard bradycardic indications. Besides the nature of the underlying bradyarrhythmia already mentioned, factors that may have predictive value include Adams–Stokes attacks/syncope before PPM implantation,[11,13] low heart rate prior to implant,[13] long duration of pacing/time after the initial implantation,[13,16] length of history of conduction disorder,[14] drug use (antiarrhythmics, beta-blockers, calcium channel blockers, and digoxin),[14] temporary pacing before PPM implantation,[17] and history of old myocardial infarction.[17] In the setting of AV junction ablation, the absence of escape rhythm immediately after ablation seems to be the most important predictor of long-term dependency, whereas the continuation of antiarrhythmic drugs does not seem to have any impact.[27] With respect to long-term pacemaker dependency after cardiac surgery, independent predictors include complete AV block as the indication,[32–34] long duration of the bypass,[32,33] history of syncope,[33] increased body mass index,[33] and preoperative left bundle branch block.[34]

Mechanisms

The data regarding the underlying mechanisms of pacemaker dependency and how this phenomenon can be modulated are scarce. An episode of prolonged ventricular asystole (cardiac standstill) in the setting of pacemaker dependency may have catastrophic consequences due to haemodynamic collapse, especially in patients who have significant underlying heart disease.[36] Remarkably, in some cases, ventricular standstill and the resultant cessation of coronary circulation create conditions (anoxia, ischaemia, and acidosis) that trigger the development of ventricular fibrillation.[36] The most important mechanism of depressed automaticity and inadequate escape rhythm is the overdrive suppression.[36–39] It has been proposed that the response to overdrive suppression is different in the diseased heart compared with the normal heart.[36] In other words, the ventricular standstill that occurs in the normal heart after overdrive suppression allows the establishment of a regular idioventricular rhythm after a few seconds. On the other hand, in some patients with structural heart disease, the depressed idioventricular automaticity and the consequent exaggeration of overdrive suppression lead to a prolonged ventricular arrest. The mechanisms that contribute to depressed intrinsic pacemaker activity of subsidiary infranodal centres include insufficient blood supply, electrolyte disturbances, anoxia, administration of antiarrhythmic or anaesthetic drugs, alterations of sympathetic activity, ageing-related abnormalities, and others.[36]

It has been consistently demonstrated in patients with PPMs that the magnitude of subsidiary infranodal pacemaker activity is affected by the rate and duration of overdrive pacing.[37–39] Schmidinger *et al.*[38] examined patients who had a PPM after AV junction ablation-induced complete AV block showing that there is a critical interaction between rate and duration of overdrive suppression. Specifically, it was shown that up to 60 s of overdrive incremental stimulation exerts an additional influence on impulse depression, whereas beyond this critical duration, the intrinsic impulse suppression is dependent only on the rate of incremental pacing.[38] Another study conducted in complete AV block patients having PPMs confirmed that overdrive pacing may suppress the infranodal subsidiary pacemakers and indicated that pacing at a rate of $\leq$50 bpm was minimal or absent, regardless of the duration of pacing.[39] At faster pacing rates, the suppression was significantly related to the pacing duration.[39] It is noteworthy that the escape rhythm in patients on dromotropic or bathmotropic drugs (antiarrhythmics, beta-blockers, digoxin, and calcium channel blockers) was slightly slower and, in some of these, was completely suppressed with overdrive pacing at 100 bpm.[39]

Unresolved issues

Despite the aforementioned data, several issues remain obscure and remain to be elucidated. The exact mechanisms implicated in the long-term pacemaker dependency are not known. Although previous studies indicate a role of short-term overdrive suppression, the relative effect of long-term continuous pacing or frequent brief episodes of pacing have not been examined. Specifically, data on the critical burden of ventricular pacing and the particular values of variables that may affect dependency (number and duration of ventricular pacing periods, mean rate of pacing, mode of pacing, rate-responsive pacing, and other parameters) in each individual are lacking. Furthermore, the exact effect of underlying medical conditions, drugs, and other potentially modifiable risk factors on pacemaker dependency is unknown. Also, there are no reported specific data for pacemaker dependency in ICD patients who do not have standard indications for pacing. Finally, the molecular and electrophysiological mechanisms of pacemaker dependency as well as the potential effect of pharmaceutical or 'electrical' therapeutic interventions have not been investigated.

Conclusion

Pacemaker dependency is observed in an appreciable number of paced patients after implantation of EPDs and may have dangerous consequences. Although there is no standard definition or consensus regarding the mode of testing, it is generally accepted that pacemaker dependency has a significant impact on the management of patients in various clinical settings. Several prognostic factors have been reported in the literature but the most important is the presence of AV block before the implantation. Further studies are needed to elucidate the underlying mechanisms implicated in this phenomenon. The putative merit of interventions in particular pacing parameters, or risk factors, as well as the modulation of specific molecular or electrophysiological targets, constitutes a subject of future research.

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