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Editorial

Comments on the 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy

Comentarios a la guía ESC 2021 sobre estimulación cardiaca y terapia de resincronización

SEC Working Group for the 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy and the SEC Guidelines Committee◇

INTRODUCTION

Cardiac pacing has been incorporated into so many areas and can be used to treat such a range of clinical conditions, that it has become a pillar of cardiology practice. Technological advances in recent years have led to marked changes in the characteristics and functions of the systems that are used, broadening the horizons for the management of a variety of clinical conditions, while minimizing unwanted effects. However, the paradigm shift goes beyond mere improvements in hardware, software, and lead structure. Compared with previous decades, huge strides have been made in how we assess, follow-up and detect patients' problems and needs. Indeed, we now talk about not just "following up" patients but also "monitoring" them, which implies a major change in the volume of data, access, responsiveness, and the way we interact with patients. Recent years have also seen the introduction of new technologies, such as leadless pacemakers, which have become highly prominent and, in the future, may become the first choice of treatment. There has also been strong renewed interest in "physiological" methods of cardiac pacing, some of our colleagues being veritable pioneers of these methods.[1] This, and much more, means that the ESC 2021 guidelines on cardiac pacing and cardiac resynchronization therapy[2] include significant changes from their previous version. The most noteworthy aspects are discussed in this editorial.

CLINICAL EVALUATION OF THE PATIENT AND INDICATIONS FOR PACING

Some of the aspects that required position harmonization are those covered in the 2018 ESC guidelines on syncope, which dealt with many areas that are also addressed in this new document.[3] Of note is the change in recommendation level regarding use of an implantable loop recorder in the workup of recurrent syncope of unknown etiology (I A). In this situation, the guidelines emphasize that the decision to use different monitoring methods must be clearly guided by the frequency of syncopal episodes, with a table provided to help select the appropriate method and duration of monitoring based on this frequency. The syncope guidelines already clearly discussed the inefficiency of 24-hour Holter monitoring in the assessment of syncope and its low cost-effectiveness despite low unit costs. In contrast, an implantable loop recorder provides an optimal yield when the number of episodes is < 1/month, a very common situation in the workup of syncope. Updates have also been made to other recommendations for diagnostic workup, such as carotid sinus massage, tilt testing, and electrophysiology study, with similar indications as the established guidelines on the subject. Electrophysiology study retains its recommendations for the assessment of patients with bifascicular block (IIa) and sinus bradycardia < 50 bpm (IIb), but the option of empirical pacemaker implantation should be considered for older or frail individuals with syncope and bifascicular block. Genetic studies have also been included in the new guidelines with a high level of recommendation (IIa) when warranted by the clinical context (young patients with progressive cardiac conductive disease or positive family history). These are based mainly on the study of recognized target genes for sinus node dysfunction (SND) and ventricular conduction (*SCN5A*), as well as genes involved in cardiomyopathies with conduction defects (*LMNA*). Imaging prior to pacemaker implantation has been given a class I recommendation.

One aspect that is stressed is the need to establish a direct correlation between symptoms and the results obtained on any of the observations or tests performed. This is especially important in SND, in which treatment with pacing has symptomatic but not prognostic benefits. Regarding therapeutic procedures, this new edition of the guidelines has some important new points. Ablation of atrial fibrillation (AF) is now an option for the treatment of bradycardia-tachycardia syndrome, a frequent manifestation of sick sinus and a common reason for pacemaker implantation in Spain.[4] The aim should be to eradicate the episodes of AF that cause the symptomatic pauses characteristic of this syndrome, while also avoiding the characteristic worsening of sinus node function caused by antiarrhythmic drugs. There is very little evidence available, but it has a class IIa recommendation, both here and in the most recent edition of guidelines on AF.[5] However, these recommendations must be contextualized. SND and bradycardia-tachycardia are very common conditions in our setting, especially in elderly patients. Ablation of AF in this population group has particular clinical, practical, and social implications, considering the frequent comorbidities and frailty of many of these patients. We must remember that pacemaker treatment in this context

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has been demonstrated to significantly improve quality of life, which is often the main priority in this population. Therefore, AF ablation represents an alternative to pacemaker implantation only in select patients and taking into account the clinical situation. In the context of atrioventricular block (AVB), the document makes clear that pacing has prognostic implications, and consequently, even in the absence of symptoms, pacemaker implantation is recommended (I). There are no changes or new information on the indications; the only point to mention is that pacing of permanent AF plus advanced AVB features as a specific entity. The definition of this recommendation includes the permanent character of AF, so that alternatives for maintaining sinus rhythm will have been ruled out, in line with what has already been advised.

Regarding the choice of pacing mode, in line with previous guidelines, DDD mode is still recommended, but VVI pacing may be considered in specific situations (very frail patients with reduced life expectancy or severe comorbidity). However, the new guidelines note that in AVB, DDD mode avoids pacemaker syndrome, but does not provide benefits in terms of morbidity and mortality. Regarding pacing in AAI mode for SND with preserved intrinsic conduction, the new guidelines appear to have put an end to the long-standing controversy and discount the use of this pacing mode over DDD. However, the 2019 American Heart Association guidelines[6] still include AAI pacing at a similar level of recommendation as DDD (reserved for specific cases), in contrast to the current ESC recommendation. These guidelines stress the importance of minimizing unnecessary right ventricle pacing by using specific algorithms and recognize that automatic atrial overpacing of some atrial arrhythmias with ATP could reduce the burden and progression to AF, giving it a new recommendation level (IIb) following the publication of the MINERVA study.[7]

Another classic debated topic is that of pacemaker implantation in patients with reflex syncope. The new guidelines harmonize the criteria with those of the syncope guidelines[3] and recommend the implantation of a DDD pacemaker in patients older than 40 years with reflex syncope with severe repercussions (frequent recurrence, unpredictable or without prodrome, resulting in injury, etc), when other measures are insufficient and spontaneous pauses (syncopal pauses $>$ 3 s or asymptomatic pauses $>$ 6 s), syncopal pauses induced in the tilt test, or syncopal pauses during carotid sinus massage have been demonstrated.[8] In these 3 clinical situations, taking into account that the hypotensive response that may be associated with these greatly modulates treatment effectiveness, pacemaker implantation may be associated with a $>$ 50% reduction in recurrence.

CARDIAC RESYNCHRONIZATION THERAPY

A clear message on cardiac resynchronization therapy (CRT) is that it has a greater benefit in patients with heart failure in sinus rhythm, left ventricular ejection fraction (LVEF) $\leq$ 35%, QRS duration $\geq$ 150 ms, and left bundle branch block (LBBB) (class I), independently of underlying disease. The other strong message is that CRT does not provide any benefit and should not be used in patients with heart failure and QRS $<$ 130 ms, unless the patient needs cardiac pacing for another reason. For patients with uncontrolled AF who are candidates for atrioventricular node ablation, the recommendation on pacing mode depends on the LVEF ($<$ 50%, node ablation plus CRT). There is a class I and class IIa recommendation for patients with LVEF $\leq$ 40% and 41% to 49%, respectively, based on the results obtained in the APAF-CRT trial (symptomatic improvement and reduction in acute exacerbations).[9] The most important change is in the level of recommendation for patients in sinus rhythm with LBBB morphology and QRS between 130 and 149 ms, which has been downgraded from class I to IIa. This is the same level as for patients with electrocardiographic morphologies other than LBBB and QRS $\geq$ 150 ms. It should be borne in mind that the 2 situations are not comparable nor is there evidence to allow their comparison. The same level of recommendation is the result of the modulation of the effects of CRT by 2 distinct variables: *a)* QRS width, and *b)* the depolarization pattern caused by LBBB. These interact safely, although there are no studies that allow evaluation of their independent effects. Although it is not expressly stated in these guidelines, it should be borne in mind that an electrocardiographic pattern other than LBBB is usually interpreted as nonspecific depolarization disturbances of the left ventricle, excluding right bundle branch block. Right bundle branch block is a situation for which there is currently no recognized indication. The recommendation to upgrade to CRT has been changed from class I to IIa for patients with pacemakers with LVEF $<$ 35%, HF symptoms, and ventricular pacing $\geq$ 20%. The justification for the decision is the lack of randomized studies and high rate of complications (except in high-volume centers). The recommendation for CRT implantation has been upped from IIa to I for patients who need ventricular pacing due to atrioventricular block and have LVEF $<$ 40% independently of the New York Heart Association (NYHA) functional class or presence of AF. Perhaps the recommendation for CRT should be expanded to patients with LVEF $<$ 50%, an inclusion criteria in the leading randomized trial on the subject, BLOCK HF.[10] This would reduce the incidence of pacemaker-induced cardiomyopathy in these patients and possibly the need to upgrade to CRT in the future.

All these recommendations are influenced by symptomatic patients (NYHA II or III); there is insufficient evidence on asymptomatic patients (NYHA I). In the absence of randomized trials, data are contradictory on the benefits of adding defibrillation therapy to CRT, particularly in nonischemic heart disease. In addition to the type of heart disease, comorbidity, age, and patient preference, these guidelines highlight the importance of cardiac fibrosis detected on cardiac magnetic resonance to predict arrhythmic events, which is included along with other variables in a decision-making flow diagram.[11] Another detail in the updated recommendations for CRT is that they have taken place in an evolving context in terms of the treatment of patients with heart failure. Recent years have seen the development of new pharmacological treatments (sacubitril-valsartan and SGLT2 inhibitors) that can induce significant reverse remodeling, improve symptoms, reduce acute exacerbations, and reduce mortality. This context differs from that of the various clinical trials that assessed CRT, a point which has generated lively debate regarding its indications and, more specifically, their timing. Some fundamental aspects must be remembered. First, the remodeling mechanisms in patients with heart failure and reduced LVEF are multifactorial: among them, the development of LBBB introduces a deleterious dynamic of ventricular depolarization that no drug can reverse. In addition, not only pharmacological treatments, but also CRT, have been shown to be able to induce significant reverse remodeling, a phenomenon that is essential in improving patients' prognosis. It should be borne in mind that some of the recent clinical trials with new pharmacological agents were carried out in a population with a substantial percentage of associated CRT. This, among other reasons, would suggest that there may be a potential additive rather than competitive nature among the different treatment modalities, provided the particular conditions and indications are respected. What is clear is that, currently, there are no direct comparative studies, so there remain several uncertainties regarding clinical treatment; these should be managed on a case-by-case basis in each patient.

ALTERNATIVE PACING STRATEGIES, REQUIREMENTS, SITES AND MODES

Of particular note, the new guidelines include a separate section on the rise, in clinical practice, of the group of techniques known as "physiological pacing". In general terms, the recommendation levels are based on a large number of observational studies, with few randomized studies, and which have focused on certain techniques. Therefore, left bundle branch pacing, an evolving outcome of physiological pacing (an area of huge interest in the device-implanting laboratories in Spain), has not received a recommendation.

Taking the information provided for each of the modalities separately, let us start with right ventricular septum pacing. This is appealing because implantation is easy (septal endocardial pacing as opposed to apical), the material resources required are no different from usual, and the technique does not have a prolonged learning curve. However, the clinical outcomes are similar to those with apical pacing, so it has not been given a higher level of recommendation. His-bundle pacing is the preferred option.[12] However, the new guidelines contain a rather conservative first approach to the indications for this technique, whether as an alternative or addition to conventional pacing with CRT. They recognize its drawbacks, such as the higher thresholds than for deep septal pacing (although no less than epicardial pacing from coronary sinus veins), lower sensing amplitude, and higher rate of lead dislodgement; these result in a lead revision rate of around 7% (conventional, 2-3%), requiring closer follow-up, and implantation of a backup lead in the right ventricle is recommended in certain patients (those with absence of an intrinsic rhythm or with devices with high capture thresholds, although there is no specific evidence supporting this recommendation). Adapted programming for each patient is recommended, taking into account the probability of undersensing or oversensing and the lack of functionality of automatic threshold measuring systems. Regarding the recommendations, they are limited by the lack of large, randomized trials. However, there are observational series,[13] crossover studies, and small randomized studies whose findings have not been reflected in these guidelines. Rather, the guidelines only include a class IIa recommendation for patients who are candidates for CRT in whom coronary sinus lead implantation is unsuccessful (the same recommendation level as for surgical epicardial lead, without taking into account the differences between the 2 techniques and the significant disadvantages of the latter). The technique has a IIb recommendation in patients with node ablation, especially with narrow QRS and as an alternative to conventional pacing for patients with a high expected percentage of pacing, although there is evidence that has not been considered for the guidelines that could increase this level of recommendation.[14] Regarding left bundle branch area pacing, the guidelines barely mention this promising technique due to its relatively recent emergence. However, they do make clear that it can avoid some of the problems with His-bundle pacing, so it is very likely that it will be added to the range of options for physiological pacing.

Another of the key updates is the inclusion of the new leadless pacing technology with specific recommendation levels. For VVI devices, the main indication is for patients with permanent AF or infrequent pacing, due to the potential harmful effects in patients with sinus rhythm, following the lessons learned from conventional pacing (with leads), although it is true that there is no specific evidence on this. But technology is evolving rapidly to give the new generation of leadless pacemakers that can maintain atrioventricular synchrony (sequential pacing, VDD).[15] The recommendation for this type of pacing system is strong (IIa) when there is no venous access in the upper limbs or there is high risk of infection, which seems reasonable. As an alternative to pacing with leads, there is a IIb recommendation taking into consideration life expectancy and patient preference. Socioeconomic considerations should be added to this, given the higher unit costs, and technical availability, as not all the device-implanting laboratories, at least in our setting, are able to provide percutaneous transfemoral device implantation. Despite this, the IIb recommendation as an alternative to conventional pacing certainly represents support for this treatment that, with technological and procedural improvements, will reach higher recommendation levels in the near future.

The expansion of the section dedicated to transcatheter aortic valve implantation aftercare is very relevant, with recommendations similar to those proposed in the 2020 AHA consensus document.[16] In new LBBB with QRS $>$ 150 ms or PR $>$ 240 ms that does not progress in 48 hours, ambulatory monitoring or electrophysiology study is recommended (IIa). We must point out that the 2 strategies have not been compared in experimental studies, which would be ideal, as advanced AVB can occur several days after implantation, especially in cases of self-expanding prostheses. Prolonged ambulatory monitoring may have an important role here. It is recommended to wait 5 days before deciding to implant a pacemaker for advanced AVB occurring in the context of acute myocardial infarction. Furthermore, and simplifying the decision-making algorithm compared with the AHA recommendations,[6] they have also suggested a 5-day waiting period before deciding on pacemaker implantation in advanced AVB after cardiac surgery. Based on consensus, the waiting period with SND after heart transplant has been extended to 6 weeks.

Another key aspect is the role of prophylactic pacemaker implantation (with or without defibrillator) in the context of neuromuscular disease (mitochondrial dystrophies and myopathies) and inflammatory diseases such as sarcoidosis, given the high risk of complete AVB and sudden cardiac death when associated with variable forms of conduction disorder on the electrocardiogram. Prophylactic pacemaker implantation may be considered even in the absence of electrocardiographic conduction disorder in conditions such as Kearns-Sayre syndrome (IIb). Pacemaker implantation is advised in cases of inflammatory disease complicated by permanent or transient AVB, such as sarcoidosis, and if LVEF is $<$ 50%, CRT-ICD should be considered directly (IIa). However, the new guidelines do not provide clear recommendations on infiltrative diseases, which are increasingly diagnosed, such as amyloidosis or Anderson-Fabry disease, in which conduction defects and sudden cardiac death are common and often unpredictable. In these conditions, the potential role of electromechanical dissociation as a causal mechanism of sudden death means that the relative benefit of treatment with pacing+defibrillation is not clear.

IMPLANTATION, PERIOPERATIVE MANAGEMENT, AND COMPLICATIONS

New sections have been introduced with a strong practical focus on perioperative management and patient-centered care. Prominence is given to those relating to perioperative anticoagulation, given the variety of drugs and new evidence available. Based on the results of the BRUISE studies,[17] bridging treatment with heparin is not recommended (III), but rather prescription of oral anticoagulation should continue (full or omitting doses depending on the drug and renal function). In the case of dual antithrombotic therapy (anticoagulation plus antiplatelet agent), it is recommended to stop the antiplatelet drug, except in cases of high thrombotic risk. For patients on dual antiplatelet therapy, management also depends on the estimated thrombotic risk after

percutaneous coronary intervention. If low, it is recommended to continue aspirin and stop the $P2Y_{12}$ inhibitor. If high, dual antiplatelet therapy should be continued unless the procedure is elective, in which case it should be postponed. If both thrombotic and bleeding risks are high, it is recommended to continue aspirin and stop the $P2Y_{12}$ inhibitor, although bridging treatment with cangrelor may also be an option, as discussed in SEC consensus documents.[18]

An important update is the recommendation that cephalic or axillary venous access should be first choice (IIa), due to the higher rate of implantation complications during implantation and lead-related complications during follow-up observed with subclavian access. The guidelines recognize the importance of the surgical technique and prevention of hematoma in avoiding complications. Interestingly, although there are no randomized studies and the evidence comes from small series or even series of patients undergoing abdominal surgery, saline rinsing of the pocket is recommended to prevent infection (IIa). Even though there is a large, randomized study showing the benefit of using antibiotic mesh in high-risk patients (pocket revision, generator replacement, pacing system upgrade or first CRT implantation), it is only given a IIb recommendation. This recommendation has not taken into account the long-term results of the WRAP-IT study[19] that confirm the beneficial effect of antibiotic mesh in this subgroup of patients.

Regarding specific complications, it is worth mentioning potential tricuspid regurgitation. Although it is accepted that the leads may interfere with valve function, a randomized study with a small number of patients showed no differences between implantation of leads positioned in the right ventricle vs in the coronary sinus. Therefore, the guidelines acknowledge that the assessment of patients who develop tricuspid regurgitation after device implantation is complex, and should take into account the not insignificant risk of removal.

MONITORING, FOLLOW-UP, QUALITY, AND PATIENT EMPOWERMENT

This relatively new area has not been discussed in detail in previous guidelines. Regarding magnetic resonance as an imaging method, the new guidelines are in line with previous expert consensus statements[20] and describe it as safe with conditional devices, following the indications of the manufacturer and waiting 6 weeks after implantation (I). During the first 6 weeks, as is the case for nonconditional devices, MRI should be considered if there is no diagnostic alternative and provided there are no epicardial leads, damaged leads, or adaptors (IIa). In patients with abandoned leads, it is permissible if it does not exceed 1.5 T, along with some other conditions (IIb). Interestingly, they do not discuss the management of patients with leadless pacemakers, which is an increasingly frequent reality in practice. The approach and the treatment of patients who undergo radiotherapy is reviewed succinctly. With regard to previous consensus statements,[20] the type of monitoring required is defined according to the characteristics of each patient and procedure. Although they mention the possibility of oversensing due to electromagnetic interference, they do not establish programming recommendations.

In the previous guidelines, the usefulness of remote monitoring was restricted to the early detection of events. The new guidelines recognize the new concept of remote management, which includes remote monitoring and remote interrogation at regular scheduled intervals (6 monthly). This update, which is of great clinical relevance, enables optimization of follow-up, especially for patients with difficulties in attending in-person clinic visits, as it provides the option of spacing them out to 12 months for CRT devices and 24 months for others. They also recognize the usefulness of remote monitoring in cases of alerts issued by the manufacturer for the early detection of events. In general terms, documentary and institutional support is provided for the new ways to treat, assess, follow-up and monitor patients afforded by these new technologies, to help guide a future that is likely to see a lot of change in the short-term.

Similar to the approach in recent editions of guidelines published by the ESC, there is an emphasis on holistic care (which includes lifestyle, diet and exercise, and cardiac rehabilitation requirements) and on following the principles of patient-centered care and shared decision-making. Obviously, device implantation should be based not only on the evidence but also on the appropriate explanation of benefits and potential risks of each option, as well as the patient's preferences and opinions. It should also take into account social and cultural aspects, something which has become more prominent with the participation of the patient thanks to the new monitoring technologies.

CONCLUSIONS

The new guidelines on cardiac pacing and cardiac resynchronization therapy contain several significant updates and lend support to new therapeutic and technological modalities, whose translation to clinical practice will be welcome and immediate, or in some cases already in practice in the laboratories. However, some aspects and future directions remain uncertain. We will have to wait for new evidence, already in the pipeline, to know the final stance on promising aspects such as physiological pacing, the development of leadless technology, and remote monitoring methods. What is certain is that these new strategies are here to stay.

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CONFLICTS OF INTEREST

The conflict of interest documents for all authors can be accessed in the supplementary data.

APPENDIX 1. AUTHORS

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APPENDIX 2. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2021.11.015

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