Revista de la Facultad de Medicina
ISSN: 2357-3848
ISSN: 0120-0011
Universidad Nacional de Colombia

Figueroa-Bohórquez, David Mauricio; Benavides, Xiomara; Garzón, Luz; Espinel, Daniel; Suarez, Luis; Uribe, María; Gómez-Aristizabal, Linda; Lozano-Márquez, Eyner

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Revista de la Facultad de Medicina, vol. 65, no. 3, 2017, July-September, pp. 483-489
Universidad Nacional de Colombia

DOI: 10.15446/revfacmed.v65n3.57498

Available in: http://www.redalyc.org/articulo.oa?id=576364413016

REVIEW PAPER

DOI: http://dx.doi.org/10.15446/revfacmed.v65n3.57498

Electrocardiographic alterations associated with heart transplantation. Triggers, mechanisms and meaning

Alteraciones electrocardiográficas en el paciente con trasplante cardíaco. Desencadenantes, mecanismos y su significado

Received: 18/05/2016. **Accepted**: 29/06/2016.

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| Abstract |

Introduction: Heart rhythm disorders are associated with increased morbidity and mortality. However, triggers and implications in patients with heart transplantation are not clear.

Objectives: The purpose of this research paper is to identify and explain the determinants for the onset of electrical conductivity alterations in patients with a heart transplant, as well as to describe the most common arrhythmias and their pathological implications.

Materials and methods: A literature review was made in the PubMed online database for a total of 411 results. In addition, clinical practice guidelines on cardiac transplantation, cardiovascular electrophysiology and infective endocarditis were searched. Sixty articles related to the objectives of this study were chosen.

Results: Surgical technique, heart denervation, sinus node trauma, graft rejection, endomyocardial biopsies and infections are the main factors that compromise organ viability and the life of transplanted patients. These factors can be observed as sinus rhythm disturbances.

Conclusions: When a cardiac arrhythmia is detected, the medical team must provide a treatment that is not limited to symptomatic and sinus rhythm control. An active search of the etiology must be initiated since it may indicate an underlying pathological process.

Keywords: Heart transplantation; Arrhythmias; Cardiac; Bradycardia; Tachycardia (MeSH).

Figueroa-Bohórquez DM, Benavides X, Garzón L, Espinel D, Suarez L, Uribe M, *et al.* Electrocardiographic alterations associated with heart transplantation. Triggers, mechanisms and meaning. Rev. Fac. Med. 2017;65(3):483-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v65n3.57498.

| Resumen |

Introducción. Las alteraciones del ritmo cardíaco están asociadas con un aumento en la morbimortalidad; sin embargo, en pacientes con trasplante cardíaco no son claros sus desencadenantes ni implicaciones.

Objetivos. Realizar una búsqueda en la literatura para identificar y explicar los determinantes en la generación de alteraciones de la conducción eléctrica en pacientes con trasplante cardíaco, así como describir las principales arritmias que pueden presentarse, explicando sus implicaciones patológicas.

Materiales y métodos. Se realizó una búsqueda en la base de datos PubMed que arrojó un total de 411 resultados. Además, se buscaron las guías de práctica clínica sobre trasplante cardíaco, electrofisiología cardiovascular y endocarditis infecciosa. Se eligieron 60 artículos que lograban responder a los objetivos de este estudio.

Resultados. La técnica quirúrgica, la denervación cardíaca, las lesiones del nodo sinusal, el rechazo del injerto, las biopsias endomiocárdicas y las infecciones son los principales factores que comprometen la viabilidad del órgano y la vida del paciente trasplantado, manifestándose como alteraciones del ritmo sinusal.

Conclusiones. Ante la detección de alguna arritmia cardíaca, el equipo médico debe proporcionar un manejo que no se limite al control sintomático y del ritmo sinusal, sino que se debe iniciar una búsqueda activa de su etiología, ya que esta puede ser la manifestación de un proceso patológico subyacente.

Palabras clave: Trasplante de corazón; Arritmia cardíaca; Bradicardia; Taquicardia (MeSH).

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Introduction

Despite the progress in pharmacological treatment, organ transplantation can lead to multiple chronic pathologies that cannot be properly addressed with medical management (1). Cardiac transplantation is reserved for patients with heart disease who evolve to advanced and symptomatic heart failure despite optimal medical management, in other words, functional status D and functional class IV according to the New York Heart Association classification (NYHA) (2).

With the development and improvement of surgical techniques, as well as the improvement of post-transplant management, the patient is expected to restore hemodynamic stability, improve functional class and have a better quality of life, reaching survivor rates at 1 year and 10 years close to 90% and 50%, respectively (2-5).

Often, survival and quality of life are compromised by the onset of arrhythmias at any time after transplantation, and triggers and implications are not clear to date. The purpose of this article is to conduct a literature review to identify and explain the variables associated with cardiac transplantation that influence alterations in sinus rhythm and electrical conduction, during or after surgery. Similarly, a description of the main arrhythmias that patients may suffer after orthotopic cardiac transplantation and its consequences is presented.

Materials and methods

A systematic review was made in the PubMed database based on multiple combinations of MESH terms: "heart transplantation", "Arrhythmias, Cardiac", "Tachycardia, Ventricular", "Tachycardia, Supraventricular", "Bradycardia", "Pacemaker, Artificial" and "Catheter Ablation". The search was limited to studies in human. Articles that addressed heterotopic heart transplantation or that were written in a language other than English or Spanish were excluded. 411 articles were obtained.

The abstracts obtained after the search were analyzed, and those that coincided with the objectives of this study were selected. In addition, the national guidelines for cardiac transplantation and cardiovascular electrophysiology were consulted in the official website of the Colombian Society of Cardiology, while information on clinical practice guidelines for infective endocarditis were obtained from the European Society of Cardiology website. In total, 60 articles were chosen and used as reference for this review.

Factors associated with the development of cardiac arrhythmias

Surgical technique

The biauricular transplantation technique was first described by Lower and Shumway in the 1960s, and is characterized by myocardium anastomosis between both donor atria and a remnant of these structures in the recipient. Later, in the 1990s, the literature described the bicaval technique, in which anastomosis occurs in the large vessels in both portions of the vena cava and around the pulmonary veins, resulting in less manipulation and alteration of the atria (6).

Currently, a strong discussion has taken place around which techniques should be preferred, since long-term results do not show significant differences, although multiple publications demonstrate the benefits of the bicaval technique with respect to the standard technique (3,7-11).

The biauricular technique has demonstrated that suture lines form scars that act as low voltage areas, and that they isolate electrically the donor tissue from the receptor tissue, which is the reason for a higher incidence of flutter-type arrhythmias in patients who undergo this surgical technique.

Furthermore, randomized controlled studies have reported that the use of the bicaval technique needs less pacemakers implantation; however, no association was established between the permanent use of this device and long-term survival (12- 14). Czer *et al.* (12) developed a study comparing the functional class of transplanted patients with both surgical techniques during physical activity, considering variables such as heart rate, oxygen consumption, carbon dioxide production and duration of exercise, without finding differences between both groups.

Denervation and reinnervation

All surgical techniques involve cardiac denervation, which causes the heart to lose its autonomic regulation and, in consequence, the variability of the heart rate as a way of physiological adaptation to different stimuli of the environment. For this reason, the transplanted organ is guided by the sinus node rhythm and only responds to chronotropic, inotropic and dromotropic stimuli of the circulating catecholamines (15), and to the changes in blood volume caused by the venous return that stimulates a determined contraction force according to Frank-Starling's law (16).

Similarly, sympathetic reinnervation is considered unpredictable, disordered, often incomplete and variable among patients, leading to aberrant reinnervation, which may cause multiple sinus rhythm disorders (17-20). A study led by Uberfuhr (20) in Germany found that about 60% of patients with orthotopic heart transplantation had some degree of sympathetic reinnervation.

Sinus node dysfunction

Sinus node dysfunction —defined as the absence of sinus rhythm, sinus node recovery time greater than 1.4 ms or secondary electrical pauses during electrophysiological examinations— is the most common cause of early implantation of pacemakers in transplant patients, that is, before 3 months after surgery (21-23). Depending on the series, a prevalence between 10% and 45% of early sinus dysfunction is reported, reaching implantation rates of up to 30% in this group of patients (12,24). Early sinus dysfunction is largely attributed to the surgical procedure, whether caused by trauma, node ischemia due to nodal artery injury, or prolonged ischemia times. Over the years, a decrease in the incidence of sinus node alterations has been reported, which has been attributed to the improvement of the surgical technique (25).

Deleuze *et al.* (13) compared the results of both surgical techniques in the postoperative period of 81 heart transplants, finding that the biauricular technique showed a higher prevalence of sinus node dysfunction, while patients treated with the bicaval technique did not require implantation of a pacemaker within the first 30 days, although 12.5% of them did (25). AV blocks and sinus dysfunction three months after the procedure are, to the same extent, the main indication of the implantation of a permanent pacemaker.

Recovery of sinus node function is common, particularly, when these changes occur rapidly after transplantation (21,26,27). Late sinus node dysfunction occurs three months after transplantation, and about 5% of patients require implantation of pacemakers for this

reason according to a study published by Luebbert *et al.* (6), who did not find a higher prevalence related to any surgical technique, age, sex or pre-transplant diagnosis.

Rejection of the graft

About 20-30% of patients have experienced graft rejection during the first year after transplantation. This process is defined as the presence of inflammatory infiltrate in the transplanted tissue. Hence, taking endomyocardial biopsies is necessary for diagnosis and classification. Based on the results of the histological examination of the sample, it can be established whether there is any degree of cellular or humoral rejection according to the International Society for Heart and Lung Transplantation in 2004 (28,29). Despite the efforts and good results that relate findings by magnetic resonance to graft rejection cases, the gold standard is still histological study (30). Some series claim that the presence of acute graft rejection is closely related to the onset of cardiac arrhythmias, especially with flutter and atrial fibrillation, but this remains a controversial issue. Ahmari *et al.* (31) from the Mayo Clinic state that the recurrence of moderate to severe acute rejections results in cardiac fibrosis that compromises diastolic function and predisposes the development of atrial flutter, and that these markers imply poor prognosis in the long term. Thus, the next step should be to rule out acute rejection of the graft to detect de novo alterations (17,32).

Chronic graft rejection in heart transplantation refers to cardiac graft vasculopathy (CGV). Although this process was initially understood as an immune-mediated process, today it is now known as a multifactorial process that includes alloimmune, autoimmune and non-immune mediated responses (24).

The progression of intraluminal changes, which ends in the occlusion of the coronary macrovasculature and microvasculature flow, begins as a lesion and apoptosis process in the endothelial parenchyma that leads to the concentric proliferation of the smooth muscle and to the failure of the cardiac graft, creating a terrain for the onset of both atrial and ventricular arrhythmias (24).

The development of CGV is the most predisposing factor to myocardial tissue ischemia and fibrous tissue formation, and the one that affects survival the most; thus, it is the main cause of death at 3 years after transplantation, together with malignant processes (30). At 5 years, 30% of transplant patients suffer CGV (24,33), and multiple episodes of acute rejection are considered as a risk factor for its development. The gold standard for this pathology is coronary angiography, which is why it is performed routinely in these patients.

Biopsies

Biopsies are routinely performed, and in cases when the medical team deems them necessary to rule out acute rejection of the graft. This procedure is usually performed under local anesthesia, has a mortality rate of 0.4% (29), and is considered the gold standard for detecting rejection (34).

Despite being relatively safe, the main complications of biopsy are ventricular perforation and cardiac tamponade, atrial or ventricular arrhythmias, pneumothorax, tricuspid insufficiency, ventricular coronary fistula, transient cardiac arrest, carotid artery puncture, infection and venous hematoma (29,35).

For this type of procedure, the transjugular route is the first option for access, whereas the femoral vein route is used in case of difficulty with jugular access or if coronary angiography is performed during the procedure.

There is no consensus as to how often routine biopsies should be taken. The Colombian cardiac transplant guidelines of 2009 suggest that 11 biopsies should be taken during the first year (29), while the international guidelines for cardiac transplantation and lung cancer of 2010 propose 18 biopsies during the same period of time (36). Nguyen *et al.* (37) recommend a maximum of 31 endomyocardial biopsies, since they demonstrated that exceeding this number of repetitions increases the risk of severe tricuspid insufficiency.

Over time, progress in immunosuppressive treatment has decreased rejection rates, which would explain the decrease in the frequency of this diagnostic procedure. However, further studies are needed to establish a global consensus in this regard, since acute rejection is usually a subclinical process with severe long-term repercussions.

During the procedure, ventricular arrhythmias are common, but they are usually temporary and transient. In the long term, third degree atrioventricular (AV) blocks have been associated (27) because of the frequency of this procedure, although this is not widely described in the literature and is considered an uncommon event.

Magnetic resonance imaging is suggested to replace endomyocardial biopsies, obtaining promising results in preliminary studies (38,39).

Infections

Immunosuppressive therapy opens the door to a large number of microorganisms that the immune system could control if it functions properly. According to the type of therapy and the postoperative time, the etiological agents of greater incidence vary (29). About 12% of deaths after transplantation within the first month are associated with infections by nosocomial bacterial microorganisms in different sites. Between the second and sixth month, infectious pathologies are usually caused by opportunistic infections and the reactivation of latent infections. Finally, microorganisms acquired in the community are the most frequent after the sixth month (29,40).

Estimations indicate that about 1.5% of cardiac transplant patients are infected with infectious endocarditis (IE), mostly by *Staphylococcus aureus* and *Aspergillus fumigatus*. Risk factors include the use of central catheters in the perioperative period and frequent endomyocardial biopsies (41).

Electrical conduction disorders are observed in 1% to 15% of IE patients, mostly manifested as AV blocks, branch blocks and atrial fibrillation. The presence of these alterations is associated with poor prognosis and higher mortality (42). Infections caused by agents such as cytomegalovirus and *Chlamydia pneumoniae* favor the development of CGV and, consequently, graft failure and cardiac arrhythmias caused by the mechanisms described above. *C. pneumoniae* infection is associated with greater severity of CGV (24).

Drugs

The average effect of amiodarone is prolonged, so it is possible to continue to observe its effects for several days in patients who took it before the transplantation. In patients who develop early sinus dysfunction, the effect of amiodarone may further compromise the electrical conduction of the transplanted organ (17).

Arrhythmia in the transplanted patient

Tachyarrhythmias

Supraventricular tachyarrhythmias

Supraventricular tachyarrhythmias have a high incidence in transplanted patients, greatly compromising their quality of life and survival. Dahu *et al.* (43) proposed five mechanisms involved in

the development of atrial arrhythmias: 1) reentrant in the donor's atrium associated with the scar or the valve; 2) focal tachycardia in the donor's atrium; 3) atrial fibrillation in the donor's atrium; 4) re-entry arrhythmias that compromise two or more reconnections between donor and recipient atrium, and 5) arrhythmias originating in the recipient atrium that pass to the donor through one or more focal reconnections.

In turn, Vaseghi *et al.* (32) reviewed supraventricular tachycardia, and proposed another mechanism related to pre-existing alterations in the electrical conduction of the donor, which are manifested as AV nodal reentrant tachycardia and re-entry tachycardia associated with abnormal beam (32,44).

Supraventricular tachyarrhythmias can be classified as:

Atrial fibrillation, which is common in the early postoperative period and is almost always associated with graft manipulation, inflammatory period and autonomic changes. The incidence of atrial fibrillation decreases progressively, becoming exceptional during the late postoperative period in the absence of vasculopathy, rejection or infection (17,32,43,45). These low numbers are associated with the isolation of pulmonary veins, cava veins and the posterior wall of the atrium, which are the main foci of generation. This occurs because the surgical scar acts as an electrical insulator between recipient and donor atria remnants (46).

When atrial fibrillation is identified, the first step to take should be discarding the clinical cases previously mentioned as possible triggers. The control of these pathologies may be sufficient in most cases to stop their development. Antiarrhythmic drugs of choice are amiodarone and procainamide, which are not usually formulated for a long time because of the high resolution rate of this type of cardiac arrhythmia, which is associated with the management of its triggers. Controlling immunosuppression levels is necessary due to the interaction of amiodarone and warfarin with ciclosporin and tacrolimus (17). In case of persistence, catheter ablation is the treatment of choice for this disorder (17).

Atrial Flutter is the most common type of arrhythmia in patients after a heart transplant. In non-transplanted patients, the isthmus-dependent atrial flutter is formed by a counterclockwise circuit, which compromises the tricuspid valve, the Thebesian valve, the opening of the superior and inferior vena cava, and the crista terminalis. In transplanted patients, a similar circuit is formed, with the difference that the posterior line of the latter conforms the atrial suture line (47). This type of arrhythmia is more common in the biauricular technique (48).

Mitral annular flutter is less common and has no major incidence on a particular type of surgical technique. Just like atrial fibrillation, the development of flutter is also associated with periods of acute rejection, infection or vasculopathy, and their identification should stimulate the active search of these entities in the transplanted patient. When these causes are discarded and treated, as well as ventricular dysfunction and valvular pathology, catheter ablation is recommended to form an electrical block line between the tricuspid ring and the atrial suture for the right atrial-dependent flutter (48), whereas ablation of the anterior line of the circuit is recommended for the left atrium (49).

Focal atrial tachycardia is caused by the formation of depolarization foci near the atrial scar that take control of the heart rhythm. Scars, together with fibrosis, predispose to the formation of areas of slow electrical conduction, and provide the substrate for the production of macroreentrants and the development of focal atrial tachycardia. Elsik *et al.* (45) reported patients in whom the focus is found in the donor's atrium, while Vaseghi *et al.* (32) describe cases in which depolarization begins in the atrial remnant of the recipient and passes into the donor tissue through bridges formed by fibroblasts, which create gap-like junctions that allow electrical transmission. Definitive treatment is focal catheter ablation.

Atrial reentrant and nodal reentrant tachycardia require a preexisting route in the donor that allows a macroreentrant. Although they have been described in the literature, they are uncommon in transplanted patients. Radiofrequency ablation is curative (32).

Ventricular tachyarrhythmias

Ventricular extrasystoles and non-sustained ventricular tachycardia may be common in the early post-transplant period. The subsequent development of sustained and non-sustained ventricular tachycardia suggests an episode of acute rejection or graft vasculopathy (18), while taking into account other rare etiologies that may have similar clinical features and may be reversible, such as idiopathic fascicular ventricular tachycardia (50).

The most common arrest rhythm in cardiac denervation in sudden death events is asystole, followed by pulseless electrical activity; both are non-defibrillating rhythms, so the use of automatic implantable defibrillators remains controversial (17,51).

Bradyarrhythmias

Bradyarrhythmias may appear during the early or late period after a heart transplant, and can be caused by sinus node dysfunction or errors in the electrical conduction, with functional or dysfunctional sinus node.

In the early postoperative period, the transplanted heart usually requires positive chronotropic agents or temporary pacemaker implantation. It has been demonstrated that the donor's sinus node is hypersensitive to these pharmacological agents, so its use must be cautious (52).

Early sinus node dysfunction puts the patient's life at risk in the early postoperative days, and its multifactorial etiology is almost always associated with circumstances that depend on the surgical procedure (12,21,53,54). As for late sinus dysfunction, the role of graft rejection in its development is controversial.

Sinus dysfunction may be paroxysmal or persistent, and may be manifested as sinus bradycardia or as a total stop of the sinoatrial node (53,54). To control these entities, a therapeutic test can be performed with isoprenaline, dopamine, dobutamine or theophylline in search of increased heart rate and recovery of sinus rhythm. If this therapy fails, the use of pacemakers should be considered (21,55).

The 2011 Colombian guide to cardiovascular electrophysiology (56) provides the following recommendations for the implantation of a permanent pacemaker:

Class I: it is indicated in symptomatic, inappropriate, persistent or not-expected-to-improve bradycardia.
Class IIA: it is considered in symptomatic, recurrent and prolonged bradycardia that limits rehabilitation or discharge during the post-surgical recovery phase of the transplant (level of evidence C).
Class IIB: it is considered in patients with syncope after cardiac transplantation although bradyarrhythmia has not been documented (level of evidence C).

Early implantation of a permanent pacemaker occurs when the heart rate has not been normalized with other interventions after three weeks (57). Early sinus dysfunction in the early postoperative period is usually not associated with damage to the electrical conduction system, so bicameral pacemakers with AAIR/DDDR function that seek physiological stimulation and preserve AV synchrony have been

widely used in the last years. However, after one year of implantation, the frequency of activity of these devices decreases, in most cases due to the recovery of the sinus function (55,57,58).

In the late postoperative period, errors in the conduction of the nerve impulse are predominant, with AV blocks being the leading cause of implantation of cardiac pacemakers in this period. This phenomenon has been attributed to the development of graft rejection, since electrical conduction tissue has been proven as a typical target of humoral response during this process (52,56,59).

Conclusions

The development of arrhythmias is a frequent issue and, in some cases, puts the life of the patient at risk. This complication is related to multiple triggers. There are factors associated with the surgical procedure itself, such as ischemia times, sinus node injury, and excessive manipulation of the atria due to the surgical technique and cardiac denervation, as well as other mechanisms related to the preoperative and post-surgical periods, such as acute rejection episodes, reinnervation, ventricular biopsies, graft vasculopathy, systemic infections, and drug effects.

The most common arrhythmias are bradycardia, which, in a significant percentage, will require implantation of permanent pacemakers. The most frequent tachyarrhythmia is the isthmus-dependent flutter, which can be treated with catheter ablation. The most common rhythm of cardiac arrest in these patients is asystole, unlike the general population, where more defibrillatory rhythms such as tachycardia and ventricular fibrillation occur.

The detection of any cardiac arrhythmia should lead to think of the possibility that this is the manifestation of an underlying pathological process that puts at risk the viability of the organ and the life of the patient. The medical team is obliged manage this condition in a way that is not limited to symptomatic control and sinus rhythm, but to initiate an active search for its etiology to give optimal therapeutic management to each patient.

Conflict of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgement

To Dr. Ana María Barón, cardiologist and cardiac transplant specialist, for her support during the development of this article.

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