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Electrocardiographic markers of ventricular repolarization in the obese population: A descriptive review

Orginal Study

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Abstract

Obesity is a global epidemiological problem that significantly contributes to the development of cardiovascular diseases. It is a proven factor for an increased risk of overall mortality and the occurrence of sudden cardiac death (SCD). The disease is accompanied by a structural and functional myocardium remodeling, which often results in ventricular repolarization abnormalities and contributes to the triggering of life-threatening arrhythmias. This heightened state of readiness for proarrhythmia is the cause of the sudden cardiac deaths which are recorded in this group of patients and which often constitute the first manifestation of ongoing cardiac pathology. One of the reasons for these arrhythmias may be abnormalities of ventricular muscle repolarization. In this descriptive review, we demonstrate electrocardiographic markers of ventricular repolarization (J point, QT/QTc/QTc-d, JT/JTc/JTc-d, ST segment, T wave and Tp-e/Tp-ed/Tp-e/QT), analyze their abnormalities in the obese population, and discuss their changes after weight loss.

Keywords

ECG • ventricular repolarization • obesity • sudden cardiac death

Introduction

Obesity is a growing global epidemiological problem. According to the latest WHO report from 2016, over 1.9 billion (39%) adults worldwide were overweight, and of these 650 million (13%) were obese. The cost of treating obesity in Europe accounts for 2% to 7% of health care expenditure, and the cost of treating all its complications is estimated at up to 20% of total healthcare costs. Numerous studies have shown that obesity significantly contributes to the development of cardiovascular diseases. Its connection with hypertension, diabetes, coronary heart disease, and stroke is indisputable. The mechanisms are manifold, yet they all lead to multi-level myocardial remodeling as well as structural, functional, metabolic, neurohormonal, and electrical remodeling which, among other things, results in significant repolarization abnormalities and contributes to the triggering of life-threatening arrhythmias (Figure 1).This heightened state of readiness for proarrhythmia is the cause of sudden cardiac deaths which are recorded in this group of patients and which often constitute the first manifestation of ongoing cardiac pathology [1, 2]. In this study, we present the characteristics of the repolarization abnormalities observed in electrocardiographic (ECG) recordings of obese patients, and their changes as the result of weight reduction.

1. VENTRICULAR REPOLARIZATION IN ECG

Ventricular repolarization (VR) is represented in the surface electrocardiogram by a fragment of the recording beginning at the J point and including the ST segment, T wave, and U wave [3]. So far, several markers of ventricular repolarization have been defined, with varying degrees of association with the observed malignant arrhythmias. These mainly include QT interval (QT), QT interval corrected for heart rate (QTc), QT dispersion (QTd), JT interval (JT) and its dispersion (JTd), Tpeak-Tend interval (Tp-e), Tpeak-Tend dispersion (Tp-ed), and Tpe/QT ratio. There are also other methods that stratify the risk of severe arrhythmias, such

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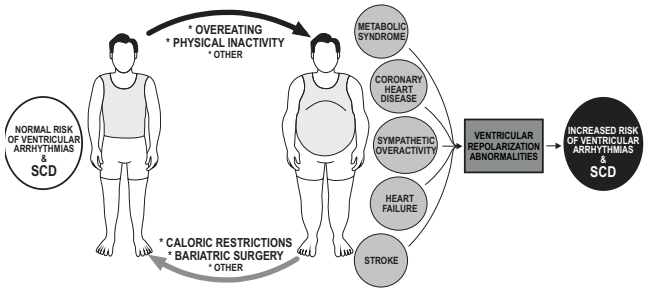


Fig. 1. Obesity-related ventricular repolarization abnormalities and the increased risk of sudden cardiac death

as heart rate variability (HRV) analysis or signal-averaged ECG (SAECG) measurements. Each of the markers of repolarization has its own history and predictive value.

2. J POINT

The J point is where the QRS complex ends and the ST segment begins. This is where the repolarization process begins. Change in the position of the J point is typical for myocardial ischemia/infarction, pericarditis, and Brugada syndrome; however, under normal conditions it should not exceed ±1 mm in relation to the isoelectric line. Rather, a variant of the norm is an early repolarization pattern (ERP), characterized by a higher J-point departure by ≥0.1 mV in at least 2 adjacent leads (excluding leads V1-V3) and observed in 1–13% of the general population [4]. When ventricular arrhythmias coexist, then there are grounds for the diagnosis of early repolarization syndrome (ERS). Some reports have suggested that ERP, especially in leads from the inferior wall, may be a symptom of electrical instability of the heart and may predispose to sudden cardiac death [5], but recent studies contradict this [6].

Early repolarization pattern has not received much attention from obesity researchers. Of the few reports, ERP is shown to occur rarely in the obese population; significantly less frequently than in people with normal body weight [4, 7].

3. QT INTERVAL

The QT interval is the fragment of the ECG recording from the beginning of the QRS complex to the end of the T wave, responsible for the process of depolarization and repolarization of the myocardium. Its most reliable measurements are obtained in leads II and V5, since it is in these locations that their highest repeatability has been demonstrated. The duration of the QT interval depends, among other things, on age, sex, and autonomic nervous system activity, but above all it depends on the heart rate, and therefore the QT interval corrected for heart rate (QTc) measurement is commonly used in clinical practice. There are many formulas that allow the QTc to be obtained, but there is no perfect one. The most commonly used is the Bazett formula [QTcB = measured QT(s)/√ RR interval(s)], but it also overestimates QTc with faster sinus rhythm and underestimates it in bradycardia. Among researchers, there are also many advocates of the Fridericia formula [QTcF=QT(s)/^{3}√RR(s)] and the Framingham formula [QTcFra=QT+0.154(1-RR)] as well as the formulas of Hodges or Ashman. There is no strong consensus on the basis of which the measurements could be standardized. Nevertheless, it is quite commonly believed that regardless of the formula used, the prolonged QTc interval is ≥450 ms in adult men and ≥460 ms in adult women. (AHA/ACCF/HRS) [8].

Prolongation of the QTc interval, especially>500 ms, is dangerous and carries the risk of presenting ventricular arrhythmias, including polymorphic ventricular tachycardia (torsades de pointes; TdP). TdP has a tendency to recur; it can degenerate into ventricular fibrillation and result in sudden cardiac death. The causes of prolonged QTc may be congenital, genetically determined, but most often are acquired (certain medications, electrolyte imbalance, nutritional deficiencies, myocardial ischemia/necrosis, cerebral stroke). One of the causes of a prolonged QTc interval is obesity. Sudden cardiac death occurs 4 times more frequently in the obese population than in the general population, and ventricular tachyarrhythmias are the most common cause of this [9].

When assessing the QT interval of the ECG recording, we not only pay attention to its duration but also to its dispersion (QTd). It is the difference between the maximum and minimum QT duration in each surface ECG lead. QTd is a measure of the uniformity of the ventricular depolarization and repolarization process and is viewed as an indicator of myocardial electrical instability. In normal conditions it should be ≤50 ms. Higher values predispose to the occurrence of ventricular arrhythmias. In a long-term retrospective observation, Elming et al. showed that QTd≥80 ms (compared toQTd≤30 ms) does not significantly increase the risk of death in the population of healthy people (normal blood pressure and ECG recording, no diagnosed disease, no chronic pharmacotherapy); however, it does almost double the risk in the general population, and increases it almost 3.5 times in the population of those with cardiovascular disease [10].

Many researchers have noticed that overweight and obesity lead to QTc and QTd prolongation [11, 12, 13, 14, 15, 16]. In an analysis of n=1029 obese volunteers, Frank et al. noticed a prolongation of the QTc interval>420 ms in 28.3% of the subjects, and found that for every 10% increase in overweight percentage points a prolongation of the QTc by 1 ms can be seen. This result was obtained independently of sex, age, and even blood pressure [12]. Omran et al., in their meta-analysis of 22 studies on this issue, showed that in obese subjects, the QTc is prolonged by an average of 21.7 ms, while the QTd is higher by an average of 15.2 ms [14]. It should be emphasized that in some publications it was noted that it is not obesity itself that leads to QTc or

QTd prolongation, but obesity-related metabolic disorders [13, 16]. In a retrospective study by Guo et al. (n=11209), metabolic syndrome was the main determinant of the prolongation of ventricular repolarization ratios. In patients with both metabolic syndrome and obesity, the QTc was similar to that found in patients with metabolic syndrome and without obesity. The QTc in both groups was significantly prolonged compared to patients without metabolic syndrome, regardless of concomitant obesity [13].

Many studies also show that weight loss leads to shortening of the QTc and QTd. Such an effect can be observed both after bariatric surgeries and as a result of the introduction of caloric restrictions [15, 17, 18, 19, 20]. Moreover, some studies show that it does not take long to obtain such results. Al-Salameh et al. reported that a significant shortening of QTc can be observed as early as 3 months after sleeve gastrectomy [17]. Other studies show that it is not necessarily the result of weight loss alone. Mukerji et al. observed a significant reduction in QTc and a decrease in QTd in obese patients after bariatric surgery, but only in the presence of concomitant left ventricular hypertrophy. In patients without left ventricular hypertrophy, weight reduction led to insignificant changes in QTc and QTd range [19].

The vast majority of publications demonstrate a significant prolongation of QTc and an increase in QTd in obese patients, as well as their shortening/reduction as a consequence of weight reduction. Such changes in the QT interval range, reflecting abnormalities in repolarization, can lead to arrhythmias and, in extreme cases, even cause sudden cardiac death. However, it cannot be ignored that obesity-related changes in the QT interval are mild/moderate, and in most cases do not exceed the limits at which one would expect life-threatening ventricular tachyarrhythmias.

4. ST SEGMENT

The ST segment is part of the QT interval: the fragment from the J point to the beginning of the T wave, which is responsible for the initial phase of the repolarization of the ventricular muscle. Normally, it should be isoelectric (in relation to the TP segment). In the obese population, this section does not undergo any specific changes. Frank et al. observed changes in the ST segment in 11% of n=1029 obese patients whose ECG was analyzed. The frequency of these rather nonspecific changes was independent of sex, but it increased with the age of the subjects, and most of all with an increase in blood pressure [12]. In another study, Alpert et al. analyzed the ECG recordings of pathologically obese subjects in comparison to those with normal body weight. The frequency of ST segment changes in the study group was minor and did not differ significantly from that observed in the control group. Moreover, even in the QTc interval range no differences were observed [21]. Only patients without hypertension and any other cardiovascular disease were eligible for this study. This may confirm the thesis that changes in the ECG record in obesity (including changes in repolarization) may result primarily from its clinical consequences (hypertension, myocardial hypertrophy, metabolic disorders), and not from the increase in body weight itself.

5. T WAVE

The T wave is the result of transmural dispersion of repolarization. Its normal duration is 120–160 ms, and its amplitude should be ≤6 mm in limb leads and ≤10 mm in precordial leads. Changes in its pattern in obese people are also nonspecific. Nevertheless, in the analysis by Frank et al., changes in the T wave pattern were present in almost 12% of obese patients. The frequency of their occurrence was not related to sex, but was higher in elderly patients and with concomitant arterial hypertension [12]. Alpert et al. observed a much more frequent flattening of the T wave in leads from the inferior wall (II, III, aVF) and the lateral wall (I, aVL, V5-V6) in the obese population compared to the normal weight population [21]. On the other hand, Eisenstein et al., when examining n=144 patients with pathological obesity, also observed, first and foremost, the noncharacteristic flattening or inversion of the T wave in leads from the inferior and lateral walls. However, what needs to be emphasized is that the abnormality, present in almost 50% of the patients in the study group, resolved after weight loss in almost all patients [22].

6. JT INTERVAL

The JT interval is that part of the ECG recording from the J point to the end of the T wave, reflecting the substantial repolarization of the ventricular muscle. Like the QT interval, it is heart rate dependent and therefore requires appropriate correction (JTc). The Bazett formula [JTc = JT(s)/√RR interval(s)] is also used for this purpose. In clinical practice, what is important is its dispersion (JTd), which is the difference between the maximum and minimum duration of the JT interval in individual surface ECG leads. JTd is one of the markers of the homogeneity of the ventricular repolarization process and the electrical stability of the myocardium. Xiang observed that JTd (as well as QTd) is more than twice as high in patients with acute coronary syndrome who developed ventricular fibrillation [23], while Fu et al. found that JT and JTc were significantly longer, and JTc-d was almost twice as high, in patients with dilated cardiomyopathy who died suddenly or who developed ventricular tachyarrhythmias, compared with those who survived or died of heart failure during the 26-month follow-up period. They concluded that JTc-d is the most important independent risk factor for sudden cardiac death/ventricular tachyarrhythmia. In their opinion, this risk is very high, especially when JTc-d >85 ms [24]. Unfortunately, the analysis of JT/JTc/JTd in the obese population was conducted only in scattered studies. Nevertheless, the available reports based on these indicators also confirm that there are significant repolarization ab-

normalities in obese patients, which in extreme cases may even result in death. Inanir et al. showed that JT is similar, but JTc is significantly prolonged in obese subjects compared to subjects with normal body weight [25]. Russo et al. observed, however, that not only JTc, but also JTc-d, was much longer/greater in obese patients than in the population of patients with normal body weight. Moreover, both these markers of repolarization were significantly reduced 12 months after bariatric surgery and weight reduction (JTc-d has normalized) [15].

7. Tp-e INTERVAL

The Tp-e is the interval between the peak of the T wave and its end. It is considered to be an indicator of the maximum dispersion of ventricular repolarization. Unfortunately, there are no hard findings regarding its correct values. On the basis of their own research, Haarmark et al. determined that Tp-e measured in lead V5 has an average value of 94±10 ms in men and 92±11 ms in women [26]. An abnormal Tp-e value is considered to be a marker of an increased risk of developing severe ventricular arrhythmias. In clinical trials, the dispersion of the Tp-e (Tp-ed) interval is also assessed. This is the difference between the maximum and minimum Tp-e intervals in all precordial leads. Also, Tp-ed does not have a well-defined range of normal values, but Castro Hevia et al. found that Tp-ed, similarly to Tp-e in fact, was significantly prolonged in patients with recurrent ventricular arrhythmias in the course of Brugada syndrome compared to a control group [27]. In other studies, it was also observed that Tp-e is more than twice as long in patients with acquired long QT syndrome, who have recurrent TdP compared to patients without recurrence of this tachyarrhythmia [28]. Scattered studies conducted in obese people are not conclusive. Inanir et al. observed that the Tp-e interval in obese patients was 16% longer than in patients with normal body weight [25]. Paech et al. noticed longer Tp-e in obese children [29]. On the other hand, Braschi et al. in their studies did not find any significant changes in Tp-e and Tp-ed in patients with uncomplicated obesity compared to the group of people with normal body weight [30].

Researchers have noticed that the Tp-e interval is significantly reduced as the heart rate increases, and therefore the Tp-e/QT ratio is often used in clinical trials. Its advantage is that it remains stable in the heart rate range of 60–100/minute. The mean value of Tp-e/QT in healthy subjects measured in lead V6 is 0.21±0.03 (range: 0.15 to 0.25), and its increase is perceived as a predictor of ventricular arrhythmias [31]. It has been found to be greater in patients with Brugada syndrome, who can generate VT/VF during programmed ventricular pacing [32]. It has also been proven that its increase >0.28 increases the risk of TdP in patients with acquired long QT syndrome [28]. Inanir et al. demonstrated a significant prolongation of Tp-e/QT in obese patients compared to those with normal body weight [25], but studies by Braschi et al. conducted in patients with uncomplicated obesity did not confirm this [30]. There are no publications available showing possible changes in Tp-e interval, its dispersion, and Tp-e/QT in patients after successful weight reduction.

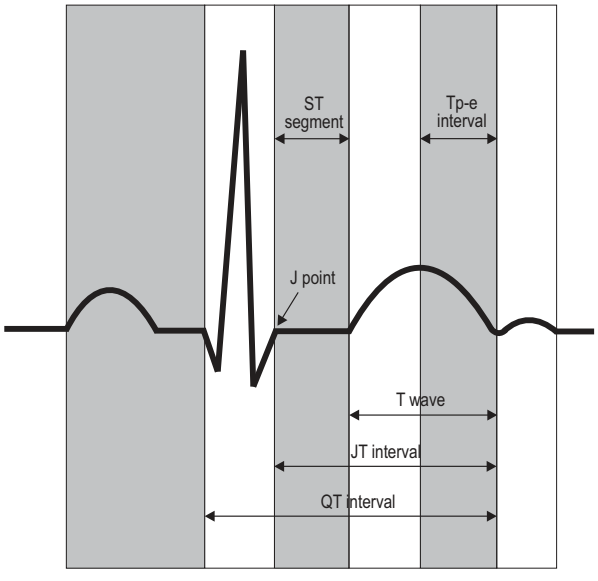


Fig. 2. Ventricular repolarization components on the electrocardiogram

8. CONCLUSION

The vast majority of studies conducted so far confirm that there are ventricular repolarization abnormalities of the myocardium in the obese population. Some of the markers presented by us already have an established position in the diagnosis of cardiac arrhythmias, but there are also those for which their clinical usefulness is still being sought. Unfortunately, studies on small groups of patients dominate. Moreover, obese patients commonly have other pathologies and/or metabolic disorders that damage the entire cardiovascular system (hypertension, myocardial hypertrophy, diabetes, premature coronary disease, obstructive sleep apnea with hypoxia and hypercapnia) that make it difficult to define the meaning and the impact of isolated obesity. Nevertheless, these repolarization abnormalities that accompany obesity should not be ignored, since the incidence of sudden cardiac death in this group of patients is several times higher than in the general population, and the reason may be the coexisting repolarization abnormalities. Classic electrocardiographic examination is a good tool for their diagnosis. It is easily accessible, inexpensive and effective. More research is needed to identify hard normal ranges within the population as well as threshold values that significantly increase the risk of arrhythmia. As a result, ECG examination could become the basic tool for monitoring the arrhythmic risk and the effectiveness of therapeutic management, both the bariatric treatment and that based on caloric restrictions.

Authors' Contribution

A.T.Z.: research concept and design, data analysis and interpretation, writing – original draft preparation, visualization, literature review; **M.S.**: research concept and design, supervising the project, data analysis and interpretation, writing – review and editing, final proofreading and approval of the version for publication.

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Conflict of Interest

The authors have no potential conflicts of interest to declare.

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