The negative effects of obesity on heart, especially the electrophysiology of the heart

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ABSTRACT
Obesity is associated with ventricular arrhythmia and sudden cardiac death. Numerous studies have shown that obesity may have effects on the heart by affecting the ventricular re-polarisation (VR). As an effective detection method for VR the measurement of the QT interval has been extensively studied in obese patients (OP). This review aims to investigate the relationship between obesity and obesity-related diseases; including diabetes, hypertension and cardiovascular diseases (CVD). This review compares the advantages and disadvantages of different QT interval measurement methods, as well as explores the possible mechanisms of obesity leading to heart disease. Finally, it also reviews the feasibility of various weight loss methods to reverse the risk of obesity leading to heart disease is discussed.

Introduction
Globally, the prevalence of obesity is growing at an alarming rate and it is a major threat to the public health in many parts of the world. A systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants during 1980–2013 shows that in 2008, there were about 1.46 billion obese adults worldwide [1], and the number of obese adults more than doubled during that 33-year period [2].

Obesity often manifests and develops with a number of chronic metabolic diseases, including dyslipidemia, insulin resistance (IR), and type 2 Diabetes [3]. Obesity and these obesity-related diseases can increase cardiovascular morbidity and mortality, which can lead to arrhythmia, heart failure (HF) and sudden cardiac death (SCD) [4,5]. Adjusting the delicate balance between food intake and energy expenditure can effectively reduce the risk of obesity-related diseases.

Comparison of different VR measurement methods
Obesity is associated with a variety of electrocardiogram (ECG) abnormalities [6]. In addition to various indicators of the shape of the heart and the heart rate changes [7], the most studied is ventricular electrophysiology. The indicators of ventricular electrophysiology are various (Table 1). There is no consensus on which indicators to use in ventricular electrophysiology.

The QT interval is measured from the start of the Q wave to the end of the T wave, including the QRS wave, the ST segment, and the T wave (Figure 1). When the U wave exists, the end point of QT interval measurement is the lowest point of the curve between the T wave and the U wave [8] (Figure 1(b)). The normal QT interval range is from 0.35 s to 0.43 s, or 0.39 s ± 0.04 s. Since the QRS wave represents the ventricular depolarisation time and the T wave stands for the VR, the QT interval is the measure of ventricular electrical activity.

The difference in heart rate will cause measurement errors of the QT interval. When the heart rate increases, the QT interval is shortened, and when the heart rate is slowed down, it is prolonged. The corrected QT interval according to heart rate is called the QTc interval [9] (Table 1). The normal QTc is defined in the range of 400 ms–440 ms. The boundary line of QTc is 431 ms–450 ms in males and 451 ms–470 ms in females. The QTc interval is often derived from ECG lead II, I or V 5 [10]. There are several formulas to calculate QTc. The Bazett formula is a early correction of QT. However, it is overcorrected at high heart rate and undercorrected at low heart rate [11]. Therefore, Fridericia proposed another QT interval formula for correcting heart rate, which was used by many experts [12] (Table 1). Compared to other methods, Sagie et al. used the linear regression analysis to pose the QTc formula more effectively when assessing the risk of death for 30 days or 1 year [13] (Table 1). Recently, a study investigated the possibility of predicting QTc values in OP by using the best-fit regression method to represent the relationship between QTc and body mass index (BMI), which allowed all

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the medical and paramedical personnel to establish the cardiovascular risk in the OP immediately [14] (Table 1).

QT dispersion (QTd) is proposed as a marker of dispersion of ventricular repolarization and can be obtained by subtracting the minimum QT interval from the maximum QT interval [15] (Table 1). QTd was originally proposed to measure the spatial dispersion of VR. It has also been reported that QTd may be a further non-invasive marker of susceptibility to ventricular arrhythmias [16]. In recent years, QTd is considered to be a sign of general abnormalities in VR [17].

JT or JTC intervals are obtained by subtracting the QRS from the QT or QTc. As the indicators of VR, JT and JTC are often used to evaluate the efficacy of antiarrhythmic drugs [18,19] (Table 1, Figure 2). JTa is the interval between the J point and the apex of the T wave. TaTe is expressed as the interval between the apex of the T wave and the end of the T wave (Table 1, Figure 2). The two are used as new repolarization parameters, which may be related to arrhythmia under clinical conditions [20].

Recently, other new parameters have been used as indicators of increased risk of arrhythmia, such as T peak-Tend (Tpe), T peak-Tend dispersion (Tpe-d) and T peak-Tend/QT ratio (Table 1). Tpe is obtained by measuring the interval from the peak of T wave to the end of T wave on the surface ECG [21].
Current studies have shown that Tpe, Tpe-d and Tpe/QT can be used as indicators of total dispersion of repolarization (TDR) \[22,23\].

The association between obesity and VR has been extensively studied (Table 2). In addition, some studies have reported that all or part of VR indicators in the OP did not change \[20,51–56\], more researches proved that the two have statistical significance. Similar conclusions have been obtained in obese animal models, and weight loss by different means could reduce the association between them \[24–26,38,44,57\], and as result obesity can affect the VR, thereby increasing the risk of arrhythmia and SCD. Except for cardiac electrical activity, some indicators of echocardiography in the OP were also abnormal \[27,30,39,45,58\].

Obesity can prolong VR, and obesity-related diseases such as hypertension, diabetes, and IR can enhance this effect. Similar conclusions can be drawn from reports on women, men, children, and animal groups.

The possible mechanisms by which obesity affects the heart

The effect of obesity on the heart is multifaceted and can be discussed from the structure, function of the heart, electrophysiological activity of the cardiomyocytes and metabolism of the body. The influences of these aspects are mutual. Obesity can not only affect the structure of the heart through fat accumulation but also causes metabolic abnormalities including dyslipidemia, increased secretion of pro-inflammatory cytokines, fibrosis \[59,60\], hyperglycemia \[61\], High uric acid(HUA) \[62\] and IR that can influence the electrophysiology and function of the heart.

Heart structure change

Changes in cardiac structure and function caused by obesity are mainly manifested by ventricular remodelling and ventricular hypertrophy, as well as ventricular diastolic and systolic dysfunction, which can cause heart failure when the structure and function are abnormally severe. In addition, elevation of the diaphragmatic level caused by abdominal obesity, and accumulation of fat under the skin and subepicardial-acting as an electrical insulation layer-could cause various changes in the surface ECG \[63\].

Metabolic disorder

Systemic hyperlipidaemia caused by obesity, especially low-density lipoprotein (LDL) \[64,65\], or excessive accumulation of lipids in the visera could lead to cardiovascular disease (CVD) \[66,67\].
lipoprotein (OX-LDL) has the biological characteristics of being rapidly phagocytosed by macrophages and smooth muscle cells, and is involved in the formation of atherosclerotic plaques. OX-LDL also has strong cytotoxicity that can change the functional state of endothelial cells, accelerating the formation of lipid fringes and arteriosclerosis.

Adipose tissue can secrete a variety of adipokines, such as leptin, adiponectin (APN) and inflammatory factors, which can affect the cardiovascular system. Leptin was discovered in 1994 [68]. The initial understanding of leptin was to act on the nervous system and inhibit the feeding behaviour of the body [69]. Later studies have shown that several peripheral tissues, including those around heart, also expressed leptin receptors [70]. There was evidence that leptin increased the oxidation of non-esterified free fatty acids (NEFA) in peripheral tissues and prevented the accumulation of fat in peripheral organs [71]. In other roles, the discovery of leptin receptors on leukocytes suggested that leptin may mediate activation of the inflammatory system. In other words, adipose tissue was a potential organ that may affect long-term inflammatory responses [72]. In addition, studies by Lin YK et al. found that leptin prolonged the duration of action potential (AP) in left atrial (LA) myocytes and affected its ionic current [73]. These studies indicated that leptin inhibited the accumulation of visceral fat, while affected the cardiovascular system through inflammation and myocardial electrophysiology.

APN is a protein secreted by fat cells. In general, APN has the function of anti-atherosclerosis (AS) [74] that can reduce the formation of foam cells and decrease the expression of scavenger receptor A. Studies have shown that a decrease in plasma APN levels were associated with increased plaque calcification[75]. APN could also enhance the oxidation of NEFA and reduce the accumulation of fat [76]. In OP, the secretion of ANP is reduced, which is not conducive to the heart. Obesity and obesity-related diseases can cause CVD by increasing the formation of lipid fringes and arteriosclerosis.

Adipose tissue is the source of many adipokines and chemokines, which can affect the cardiovascular system through inflammation and myocardial electrophysiology. Adipokines include leptin, adiponectin (APN) and inflammatory factors like interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6) [80], interleukin-8 (IL-8) tumour necrosis factor alpha (TNF-α), etc. can cause inflammation and thrombosis in the body by injuring endothelial

Table 2. The association of obesity and cardiac indicators.

| Groups                             | Indicators                          | Results                                                                 | References |
|------------------------------------|-------------------------------------|------------------------------------------------------------------------|------------|
| OP didn’t combine with other diseases | QT, QTc, QTd, QTd-apex, Tpe, Tpe-d, Tpe/QT, P, QRS, LVM | OP associate with a statistically significant increase in QT, QTc, QTd, QTd-apex, Tpe, Tpe-d, and Tpe/QT compared to normal subject: Leftward shifts of the P wave QRS and T wave axes, various changes in OP wave morphology, low QRS voltage could be seen in obese subjects; In OP, LVM may affect QTc; Weight loss associated with a significant education in QTd and QTc. | [6,24,25,26,27,28,29] |
| OP combined with obesity-related diseases | P, QRS, QTc, QTd, LVM, CV (RR), HRV | Obesity and its related diseases such as hypertension and diabetic were positively correlated with P, QRS, QTc, QTd, LVM, and negatively correlated with CV (RR) and negatively correlated with CV (RR), and positively correlated with QTc and QTd. | [30,31–35] |
| Male                               | QT, QTc                             | In the male population, obesity was associated with prolonged exposure to these VR indicators.                                                                                           | [36,37]    |
| Female                             | P, QTd, QTc, LVM                     | Obesity led to a significant increase in P wave dispersion, LVM, QTc and QTd.                                                                                                                | [38,39,40–43] |
| Children                           | QTc, QTd, JTd, TDR, LVM, LVM index  | LVM, LVM index, TDR, JTd, QTc and QTd were significantly greater in OP than in the control group.                                                                                              | [44,45,46–48] |
| Race                               | QTc, resting heart rate             | Among Mexican Americans, persons with obesity were more likely to have longer QTc intervals and higher resting heart rates.                                                                 | [49]        |
| Animal mod                         | QRS, Q, T, QTd, resting heart rate  | Q wave and T amplitude were reduced, while R amplitude, QTd and resting heart rate increase; Compensatory shortened QT interval and decreased QRS amplitude could be seen in overweight rats. | [50]        |

Abbreviations: LVM: Left ventricular mass; LVH: left ventricular hypertrophy; CV (RR): coefficient of variation of RR intervals; HRV: heart rate variability; TDR: transmural dispersion of repolarization.
cells, producing monocyte tissue factor, increasing platelet activation and fibrinogen expression, thereby affects CVD [81]. Among them, TNF-α can also activate NF-κB, induce oxidative stress, which causes endothelial damage and AS [61].

When fat exceeds the load capacity of adipose tissue, free fatty tissues accumulate in other internal organs such as the heart, the liver, the pancreas, and the skeletal muscle. Cardiac dysfunction is closely related to cardiomyocyte-specific lipid deposition. In OP, the expression of lipid metabolism-related enzymes such as cardiac-specific lipoprotein lipase (LpL), acyl-CoA synthetase [82], FA transporter (FATP1) [83], and fatty triglyceride lipase (ATGL) [83] in the heart is higher than that of the control group, which eventually lead to heart hypertrophy and enlarged heart chamber.

Lipid deposition in skeletal muscle can lead to CVD. The skeletal muscle regulates the metabolism between glucose and lipids. In obese Individuals, the accumulation of lipids in skeletal muscle can cause mitochondrial dysfunction [84]. IR in skeletal muscle can trigger systemic IR, which induces increased FFA uptake and lipid accumulation in the heart, ultimately leading to cardiovascular disease [85].

Free fatty tissues accumulate in liver can cause CVD. Non-alcoholic fatty liver disease (NAFLD) is often associated with obesity and is one of the consequences of systemic visceral fat accumulation. NAFLD may induce thrombosis, cardiomyocyte hypertrophy and apoptosis through the release of coagulation proteins, fibrinogen [86-88] and inflammatory factors [89,90], which contributes to CVD.

**Adverse effects of left ventricular function**

Dysfunction can be manifested as diastolic and/or systolic dysfunction, shortened ejection fraction [85]. The adverse effects of obesity on cardiac function are often manifested in the left ventricle, with left ventricular remodelling, diastolic dysfunction, and reduced ejection fraction. Increased plasma volume caused by hyperlipidaemia and high blood pressure secondary to obesity can lead to increased ventricular afterload; atherosclerosis due to obesity can cause systolic and diastolic dysfunction [91].

**Myocardial electrophysiological changes**

The resting membrane potential of the heart is maintained by the inwardly rectifying K⁺ current (I K1). In the working cells of the heart, phase 0 depolarisation of action potential (AP) is caused by fast sodium current (I Na). Repolarization is controlled by fast transient outward potassium currents (Ito), the rapid component of the delayed rectifier K current (IKr) and the slowly activating component of the delayed rectifier (IKs). The 2 phase is the plateau, which forms a short equilibrium by the L-type Ca (ICa, L) inflow and the K outflow. In the atrium, the repolarization is largely controlled by the ultra-rapid delayed rectifier K current (I Kur) [92].

Common types of arrhythmias in OP are long QT syndrome (LQTS) and atrial fibrillation (AF). LQTS is usually defined by a decrease in re-polarisation current or an increase in depolariisation current. In the case of AF, increasing the outward potassium current or reducing inward calcium current may accelerate atrial re-polarisation, resulting in shortened AP duration and atrial refractory, thereby promoting ectopic firing and single/multiple wave re-entrant mechanisms. Multiple metabolic disorders caused by obesity may affect the electrophysiology of the myocardium by changing the density of ion channels. However, in the high-fat diet-induced obese animal model, the mRNA and protein expression of various ions were inconsistent, indicating that the effects of obesity on myocardial electrophysiology are far more complicated than we think [93].

**The treatment of obesity**

The health risks that obesity brings to human beings are far-reaching, so it is necessary to take active measures to lose weight. According to the surgical procedure, bariatric surgery can be divided into gastric bypass (Roux-en-Y gastric bypass; duodenal transposition; biliary-pancreatic shunt and Roux-en-Y gastric bypass), adjustable gastric banding, sleeve gastrectomy, and vertical occlusion gastroplasty. In the early days, most bariatric surgeries was vertical occlusion gastroplasty. However, in the United States, this procedure was associated with a number of complications, which have essentially been halted. Gastric bypass has resulted in more effective weight loss but is associated with more complications. Adjustable gastric banding is associated with lower mortality and comorbidities, while there is a higher rate of re-operation than gastric bypass and less weight loss. Sleeve gastrectomy, which is increasingly popular, reduces body weight more than adjustable gastric banding and is comparable to gastric bypass surgery [94].

Epidemiological evidence suggested that performing bariatric surgery often improved the effects of obesity on the cardiovascular system and reduces the risks of CVD. In patients undergoing sleeve gastrectomy, P wave dispersion (PWD) and QTd values were shown to be weakened [95], and QTc was shortened [96]. Similarly, shorter QTc was shown after jejunal Roux-en-Y gastric bypass surgery [97]. A decrease in heart rate variability (HRV) and QT variation index (QTVI) after laparoscopic gastric banding (GB) and biliary-pancreatic shunt (BPD) indicated an improvement in autonomic nervous system (ANS) dysfunction in OP [98]. Vertical band-shaped gastropasty (VBG) could shorten the QTc interval [99], but some studies have shown that only OP with left ventricular hypertrophy could have an improvement in VR indicators [100,101]. Low-calorie diet [102,103] and aerobic exercise are also effective weight-loss methods [104]. However, it should be noted that there have been reports of SCD during a low-fat diet [105,106]. Therefore, when performing such treatment, it should be carried out under strict medical supervision.

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