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PhD THESIS

THE IMPACT OF DIABETES MELLITUS ON THE IMPLANTATION AND FUNCTION OF INTRACARDIAC DEVICES

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T i m i ș o a r a

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I. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disturbance that affects hundreds of millions of people worldwide and causes many pathologic changes throughout the body, including the cardiovascular system. The relationship between DM and vascular disease has been well studied. However, the connection between DM and conduction disturbances, let alone bradyarrhythmia and pathologies that necessitate an intracardiac device, is a topic that has not seen so much spotlight as these types of cardiac pathologies necessitate the implantation of an intracardiac device. This device's optimal function is key to keeping patients alive and functional individuals of society. Thus, DM affecting key functional parameters would worsen the burden of both diseases. Bradyarrhythmia defines a wide variety of conduction and electrical impulse generation disturbances, which can be very rarely anticipated. In the absence of specific emergency and long term, treatment can often lead to death. We have observed in a clinical setting that these pathologies often overlap. In the myriad of studies linking cardiovascular disease to DM, few studies exist regarding a possible link between the diseases mentioned above. This study aims to analyze a statistically significant number of patients that have been implanted with permanent pacemaker patients from the Institute of Cardiovascular Diseases Timisoara and the "Pius Branzeu" Clinical County Hospital Timisoara. The study aims to find whether DM is a risk factor for life-threatening bradyarrhythmia, which requires the implantation of intracardiac devices. The study focuses mainly on pacemakers and includes cardiac resynchronization therapies and intracardiac defibrillators.

The study aims to investigate how DM affects the well-being of patients with intracardiac devices and whether DM and the wide variety of metabolic disturbances it is responsible for are factors that may affect the functioning

parameters of these devices. In this study, we included patients with a wide variety of implantable cardiac devices: single chamber pacemakers, dual-chamber pacemakers, and more complex devices such as three lead pacemakers for cardiac resynchronization therapy (CRT) as well as single-chamber defibrillators and three lead defibrillators (CRT-D). This amounts to a large study group with extremely diverse pathology, ranging from rhythm disturbances such as complete AV blocks and SSS to malignant arrhythmias such as ventricular tachycardia and ventricular fibrillation and patients with dilative cardiomyopathy.

II. LITERATURE REVIEW

1. DIABETES MELLITUS

DM is a metabolic imbalance in which the plasmatic concentration of glucose is frequently above the standard threshold. Two main mechanisms are to blame for this: the presence of factors that stand in the way of insulin fulfilling its role of introducing glucose in the cell or insufficient insulin secretion. Generally, DM is a progressing and chronic state; however, there are situations in which it can be transient.

DM is classified depending on the physiopathologic process that leads to it. The two main branches are type 1 and type 2 DM. A state of abnormal glucose equilibrium precedes both diseases. T1DM is the result of partial or total insulin deficiency. Patients with a high risk of developing T1DM can be identified before the disease sets in by searching for serum autoantibodies that target insulin-secreting cells in the pancreas or screening for genetic markers.

Type 2 diabetes mellitus (T2DM) encompasses a diverse group of diseases, their pathological bases being a resistance to the action of insulin, insufficient insulin secretion, or high gluconeogenesis. A state of abnormal

glucose homeostasis most often precedes T2DM. This "Prediabetic" state is defined by the alteration of fasting glycemia and lowered glucose tolerance.

In the past, the types of DM were classified as insulin-dependent and noninsulin-dependent diabetes mellitus to define T1DM and T2DM, respectively. These terms are currently considered obsolete because people with type II diabetes require insulin to achieve glycemic control in not-so-rare cases.

T1DM encompasses about 5-10% of total cases. Most cases are diagnosed before individuals reach 30 years of life, with most individuals diagnosed between 5 and 7 years old. T1DM is considered one of childhood's primary chronic diseases. although the autoimmune complications that lead to the destruction of pancreatic beta cells can trigger at any age. A wide array of autoantibodies destroy pancreatic β-cells; these include anti-insulin, anti-islet, anti-GAD, anti tyrosine phosphatase IA-2, and IA-2β antibodies. One or more of these antibodies can be found in about 85-90% of patients when the disease has manifested, and the initial diagnosis is made. HLA genes also seem to be at fault, including DQA and DQB genes. The process is not yet fully understood; HLA DR/DQ can be a predisposing factor.

It is estimated that between 5% and 10% of patients diagnosed after 30 years of age have T1DM. Although the incidence of T1DM is directly proportional to advancing in age, it is more and more frequently diagnosed in young people, especially among obese adolescents.

Around the 90s, endocrinologists noted the existence of a type of diabetes that engulfed characteristics from both type 2 and type 1 DM; this rare condition was named MODY (maturity-onset diabetes of the young). It has been classified as a subtype of diabetes caused by monogenic defects, with the autosomal dominant inheritance manifesting in young adults more frequently before 25 years of age. MODY is a rare disease (under 1%) and is often misdiagnosed as type I or even type II diabetes mellitus. Mutations of the GCK

genes (which are responsible for type 2 MODY) and nuclear hepatocyte factor HNF 1A/4A (responsible for MODY type 1 and 3) are considered the molecular bases that lead to the installment of MODY. Individuals with the modified GCK gene are usually oligosymptomatic, have stable glycemic levels, and often do not require medication. Unluckier are those who inherit the HNF1A and HNF4A mutations. In these individuals, insulin-secreting β-cells are destroyed in time, leading to high glycaemic values and the sum of complications following the metabolic disturbance.

2. CARDIOLOGY

The generation and propagation of the electrical impulse with a role in stimulating the myocardium is the main function of the cardiac conduction system. The initial impulse is generated in the tissue of the atrioventricular node, which possesses impulse-generating properties, a property called automatism, and the ability to conduct the impulse slowly. Rapid impulse transmission is a specific property of the ventricular conduction tissue, which is essential to achieve a physiologic and synchronized ventricular contraction. The heart's conduction system generates over two billion beats over its lifetime. Pulse generation or propagation abnormalities result in Brady and tachyarrhythmias that clinically manifest through signs of heart failure, syncope, or sudden cardiac death.

The atrial myocardium then swiftly transmits the impulse to the atrioventricular node, a small structure located in the interatrial septum near the coronary sinus, where the electrical impulse is physiologically delayed. Due to this delay, the ventricles can fill correctly before the atria constrict, contributing to the final phase of the diastole. The annulus fibrosus and central fibrous body comprise a plane of connective tissue that electrically isolates the atrial and ventricular myocardial tissues to maintain ventricular depolarization physiologically. Otherwise, the ventricles would contract anarchically due to the

action potential that would travel through the myocardium. Fortunately, the conducting atrioventricular bundle of His-Bundle is the only physiological electrical route that links the atrial to the ventricular myocardium. This electrical communication to the atrioventricular goes through the crest of the ventricular septum.

Further on, the Purkinje fibrous network right and left bundle branches transmit the impulse to the ventricular myocardium. Thus, the ventricular conduction system is comprised of these fast-conducting structures: the His bundle, the left and right branches, and the Purkinje network. The conductive cardiac system is divided into impulse-generating cells, which possess slow conduction abilities, and fast-conduction cells located at the ventricular level. The main pulse generator of the heart is the sinoatrial node, located at the junction between the superior vena cava and the right atrium. Firstly, the impulses generated at this level quickly cross the atrial myocardium, the rapid propagation thus ensuring the synchronous contraction of the atria.

The stimulation of the atrioventricular node represents the next stage in propagating the impulse. The atrioventricular node has a physiological role in slowing down the electrical impulse, thus delaying ventricular contraction. This is necessary to ensure an excellent diastolic filling and avoid a possible synchronous contraction with the atria, which would lead to a decrease in beat volume. The impulse is accelerated again as soon as it reaches the His fascicle, which crosses the central fibrous structure of the heart. This fibrous tissue's role is to provide electrical insulation between the atria and ventricles. Next, the impulse is transmitted to the ventricular myocardium through the His-Purkinje network. Therefore, the ventricular conduction system is composed of the His bundle, the right, and left branches, and the distal Purkinje fibers. The impulse transmitted through these fibers controls the ventricular myocardium contraction starting with the apex and ending with the base, ensuring the synchronous contraction of the muscle fibers of the two ventricles.

III. RESEARCH

1. CLINICAL TRIAL

1.1. MATERIALS

The present research began with a pilot study in which the variety of intracardiac devices and their performance and reliability were analyzed.

In a retrospective study, we included a group of 351 patients admitted to the Institute of Cardiovascular Diseases from Timisoara, Romania, implanted with a wide range of intracardiac devices. Patients were identified according to their unique registration numbers. Their medical data were searched in the hospitalization records and the national diabetes registry for the presence or absence of DM. Additional information regarding DM was obtained from the regional diabetes registry.

Beyond the principal analysis, we performed secondary studies. One of the secondary studies included 48 patients suffering from diabetic cardiomyopathy (DCM) and heart failure with reduced ejection fraction (HFrEF). The patients were implanted during January 2020 and June 2021 with three-lead pacemakers CRT (CRT-P) and three-lead intracardiac defibrillator (CRT-D) devices. This sample was taken as a separate group due to the disruption caused by the COVID-19 pandemic. Only this group of patients had reliable and more complex echocardiographic data available. This group study analyzed the possible effects of echocardiographic strain parameters and DM on pacing/sensing parameters in patients with dilative cardiomyopathy.

According to current European Society of Cardiology (ESC) guidelines, all patients were symptomatic despite optimal medical therapy (OMT), had LBBB, and were implanted with these devices according to the current European Society of Cardiology (ESC) guidelines. Patients with permanent atrial fibrillation who received biventricular pacemakers (CRT-P) were also included in the study. The main goal was to evaluate the impact of global and focal longitudinal strain

on pacing parameters. Before the implantation procedure, all patients performed transthoracic echocardiography (TTE).

In another substudy, performed during the COVID19 pandemic, we included another subgroup of 35 patients hospitalized for intra-cardiac device-related pathology. In this substudy, we analyzed the impact of a pandemic on the implantation of intra-cardiac devices in a population of patients from Western Romania. In addition, we compared the results according to the diabetes presence.

1.2. METHODS

Medical data were obtained from the patients' records files: age, BMI, cardiovascular diseases, and the presence or absence of diabetes.

1.2.1. METABOLIC LABORATORY TESTS

We recorded available blood test results that were linked to metabolic disturbances: glycemia, serum creatinine, estimated GFR (eGFR), total cholesterol, triglycerides, very-low-density lipoprotein cholesterol (VLDLc). Also, we calculated some indices previously validated in the literature for predicting insulin resistance, TyG index, and the product of TyG index and BMI.

Product of triglycerides and glucose (TyG) index was calculated as ln [Fasting triglyceride (mg/dL) x Fasting glucose (mg/dL)]/2.

By analyzing this data in this group of patients, we established whether DM and the sum of metabolic disturbances it produces could significantly impact the patient need to implant an intracardiac device and its functionality.

1.2.2. TRANSTHORACIC ECHOCARDIOGRAPHY

All patients admitted also had been investigated through echocardiography. While we had at our disposal a more considerable amount of measurement data, the following echocardiographic parameters were selected due to the likelihood of their relevance by our studied biological and electrophysiological parameters:

- Left ventricular ejection fraction measured via the Simpson method.
- Telediastolic volume.
- Left atrium diameter.
- Left atrium volume.
- Mitral valve E wave.
- Mitral valve A wave (in patients in sinus rhythm).
- Right atrium diameter.
- Systolic pulmonary artery pressure.

These parameters were analyzed using General Electric's lineup devices: the Vivid E90 and E95 devices.

For our subgroup of 48 patients with dilative cardiomyopathy and severely altered systolic function, we had the possibility of performing and accessing speckle tracking data on the beforehand mentioned devices. Therefore, the following measurements were performed for this group in particular.

- End-diastolic volume,
- Ejection fraction using the Simpson method.
- Global and segmental longitudinal strain
- Longitudinal contraction of the right ventricle.
- Pulmonary artery systolic pressures
- Left atrial diameter
- Left atrial volume
- Tricuspid annular plane systolic excursion (TAPSE)

1.2.3. ELECTROCARDIOGRAPHIC (ECG) INVESTIGATIONS

On all the participants in our study, a standard 12 lead ECG with a standard paper speed of 25 mm/s and a voltage of 10 mm/mV (standard functioning parameters) was performed upon admittance. The ECG was done to establish or/and confirm the patient's pathology. This investigation also provided us with valuable data, as in the case of patients with DCM and LBBB, one way of quantifying the efficiency of the CRT was the width of the QRS complex.

1.2.4. IMPLANTATION TECHNIQUE AND PACING PARAMETERS

All patients in our study lot were implanted with an intracardiac device. There is a wide variety of devices currently in use, ranging from single lead pacemakers to CRT-D devices. All of these patients suffering from bradyarrhythmia were implanted following the ESC guidelines available at the moment of implantation regarding the evaluation and management of patients with bradycardia and cardiac conduction delays. Patients with dilative cardiomyopathy and heart failure requiring CRT therapy were treated following the most recent guidelines available at that time. The patients who presented with malignant arrhythmias were again subjected to treatment done under the latest available guidelines.

Implantation techniques were similar in most procedures. Single and dual-chamber pacemaker implantation was performed by inserting the lead or leads via the physiological venous route. The cephalic vein identified in the deltopectoral groove was the first choice for venous access, depending on the patient's anatomy. We usually prefer searching for venous access on the patient's left side in our clinic. Once an incision is performed in the deltopectoral space and the cephalic vein identified, the leads are inserted into the right ventricle and right atrium, under radioscopic guidance, using a system of

introductory sheaths, depending on particular patient anatomy. The choice between dual or single chamber PM depends on the presence or absence of sinus rhythm. For example, suppose the patient is in permanent atrial fibrillation. In that case, there is no reason to implant a dual-chamber pacemaker other than the idea of conversion to sinus rhythm later.

If the cephalic cannot be used due to unfavorable patient anatomy or the absence of the vein altogether, the way of the subclavian vein can be attained. The cannulation of the subclavian vein is done using the Seldinger technique. The Seldinger technique uses a large needle to puncture the subclavian vein by either anatomical reference points, radioscopic guidance, or fluoroscopic guidance. After the needle has been inserted into the vein, a metal guidewire is inserted. The guidewire is a path for introducing a dilator and a special sheath. After removing the dilator, the sheath is ready for lead introduction. Special introduction “peel-away” sheaths are usually used, which facilitate their removal.

After the leads are placed in the right cardiac chambers accordingly, they are sutured to the vein using a non-resorbable line or to the surrounding tissue if the access has been done via the subclavian route. A pocket is then made in the pectoral region by dissecting the layers between the subdermal tissue and the fascia of the pectoral muscle. The pocket must be no larger than the actual device in order for it to fit precisely without moving around. The device is placed in the pocket, and a double layer suture is done for the subcellular tissue and the skin. A compressive bandage then covers the incision.

For the evaluation of pacemaker performance, we considered analyzing the following parameters:

- Right Atrial sensing
- Right ventricle sensing
- Right ventricle pacing threshold

These represent common pacemaker and defibrillator operating parameters. Sensing is measured in mV and represents the quality of the signal

received by the lead from the atrial or ventricular endocardium. The higher the number, the better. Generally, lower threshold limits regarding sensing are considered 0.5 mV for atrial leads and 1.5 mV for ventricular leads. However, these numbers can range vastly, these being the absolute limits of functionality for these parameters. Lower values or numbers around these values would signify a device not functioning properly, thus not receiving adequate signals from the myocardium. We consider optimal values to be > 3mV for the atrium and > 10 mV for the ventricle.

Pacing thresholds represent the lowest intensity current transmitted by the pacing lead towards the myocardium, which causes an efficient and repeated depolarization of the atrial or ventricular myocardium—generally, the lower pacing threshold, the better. Therefore, we consider ideal pacing thresholds 1 ± 0.5 V for ventricular and atrial pacing.

For the patients in the cohort with dilative cardiomyopathy in which cardiac strain was also analyzed, in addition to the parameters above, due to the presence of an additional lead in the coronary sinus, we also took into consideration the sensing and pacing thresholds for the coronary sinus lead, with the same ideal sensing values considered > 10 mV and a pacing threshold of 2 ± 0.5 V being considered ideal.

1.3. RESULTS

1.3.1. GENERAL CHARACTERISTICS OF STUDIED PATIENTS

The present research included 351 patients, men being significantly more prevalent, 62.96% (221/351), and women older than men, the median age was 71 in women, respectively 68 in men. The BMI, fasting glycemia and lipid profile were similar in men and women. However, the median serum creatinine ranged between 0.57 mg/dl and 6.19 mg/dl with a median of 1.24 mg/dl in men,

compared to a median of 1.09 mg/dl with a maximum of 3.70 mg/dl in women. Among the studied patients, 28.20% (99/351) were diagnosed with T2DM.

Out of the total study group, 75.49% (265/351) had a pathology related to PM: 41.13% (109/265) suffered the implantation of a new PM, 31.32% (83/265) had dysfunctions of the existing one – mostly depleted battery needing replacement – and 27.55% (73/265) were PM carriers hospitalized for another cardiovascular complication. The prevailing indication for PM implantation was AVB, followed by SSS and slow AF, and only 1.99% (7/351) with CSHS. Other 16.52% (58/351) patients required CRT for dilated cardiomyopathies (CMD) of various etiology and chronic heart failure (CHH) with reduced ejection fraction: 36.20% (21/58) had new implantations, and 63.80% (37/58) were carriers. 32.43% (12/37) of the carriers presented a depleted battery and 67.57% (25/37) other cardiovascular problems – mostly decompensated heart failure.

67.67% (67/99) of the T2DM patients were hospitalized during the study due to PPM pathology. Among them, 38.8% (26/67) of diabetic patients required the implantation of a new device for various bradyarrhythmia – the most frequent was AVB, followed by SSS. The rest of the patients had either dysfunction of the existing PPM (in most cases battery replacement) or were admitted for a cardiac complication, mostly decompensated CHF.

The group of patients with diabetes had higher median values of BMI, glycemia, total cholesterol, triglycerides, VLDLc, insulin resistance indices – TyG index and the product of TyG and BMI, respectively serum creatinine, LA volume, and sPAP.

IV. CONCLUSIONS AND PERSONAL CONTRIBUTION

- Patients with DM are more likely to require an implantable cardiac device.
- The LV sensing threshold increases directly proportional to the elevation of LV-GLS values.
- The presence of ventricular tachycardia or diabetes mellitus decreases the LV sensing threshold.
- Advanced HF (NYHA) stages decrease the LV sensing value.
- Lower values of LV-GLS, and TAPSE increase the LV pacing threshold as well as the presence of diabetes mellitus
- The RA sensing threshold has significantly lower median values than patients without diabetes, 2.25 mV vs. 3.20 mV
- Patients with diabetes are more likely to have altered sensing values, lower than 2.5 mV for RA and lower than 11.6 mV for RV.
- Diabetes patients have higher median values of the RV pacing threshold compared to non-diabetes patients, 1 V vs. 0.50 V
- The RV sensing above 10 mV is strongly negatively influenced by altered glycemia values, BMI, TyG index, TyG*BMI index, LA diameter, LA volume, RV pacing, and EDV.
- Renal function is an influencing factor for RA sensing outcome but does not influence RV sensing outcome. Altered glomerular filtration increases the likelihood of a reduced RA sensing threshold.
- A TyG*BMI index below 124 could predict a successful RA sensing, respectively a TyG*BMI index below 137 could predict a successful RV sensing
- TyG*BMI index is a potential biomarker to assess the optimal values of RA or RV sensing