UNIVERSITÀ DEGLI STUDI DI PADOVA

Sede Amministrativa: Università degli Studi di Padova

Dipartimento di Medicina

CORSO DI DOTTORATO DI RICERCA IN: Scienze cliniche e sperimentali.
CURRICOLO: Metodologia clinica e medicina dell'esercizio. Scienze endocrinologiche, diabetologiche e nefrologiche.
CICLO: 34°

TITOLO TESI

Exercise and workload-indexed blood pressure in people with severe obesity before and after bariatric surgery.

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INDICE

ABSTRACT

Introduction: Obesity is accompanied by increased resting blood pressure. Exaggerated blood pressure during exercise correlates with cardiovascular events independently from baseline blood pressure levels. High workload-indexed blood pressure (W-SBP) and particularly a value ≥10 mmHg/METs is significantly associated with the risk of mortality.

Aim: to evaluate blood pressure response and W-SBP during a cardio-pulmonary exercise test (CPET) before and after bariatric surgery (BS).

Methods: 257 patients with severe obesity performed maximal incremental CPET one month before and six months after BS using the same incremental protocol. Systolic blood pressure was measured at rest (SBPrest), at the same submaximal intensity of 3 METs (SBPsubmax), at peak exercise (SBPpeak) and in the recovery phase. The submaximal and maximal W-SBP (W-SBPsubmax and W-SBPpeak, respectively) were calculated with a dedicated formula.

Results: Age was on average 45.5 ± 10.3 years, BMI before BS was 43.9±6.4 Kg/m^2 and 73.5% were females. SBPrest decreased significantly after BS (-10.2±15.8 mmHg; p <0.0001), also when considering percentage variation. SBPsubmax and SBPmax showed significant reduction after BS both as absolute change (-15.0±19.7 mmHg and -10.3±25.1 mmHg; p<0.0001, respectively) and as percentage change. Furthermore, W-SBP decreased significantly during submaximal exercise (-3.0±12.2 mmHg/METs; p<0.0001) and at peak of exercise (-2.1±4.8 mmHg/METs; p<0.0001), despite a higher exercise tolerance after BS, determined as the workload reached at the peak of exertion (Figure 1). A logistic regression analysis showed that the probability to have W-SBPpeak ≥ 10 mmHg after BS was independently determined by age, W-SBPpeak and functional capacity before BS.

Conclusions: After BS, a marked reduction of resting and exercise blood pressure values was observed. W-SBPsubmax and W-SBPpeak, as an expression of load-independent pressure response, decreased significantly, despite a significant increase in exercise tolerance after BS. Age, W-SBPpeak and functional capacity at baseline significantly determined the probability to have high W-SBPpeak post BS.

RIASSUNTO

Introduzione: La condizione di obesità severa si accompagna a valori pressori elevati a riposo. Un'esagerata riposta pressoria durante esercizio correla con gli eventi cardiovascolari indipendentemente dai valori pressori basali. Un'elevata pressione indicizzata al carico di lavoro (W-SBP) ed in particolare un valore superiore ai 10 mmHg/METs è significativamente associata al rischio di mortalità.

Scopo: Valutare la risposta pressoria all'esercizio e la W-SBP durante test cardiopolmonare (CPET) prima e dopo chirurgia bariatrica (BS).

Metodi: 257 pazienti con obesità severa hanno eseguito CPET un mese prima e sei mesi dopo BS utilizzando lo stesso protocollo incrementale. La pressione arteriosa sistolica è stata misurata a riposo (SBPrest), ad un'intensità sottomassimale pari ad un carico di lavoro di 3 METs (SBPsubmax), al picco dell'esercizio (SBPpeak) e nella fase di recupero. La W-SBP durante esercizio sottomassimale (W-SBPsubmax) e al picco dello sforzo (W-SBPpeak) è stata calcolata con una formula dedicata.

Risultati: l'età media dei soggetti era di 45.5 ±10.3 anni, il BMI prima della BS era 43.9±6.4 Kg/m2 e il 73.5% era di genere femminile. SBPrest risultava significativamente diminuita dopo BS (DeltaSBP -10.2±15.8 mmHg; p <0.0001), anche considerando il calo percentuale. SBPsubmax e SBPpeak apparivano ridotte dopo BS sia come variazione assoluta (-15.0±19.7 mmHg e -10.3±25.1 mmHg; p<0.0001, rispettivamente), sia come variazione percentuale. Inoltre, W-SBP dopo BS era significativamente inferiore sia durante esercizio sottomassimale (-3.0±12.2 mmHg/METs; p<0.0001) sia durante esercizio massimale (-2.1±4.8 mmHg/METs; p<0.0001), mentre la tolleranza all'esercizio, intesa come carico di lavoro raggiunto al picco dello sforzo era aumentata. Una regressione logistica ha mostrato che i principali determinanti della probabilità di avere una W-SBPpeak ≥10 mmHg dopo BS erano l'età, la W-SBPpeak e la capacità funzionale prima della chirurgia.

Conclusioni: Dopo BS si è osservata una marcata riduzione della pressione arteriosa a riposo e durante esercizio. Inoltre, anche le W-SBP massimale e sottomassimale, espressioni della risposta pressoria indipendente dal carico di lavoro, sono risultate significativamente diminuite, a fronte di una maggiore capacità di esercizio. La riduzione della W-SBPpeak dopo BS appare determinata dall'età, dalla W-SBPpeak e dalla capacità funzionale di partenza.

1. INTRODUCTION

1.1 OBESITY

1.1.1 Obesity: epidemiology and etiology

The World Health Organization (WHO) defines overweight and obesity as a disease characterized by an excess of body fat that represents a risk factor for health. The most widely used criterion for defining and classifying overweight and obesity is the body mass index (BMI) calculated as the ratio of weight in kilograms to height expressed in meters squared (kg/m^2). Overweight corresponds to a BMI between 25.00-29.99 kg/m^2; obesity to a BMI ≥ 30.00 kg/m^2. Obesity is then classified in class I (mild obesity) for BMI between 30.00-34.99 kg/m^2, class II (moderate obesity) for BMI between 35.00-39.99 kg/m^2 and finally class III (severe obesity) for BMI ≥40.00 kg/m^2. BMI is simple to calculate, and easily applicable in any type of context (clinical and non-clinical), but is not without issues. Many factors can influence its correspondence to body fat and many other anthropometric measures, such as waist circumference and waist-to-hip ratio, are proving their relationship with obesity-related comorbidities and cardiovascular risk [1,2]. The prevalence of overweight and obesity is increasing worldwide, i.e. across European Society of Cardiology (ESC) member countries the prevalence augmented from 9.6% to 22.6% between 1980 and 2016 [3]. WHO reported that more than 1,3 billion adults are living with overweight and 600 million with obesity worldwide [4]. Based on estimates, if the growth trend of overweight and obesity will remain the same, by 2030 the overweight will affect 38% of the adult population and obesity 20% in the world [5]. In the U.S. this increase has been documented across every age, sex, race, and smoking status [6]. In Italy, 46.1% of subjects ≥18 years presents excess of weight. In particular, more than a third of the adult population (35.4%) have overweight and 10.7% is affected by obesity. There are also huge regional differences between North, Center and South. The southern

central regions have the highest prevalence of overweight and obesity among adult population increasing with age. The prevalence of overweight varies from 16% to 46% and obesity from 2.5% to 15.5%, going from the age group 18-24 years to 65-74 years. Moreover, overweight is more prevalent among men than women (overweight: 44% vs 27.3%; obesity: 10.8% vs 9%)[7].

Obesity originates from the imbalance between energy intake and energy expenditure. Nevertheless, obesity is a multifactorial and complex disease in which also genetic, physiologic, environmental, microbial, psycho-social, economic, and political factors are involved [6]. The role of genetic in the genesis and continuation of obesity refers to mutations in different genes responsible for appetite control and metabolism and about 127 sites in the human genome have been reported to link with the development of obesity [8,9]. The monogenic forms of obesity are rare disorders, while the most common form of obesity is caused by the interplay between environmental factors and multiple genes [8]. Furthermore, the polygenic basis of obesity implies an inter-individual variability that influence the sensitivity of different subjects also if under similar environmental conditions [10]. To date, genetic variations of fat mass and obesity (FTO) gene are the strongest predictors of human polygenic obesity. Some genes associated with BMI analyzed through candidate gene approach are LEP and LEPR encoding for leptin and leptin receptor [8]. Leptin is secreted by fat cells and acts mainly at the hypothalamic level. High levels of leptin reduce food intake and increase energy expenditure. Other genes involved are those coding the proopiomelanocortin (POMC), the proenzyme convertase 1 (PC-1) and the melanocortin type 4 receptor (MC4R). In most cases these genes contribute to the genetic predisposition which, together with environmental factors, lead to the development of the disease [9]. Furthermore, in the last decades the total amount of physical activity progressively diminished for several reasons including the prevalence of sedentary work activities. This has led to a reduction in physical activity

and energy expenditure during working hours. Concurrently, sedentary behavior and a tendency to physical inactivity during leisure time have increased. Combined with diet, these factors have synergistic and cumulative effects that hamper to maintain or obtain an optimal body weight throughout life [11,12]. The increased general availability of food has led to substantial dietary changes. There has been a transition from high-carbohydrate and fiber diets to high-fat diets. The factors that have allowed this change in eating habits are many, including the large-scale distribution of prepackaged food, the easy availability of cheap and high calorie food, the addition of salt and fat in foods and sugars in beverages. At the same time, by contrast, consumption of whole grains, fruits, and vegetables has diminished [10]. Sedentary behavior is, indeed, higher in overweight and obesity than in normal weight subjects [13]. Large evidences has shown that 150-250 minutes/week of moderate intensity physical exercise can prevent weight gain in subjects with normal weight and also to promote significant weight loss or weight maintenance (if accompanied by dietary restriction) in people with overweight or obesity [14,15]. In addition, the number of hours of sleep may affect body weight [16]. The association between sleep duration and weight gain configures a U shape-curve: higher risk of weight gain is attributed to sleeping less than 6 hours/night or more than 8 hours/night, while lower risk belong to those who sleep between 6 and 8 hours/night [17]. Another element clearly related to obesity is socio-economic status. Nowadays, in the USA, people with lower income have a higher risk of overweight or obesity [18]. This association is more marked in the female gender, compared to males. The level of education is also an important risk factor. A significant inverse relationship has been demonstrated between education and overweight and obesity [18]. Finally, people with obesity and overweight have a high frequency of eating disorders, i.e. binge eating. In addition, patients with obesity may have a wide range of wrong eating behaviors, such as night eating and

emotional eating, that are not necessarily classifiable as major psychopathologies, but can significantly impact on body weight [19].

1.1.2 Clinical aspects

Obesity is associated with an increase in overall mortality compared to normal weight. Mortality increases proportionally with increasing BMI. For each BMI increase of 5 kg/m^2 above 25 kg/m^2, the overall mortality increases by 30% [3,20]. Obesity reduces life expectancy by about 2-4 years, but in people with severe obesity with early onset, life expectancy can be reduced by as much as 10-13 years [21]. Insulin resistance is a condition always detectable in obesity. The risk of insulin resistance is greater in people with overweight or obesity than in normal weight subjects and increases with increasing BMI and more closely with visceral fat [22]. One of the mechanisms linking visceral obesity and insulin resistance is the high leptin and low adiponectin secretion. This particular adipocytokines pattern is involved in the pathogenesis of insulin resistance [23]. Another characteristic of visceral fat is the intense lipolytic activity, which makes it more resistant to the inhibitory action of insulin on lipolysis. This leads to an increase in the release of non-esterified fatty acids and represents a fundamental pathogenic event for the onset of insulin resistance [24,25]. Finally, visceral adipose tissue secretes cytokines such as TNF-α and IL-6 which contribute to the onset of a low grade inflammatory state crucial for insulin resistance and also act as a link with cardiovascular risk [26]. Insulin resistance is a key component of metabolic syndrome and a strong predictive factor for the development of type 2 diabetes mellitus in people with overweight or obesity [27]. Another typical consequence of obesity is the presence of dyslipidemia. Dyslipidemia in subjects with obesity results particularly hazardous due to the typical pattern constituted by high triglycerides, low High-density lipoprotein (HDL)-cholesterol, normal or high Low-

density lipoprotein (LDL)-Cholesterol and increases fraction of small and dense LDL. This particular lipid profile is extremely atherogenic and contributes significantly to increase cardiovascular risk [28,29]. The further increase of cardiovascular risk in people with obesity is often determined by the presence of arterial hypertension. Arterial hypertension is closely related to overweight and obesity. It has been shown that people with obesity, despite normotensive, have a higher blood pressure values than those with normal weight [30]. The prevalence of hypertension in people with obesity exceed 60%, on the other hand 78% of hypertension in men and 65% in women can be attributed to excessive weight gain [31]. Coexisting obesity and hypertension increase the risk of mortality and cardiovascular events and facilitates the occurrence of resistant hypertension [32]. Being in the normal weight range and weight loss are crucial for prevention and management of arterial hypertension [33]. Moreover, there is a strong association between body weight and gastrointestinal diseases. First, gastric physiology and neuro-hormonal regulation of satiety are altered in obesity, then gastro-esophageal reflux disease (GERD) is very common especially in patients with obesity [34]. Among people with obesity is also more likely to find complications of GERD such as Barrett's esophagus, erosive esophagitis and adenocarcinoma [35]. Obesity is also strictly associated with hepatic disease due to the fat accumulation in the liver such as NAFLD (Non Alcoholic Fatty Liver Disease) and NASH (Non-Alcoholic Steato-Hepatitis). NAFLD is currently the most common form of chronic liver disease and its incidence has increased in parallel with the increased incidence of obesity [36]. NASH represents the first step towards liver cirrhosis, a condition in which the genesis of hepatocarcinoma is very likely. The best strategy to counter NAFLD and prevent its progression towards the most severe forms of liver disease is precisely the correction of lifestyle, physical activity and weight loss [37,38]. One of the most disabling consequences of obesity is type 2 diabetes. Many mechanisms contribute to the development of type 2 diabetes in people with obesity,

such as insulin resistance, low grade inflammation, increased circulation of non-esterified fatty acids, hormones etc. and when pancreatic β cell became dysfunctional, predominantly in predisposed subjects, the lose the ability to regulate blood glucose levels [39]. For instance first-degree relatives of individuals with type 2 diabetes, have already impaired β-cell function, despite normal glucose levels [40]. Furthermore increased caloric intake, fat and sugar consumption together with sedentary lifestyle lead to nutrient storage, obesity and also to reduction in insulin release [39]. Obesity is an established risk factor for cancer as confirmed from the high prevalence of cancer in people with excess weight [41]. Esophageal adenocarcinoma and colorectal cancer are most associated with obesity in men and endometrial adenocarcinoma in women, but obesity has been linked to many anatomical locations of cancer [41]. The most significant impact of obesity on the musculoskeletal system is associated with osteoarthritis. The joints most early affected are those of the lower limbs. There is, in fact, a proven association between obesity and knee arthritis [42] Obesity is also the main cause of the onset of obstructive sleep apnea syndrome (OSAS) which in turn increases the risk of diurnal hypoventilation syndrome, arterial hypertension, congestive or pulmonary heart failure and diabetes [42].

1.1.3 Treatment

The aim of the treatment of obesity should go beyond weight loss and the goal of global health improvement. Much of attention should be paid to the change of anthropometric parameters (such as waist circumference and waist-to-hip ratio) and body composition (preservation/improving free fat mass and reduction of fat mass). Furthermore, action addressed to the prevention and treatment of comorbidities and to the increasing of quality of life, should drive the therapeutic choice that must be as individualized as possible. This comprehensive approach could optimize the patients' management, achieving many goals by treating obesity [43,44]. Moreover, management and treatment

of patients with obesity should also focus on the weight maintenance and prevention of weight regain in order to prevent the weight "cycling" that has been linked with the risk of obesity-related comorbidities [45]. The weight reduction targets must be clear, shared and achievable and appropriate follow-up is required as well as for any chronic disease [46].

The essential element of obesity treatment is **dietary treatment** which starts with increasing patients' awareness of their eating behavior and their motivation to change their lifestyle. Dietary strategies are based on different approaches such as calorie reduction and the right balance of macronutrients [43,47]. In general, the change should lead to a healthy eating with high consumption of vegetables, legumes and whole grains and low-fat dairy products and meats, and certainly increased intake of seafood. On the contrary, remove from the everyday diet foods with added and processed sugars, solid fats, sugary drinks and alcoholic beverage as well as bad eating habits (oversized portions, snacking, eating in the night time, binge eating, etc.). Dietary intervention should be individualized and well integrated with life habits, physical activity and co-morbidities also with the intervention of a specialized professional figure such as a nutritionist or dietitian [46].

Further milestone of the treatment of obesity is regular **physical exercise**. Recent recommendation from the European Association for the Study of Obesity (EASO) Physical activity working group pointed out all the benefits and effects of prescribing exercise programs in people with overweight or obesity. In this paper and in the papers that summarized the existing literature on different effects of physical activity are displayed the multiple benefits and the low incidence of risks[15]. Aerobic training reduces body weight and body fat and, both alone or combined with resistance training, combined with a weight-loss diet, leads to an additional weight loss. Aerobic training and high intensity interval training (HIIT) reduce abdominal visceral fat. Resistance training performed

during a weight-loss diet counteract the loss of lean body mass. Physical activity practiced for ≥250 min/week helps weight maintenance [48]. Exercise training programs (aerobic, resistance, or HIIT) improve insulin sensitivity and reduce systolic and diastolic blood pressure (of about 3 and 2 mmHg) in people with overweight or obesity with or without type 2 diabetes, and with or without hypertension. Furthermore the effect of exercise training programs is effective also in reducing intrahepatic fat [37]. All type of exercise training increase VO_2max compared with no exercise, but HIIT and aerobic training are more effective than resistance training alone. Resistance training alone or combined with aerobic training, but not aerobic training alone improves muscle strength in groups of adults with overweight or obesity [49]. Exercise training does not increase average energy intake and leads to a small increase in fasting hunger. On the other hand, adhering to exercise training programs improves satiety [50]. Exercise training after bariatric surgery results in an additional weight and fat loss, improves cardiorespiratory fitness and muscle strength, and reduces the loss of lean body mass. Aerobic training improves insulin sensitivity after bariatric surgery [51]. Regular exercise programs increase quality of life's physical component, improve self-efficacy and autonomous motivations for exercise, vitality and mental health, while are not able to reduce depression. Combined type of exercise induce greater improvements in quality of life [52]. Digital behavior change interventions with goal setting, social incentive and graded tasks and face-to-face behavior assessing behavioral practice and rehearsal conduct to an increase in physical activity outcomes [53]. An individualized exercise prescription and adequate follow-up should also be implemented for physical activity to improve compliance. .

In many cases, the lifestyle is not enough to counteract obesity, so **pharmacological treatment** may be indicated; in particular, current guidelines recommend this approach for people with BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with an obesity-related disease. Drugs for obesity are effective in maintaining compliance, improve quality of life and prevent

obesity-related co-morbidities [46]. Orlistat is a selective inhibitor of pancreatic lipase, counteracting intestinal digestion of fat. The efficacy and safety of the drug is proven and is also documented that gastrointestinal symptoms and a reduction in fat-soluble vitamin absorption are common [54–56]. Lorcaserin is a serotonin type 2C receptor agonist with hypophagic effects. This drug is effective in reducing body weight and improve fasting glycaemia and glycosylated hemoglobin. Adverse events are blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea [57,58]. Phentermine/topiramate is a combination of an atypical amphetamine analogue (phentermine) with the principal effect of appetite suppression and an atypical anticonvulsant drug (topiramate). Adverse events linked to this treatment are dry mouth, constipation, insomnia, palpitations, dizziness, paraesthesia, disturbances in attention, metabolic acidosis and renal calculi, headache, dysgeusia, alopecia and hypokalaemia [57,58]. Bupropion/naltrexone combines a non-selective inhibitor of the transporters of dopamine and norepinephrine (bupropion) and an opioid receptor antagonist (naltrexone). The anorectic effect of the bupropion/naltrexone combination should derive from the activation of POMC neurons in the arcuate nucleus. Common reported adverse events are nausea, headache, dizziness, insomnia and vomiting [59]. Liraglutide is a GLP-1R agonist. Main actions are the insulin release, the glucagon reduction and appetite suppression. Usual adverse effect are nausea and vomiting, but they are often transient [60,61]. When all other therapeutic attempts have failed, bariatric surgery remains the best option. Its effects on weight and co-morbidities are clear, so in cases that meet the inclusion criteria it appears to be a valid choice [62]. Indications for **bariatric surgery** include age 18-60 years, BMI ≥ 40.0 kg/m ^{2} or between 35.0 and 39.9 kg/m ^{2} and co-morbidities [62]. Obesity and in particular severe obesity, is a chronic disease, so all the professionals involved (doctor, patient and surgeon) must make a long-term commitment in the management of co-morbidities before and after surgery and for the follow-up.

Currently the primary purpose of surgery is to determine metabolic changes and not just weight loss [46]. It is known that the effect of bariatric surgery on enteric gut hormones (i.e. GLP-1 and pancreatic polypeptide YY), significantly determine the beneficial effects of this therapeutic approach [62]. Laparoscopic adjustable gastric banding consists in a silicone band placed around the upper part of the stomach that limit food passage [62]. Roux-en-Y gastric bypass is the separation of the upper part of the stomach and of the small intestine (jejunal level) that become a pouch, and the anastomosis between the distal part of the intestine and the new stomach pouch. The excised middle fragment of intestine is rejointed to the small intestine further down. Food go through the small pouch and flows directly into the distal part of the small intestine limiting absorption of nutrients [63]. Sleeve gastrectomy consists in the excision of the stomach (about 80%). The residual stomach has lower motility and limit food ingestion, thereby reducing caloric intake [64]. Biliopancreatic diversion with a duodenal switch is a surgical procedure executed in two-stage. A sleeve gastrectomy is performed for making a tubular pouch. Then the small intestine is resected in two sites; the distal part anastomosed to the duodenum, while the end of the middle fragment is then anastomosed to the small intestine [65]. Bariatric surgery is an effective and cost-effective treatment, but it is not free from consequences and complications for the patient such as the dumping syndrome, nutritional deficiencies and psychological concerns [64]. Nevertheless, in order to optimize results it is recommended to manage the patients with obesity in multidisciplinary team, with adequate follow up and monitoring, based on evidence-based approach [46].

1.2. OBESITY AND ARTERIAL HYPERTENSION

Many epidemiological studies worldwide have demonstrated the high prevalence of hypertension among people with obesity. In the US the prevalence of hypertension is 43.6% in subjects with obesity, 27.8% in subjects with overweight, and 15.3% in normal weight adults [66]. A higher BMI is also associated with an increased risk of developing hypertension over time as reported from the Framingham Heart Study where relative risk for new onset of hypertension over time were quite doubled in man and women with obesity [66]. Previous literature has also highlighted the role of lifelong weight gain in increasing blood pressure. Young adults with a stable BMI did not experienced significant changes in blood pressure values, while those who had increased their BMI had a significant increase in blood pressure during the following 15 years [66]. The development of arterial hypertension in people with overweight or obesity is the result of a complex interaction between hemodynamic, nervous and endocrine pathways.

Impaired **renal mechanisms** are documented in people with obesity. First, the excess of perirenal fat physically compresses the kidneys and vascular structures, increasing the renal interstitial pressure and the fractional resorption of sodium. In addition, the retroperitoneal and renal sinus fat can cause inflammation and this can further impair kidney function. The accumulation of fat in and around the kidneys can also have lipotoxic effects (oxidative stress and mitochondrial dysfunction) [67]. In addition, people with obesity demonstrates a hyperactivity of the renin-angiotensin-aldosteron system (RAAs) due to an increased renin secretion induced by renal sympathetic hyperactivity and perirenal and retroperitoneal fat compression, and for the production of angiotensinogen by the adipose tissue [68]. Further role in the genesis of hypertension in people with obesity could also be played by the activation of the mineralcorticoid receptor (MR) independently from aldosterone even if with mechanism not completely clarified [69]. Another aspect that binds obesity to the genesis of arterial hypertension is **arterial**

stiffening and endothelial dysfunction that are believed to precede the development of hypertension in people with obesity. Arterial wall stiffening is linked to numerous factors including smooth vascular musculature dysfunction, collagen accumulation in the extracellular matrix and loss of elastic fibers in the arterial wall [70]. Endothelial dysfunction refers to a reduced nitric oxide (NO) availability, abnormal reactivity to vasomotor stimuli and high expression of pro-inflammatory and pro-thrombotic factors. Obesity determines also a chronic state related tolow grade inflammation that in turn activate endothelium causing a reduction in nitric oxide activity and nitric oxide production [71]. Endothelial dysfunction plays a key role in hypertension in patients with obesity and is closely related to insulin resistance [72]. In obesity associated with **insulin resistance** and hyperinsulinemia the mechanism of tubular sodium resorption is enhanced, leading to chronic sodium retention, blood volume expansion, and increased blood pressure. Insulin also play a sympathetic-excitatory action by boosting the release of norepinephrine which in turns activate RAAs [73]. Furthermore, **leptin** is involved in the link between obesity and hypertension because, similarly to insulin, is able to stimulate the sympathetic system mainly at the renal, adrenal and brown adipose tissue levels [73]. Leptin can also induce endothelial dysfunction by reducing the expression of nitric oxide synthase [74]. **Sympathetic hyperactivation** in obesity is not generalized but selective for some body districts and, in particular, is localized on kidney and skeletal muscle, while sympathetic cardiac activity is reduced or just slightly increased (Rumantir et al., 1999). Nevertheless, people with obesity and hypertension show increased sympathetic and reduced parasympathetic cardiac activity. Several mechanisms may justify this autonomic nervous system pattern in obesity and those most involved are the altered baroreceptor function, the increase of circulating free fatty acid that raise α1-mediated vasoconstriction, the noradrenergic spillover due the angiotensin, the effect of the endocrine profile in obesity (leptin, adiponectin and insulin), and the frequent

coexistence of obesity and obstructive sleep apnoea syndrome [75–79]. Obesity and hypertension may have additive effects in increasing cardiovascular risk, so the adoption of a healthy lifestyle oriented to weight loss, also increases the efficacy of antihypertensive drugs with an independent beneficial effect on cardiovascular risk. It is known that for each kilogram of weight loss blood pressure decrease by about 1 mmHg with also a slowdown phenomenon which, however, provides for a decrease of 6 mmHg per 10 Kg of weight loss [32,80]. Obesity determines a particular cardiomyopathy directly and indirectly due to hypertension induced by obesity, diabetes and coronary artery diseases. Endocrine dysfunction in patients with obesity, as well as hypertension leads to pathologic myocardium remodeling with left ventricular hypertrophy and diastolic dysfunction resulting in hypertensive and obesity cardiomyopathy. The increase in left ventricular mass is a key element for the worsening of ischemic disease and also for the development of heart failure with preserved ejection fraction [81,82].

1.3. EXERCISE BLOOD PRESSURE

Exercise testing is widely used for detecting many underlying pathological conditions often hidden at rest, such as coronary artery disease, reduced cardiorespiratory fitness, high cardiovascular risk, chronotropic competence and arrhythmias. During the exercise stress test, blood pressure behavior is a marker of an appropriate hemodynamic response. As known blood pressure depends on cardiac output and peripheral vascular resistance. During exercise, systolic blood pressure progressively increase with increasing intensity, while diastolic pressure remains quite the same or slightly decrease due to exercise-linked vasodilatation [83]. During exercise the increase of cardiac output outweighs the reduction of vascular resistance causing an elevation of mean arterial pressure [84]. After maximal exercise, systolic blood pressure promptly decline reaching pre-exercise or lower levels within 6 minutes of recovery [83]. Low exercise BP is a poor prognostic index related to cardiac dysfunction, but also an exaggerated or hypertensive response to exercise may reveal high cardiovascular risk. There are no universally acknowledged thresholds for the definition of an hypertensive response to exercise, but the currently accepted limits are a systolic blood pressure of ≥ 210 mmHg for males and ≥ 190 mmHg for females and a diastolic BP ≥ 110 mmHg for both males and females at any exercise workload. In addition, studies indicate that a blood pressure higher than 175 mmHg at submaximal intensity may indicate an exaggerated blood pressure response to exercise [85–87]. Many studies speculated that an exaggerated blood pressure response to exercise could predict the future development of hypertension. Exaggerated exercise blood pressure is more prevalent in people with high-normal blood pressure and masked hypertension that are both associated with the future development of overt hypertension. These conditions may often overlap, indicating the same susceptibility to hypertension development [84]. Exaggerated blood pressure to exercise was found to be associated with cardiac sign of hypertension-related organ damage such as left ventricular

mass, left ventricular hypertrophy and concentric remodeling, also in patients with type 2 diabetes when compared to those with normal exercise blood pressure. Moreover, early markers of left ventricular systolic dysfunction such as impaired left ventricular strain rate and peak systolic strain have been associated with hypertensive response to exercise, suggesting that these findings may reflect also the presence of an early hypertensive heart adaptation [88–90]. Previous literature confirmed also that hypertensive response to exercise correlates with adverse cardiovascular events and mortality (both cardiovascular and all-cause). Furthermore, for each 10 mmHg rise in blood pressure at moderate intensity a 4% increase in CV events and mortality was found. These findings are consistent with the evidence of a prognostic value of blood pressure recorded during low intensity activity such as everyday ambulatory activities [91]. Indeed, ambulatory blood pressure is more accurate in indicating the real pressure load than office blood pressure. People spend a lot of time in light intensity activities, so high blood pressure at submaximal exercise may mirror uncontrolled or high blood pressure [92]. Many pathophysiological mechanisms may contribute to increase exercise blood pressure. First, metabolic alterations such as lipid profile may contribute with its chronic atherogenic and stiffening effect [93]. Also insulin resistance has been associated with exercise systolic blood pressure both in diabetic and non-diabetic subjects [94,95]. Furthermore, vascular function is a key element in the determination of blood pressure. The ability to dilate appropriately with exercise is a determinant, together with the characteristic impedance of the first tract of the aorta of the input impedance (ratio of pulsatile pressure to pulsatile flow) and thus of the rise in systolic blood pressure [96,97]. Indeed, also endothelium-dependent vasodilation, arterial stiffness and central pulse pressure could represent involved mechanisms [98–100]. Pulse pressure amplification increase during moderate intensity exercise in healthy individuals but not in older or dyslipidemic subjects[101]. Furthermore, sympathetic system may influence the vasoactive state during exercise.

Thus, conditions that increase sympathetic activity may be related to high blood pressure during exercise [102]. Other studies indicated that markers of vascular inflammation (i.e. C-reactive protein and IL-6) had possible relationships with exercise blood pressure [103].

1.3.1 Workload-indexed blood pressure

Current guidelines define the hypertensive response to exercise using absolute threshold values [83,104]. This approach may be helpful in defining the risk of acute adverse events during stress testing, but is questionable in predicting the risk of cardiovascular events or mortality in the future. In this regard, the literature has led to ambiguous results about the correlation with mortality and much of the variability depends on the blood pressure threshold and on the population considered in the study [91,105]. In fact, due to the linear correlation between external workload and cardiac output increase during exercise, subjects with high functional capacity and lower risk of cardiovascular events, such as athletes and healthy subjects, show a higher blood pressure at peak of exercise than subjects with chronic disease and reduced functional capacity. Furthermore, due to the close and positive relationship between functional capacity and survival, the result is that in some studies that consider patients with heart or chronic disease, the risk of mortality is higher for those with the lower exercise blood pressure [106,107]. Relating systolic pressure to the workload could overcome this problem. Current guidelines indicate a value of 10 mmHg/MET as an average increase. However, a recent study that evaluated the association of the workload-indexed pressure with all-cause mortality in a large population of males, pointed out that 10 mmHg/METs was the 95^{th} percentile for the risk of mortality in the subgroup of subjects at lower cardiovascular risk. Therefore, this value should be considered an upper limit rather than an expected response [108]. Moreover, in the above-mentioned study, the group of subjects at high cardiovascular risk at baseline showed a median workload-indexed pressure equal to 6.4 mmHg/METs [108]. To date workload-indexed blood pressure has not been widely studied in different populations

with different disease. This information could help to better understand the clinical value of this parameter.

2. EXPERIMENTAL BACKGROUND

Obesity is a disease that is visibly increasing worldwide with spreading diffusion of its related cardio-metabolic consequences [46]. Hypertension is more frequent among people with obesity who result more often on anti-hypertensive treatment, but also less likely to achieve blood pressure control [109]. Obesity and hypertension are closely linked at a pathophysiological level, by a series of hormonal and metabolic pathways mutually connected [110]. As known adipose tissue is an endocrine organ that secrets adipokynes and expresses receptors for numerous endocrine substances involved in several mechanisms regulating metabolism, immunity and blood pressure [111]. Among the main mechanisms involved in the genesis of hypertension related to obesity are insulin resistance, the activation of the renin-angiotensin-aldosterone axis and the activation of the sympathetic nervous system, as well as the induction of the low grade inflammation status [111–113]. It is well known that high blood pressure at rest is strongly correlated with cardiovascular events and mortality, but relatively recent findings have emphasized the role of blood pressure during exercise [114,115]. Exaggerated blood pressure response during exercise was found to be related to unfavourable cardiac remodelling, a higher risk of future arterial hypertension and cardiovascular disease [91,116,117]. In previous studies, healthy subjects with high waist circumference showed a higher exercise blood pressure than those with a lower waist circumference and many authors confirmed that obesity and hypertension have a synergistic effect in increasing cardiovascular risk [32,118]. Bariatric surgery (BS) is one of the most effective treatments for obesity and for many of its cardiovascular comorbidities including arterial hypertension [119]. Moreover, it has been demonstrated that bariatric surgery is more effective than non-surgical therapies for obesity in improving systolic and diastolic pressure values and reducing the need of antihypertensive drugs [120]. Recently Sénéchal-Dumais et al. reported that bariatric surgery is effective in reducing hypertensive response during exercise [121].

Nevertheless, little is known regarding exercise blood pressure and workload-indexed blood pressure in subjects with severe obesity. During exercise, as well as during common activity of daily living, systolic blood pressure rises with the increment in workload, due to the linear relationship between cardiac output and workload[122]. This relationship between workload and cardiac output can make it difficult to adopt an absolute cut-off in order to define exaggerated blood pressure response to exercise. Furthermore, the workload-indexed blood pressure has been related to an increased risk of mortality, and in particular, from a prognostic point of view, a workload-indexed blood pressure of 10 mmHg/MET appears more as an upper limit than as an average increase [108].

The aim of this study was to evaluate the blood pressure response during exercise in people with severe obesity before and after treatment with bariatric surgery. In particular, the study was focused on submaximal and maximal workload-indexed blood pressure that represents an innovative and promising index of haemodynamic charge during exercise.

3. MATERIALS AND METHODS

3.1 Study design and clinical examination

For this longitudinal observational study, 257 patients with severe obesity (PwO) included in the diagnostic, therapeutic and assistance pathway of the Veneto Region and enlisted by the Center for the Study and Integrated Treatment of Obesity of the Padova University Hospital, were enrolled between March 2014 and June 2020. All participants in the study suitable for surgery, underwent sleeve gastrectomy (SG). All subjects were evaluated with incremental, maximal cardiopulmonary exercise testing (CPET) one month before and six months after bariatric surgery. The average follow-up between the first and second tests was 233±71 days; the average distance between surgery and the second test was 209±71 days. All enrolled subjects had a body mass index (BMI) ≥35 kg/m^2 with obesity-related comorbidities or a BMI ≥40 kg/m^2 with or without comorbidities. Furthermore, 17 healthy

and normal weight subjects (HS) were enrolled as controls. Patients with active cancer, chronic inflammatory diseases, infectious diseases, and alcohol or drug abuse were excluded from the study. Each participant gave their written informed consent. The study was conducted in accordance with the principles of the Helsinki Declaration. The protocol was approved by the "Padua Ethical Committee for Clinical Research" (2892P, 10/06/2013). Personal medical history, physical examination and measurement of body weight, height and abdominal circumference were performed for each patient. BMI was calculated as body weight (Kg)/height $(m)^2$. In PwO a complete blood biochemical analysis was performed after an 8-hour fast, in particular in the present study, fasting plasma glucose (FPG) and lipid profile were considered. Biochemical measurements were performed using diagnostic kits standardized according to the World Health Organization First International Reference Standard. In the post-surgical examination, the improvement of hypertension and diabetes mellitus was evaluated through the pharmacological treatment status. Estimated 10-years cardiovascular risk and lifetime risk of cardiovascular disease were calculated by using the ASCVD risk score [123,124].

3.2 Cardiopulmonary exercise test

All subjects underwent cardiopulmonary exercise test (CPET) one month before and six months after sleeve gastrectomy. The test was carried out on a treadmill or, in a small percentage of subjects (8.9%; n=23), on a bike ergometer, in relation to patients' clinical characteristics or limitations (e.g. musculoskeletal disabilities/problems). During the test, heart rate, blood pressure, and 12-lead electrocardiographic tracing were monitored. Ventilatory parameters were sampled breath by breath with the Jaeger-Masterscreen-CPX (Carefusion). Patients' Rate of Perceived Effort (RPE) was evaluated through the Borg scale [125]. Bruce's modified incremental ramp protocol was used for treadmill testing; for the bike ergometer, the incremental protocol was 15 Watts per minute or 10 Watts per minute. All patients performed the same protocol before and after the sleeve

gastrectomy. The execution of a different protocol was considered an exclusion criterion. The criteria used to define the maximum effort were the achievement of an RER ≥1.10 and/or a maximum heart rate ≥85% predicted by age (Karvonen's formula) and/or a score in the RPE Borg's scale ≥ 17/20. All patients who did not meet at least two of these three criteria were excluded from the study in order to ensure maximum effort. The workload was expressed as METs (Metabolic Equivalent of Tasks). Trained medical personnel measured blood pressure with auscultatory method and by using an aneroid sphygmomanometer equipped with a cuff adequate for the patient's arm size. Systolic pressure was determined at Korotkoff's Phase I (Appearance of Tone); diastolic pressure between Korotkoff's Phase IV (Tone Damping) and Korotkoff's Phase V (Disappearance of Tone). Resting systolic and diastolic blood pressure (SBPrest and DBPrest, respectively) was measured when the patient was seated, after at least 5 minutes rest, before the cardiopulmonary exercise test, and the average of at least three measurements was considered. Blood pressure during exercise was evaluated on average every 3 minutes and at the time of maximum effort (SBPpeak and DBPpeak) as recommended by the American College of Sport Medicine guidelines [104]. Submaximal systolic and diastolic blood pressure (SBPsubmax and DBPsubmax, respectively) was recorded at stage 1 of Bruce's protocol or at the third minute of exercise for tests carried out on a bike ergometer. In order to make the submaximal pressure values comparable, an intra-individual difference of sub-maximal of less than 1 METs between the tests before and after surgery was tolerated. Finally, systolic and diastolic blood pressure in the recovery phase (SBP recovery and DBPrecovery) was measured with patient in supine position at the end of the recovery phase. The submaximal workload-indexed Systolic Blood Pressure (W-SBPsubmax) was calculated with the formula: ΔSBPsubmax/ΔMETs corresponding to SBPsubmax-SBPrest/METs submax-1. The maximal workload-indexed Systolic Blood Pressure (W-SBPmax) was calculated with the formula: ΔSBPmax/ΔMETs corresponding

to SBPmax-SBPrest/METsmax-1. The threshold of 10 mmHg/METs was considered as the cut-off for an exaggerated blood pressure response to exercise [108].

3.3 Bariatric surgery

Indications for performing bariatric surgery were those reported in the guidelines of the American Society for Metabolic and Bariatric Surgery (ASMBS): BMI ≥40 or BMI ≥35 kg/m^2 with comorbidity, long history of primary pathological obesity, failure of dietary therapy and between 18 and 65 years of age [126]. The bariatric procedures were performed by using laparoscopic surgery. Patients who were candidates for bariatric surgery had been previously evaluated by the surgical, nutritional and psychological services. After the surgery, patients were prescribed a supplementary dietary therapy that includes a multivitamin and, if necessary, iron supplements and antiacids.

3.4 Statistical analyses

Mean, standard deviation (SD) and percentages were used to describe continuous and dichotomous clinical parameters, respectively. Normal distribution of continuous variables was tested with the Shapiro-Wilk test. When not normally distributed continuous variables were logarithmically transformed to conform to normal assumptions. The differences between variables (before and after bariatric surgery) were analyzed through t-test for paired data. Differences between patient groups for variables not normally distributed and not expressed in logarithm were evaluated by Mann-Whitney U-Test. Chi-square test with McNemar correction was used to compare dichotomous variables before and after bariatric surgery and Pearson's Chi-square test for dichotomous variables between independent groups. Spearman's or Pearson's correlation test was used to study correlations between continuous variables. A stepwise logistic regression analysis was performed to provide independent determinants of workload-indexed blood pressure ≥10 mmHg/METs after bariatric surgery. All tests were

considered two-tailed and the p-values <0.05 were considered statistically significant. Statistical analyses were conducted using the software Statistical Package for Social Science (SPSS Inc., Chicago, Illinois, USA) ver.20 software package.

4. RESULTS

4.1 Characteristics of the population

The study population consisted of 257 PwO including 189 (73.5%) females, average age was 45.5±10.3 years, with an average BMI of 43.9±6.4 Kg/m^2 and with a mean waist circumference of 130.0±16.0 cm. The prevalence of the main comorbidities associated with obesity revealed that 40.1% (n=103) of subjects had arterial hypertension; 29.6% (n=76) presented type 2 diabetes and 24.1% (n= 62) dyslipidemia. The prevalence of obstructive sleep apnea syndrome (OSAS) was 19.8% (n=51) and of arthropathy 30.4% (n= 78). Main characteristics of PwO before surgery are summarized in Table 1.

Table 1. Characteristics of the population of people with obesity before surgery

N 257	
Female gender n (%)	189 (73.5)
Age (years)	45.5 ±10.3
BMI (Kg/m^2)	43.9 ± 6.4
Waist circumference (cm)	130.0 ± 16.0
10-Year ASCVD Risk (%)	4.5±5.4
Optimal 10-Year ASCVD Risk (%)	1.4±1.2
Lifetime ASCVD Risk (%)	40.4±13.6
Optimal Lifetime ASCVD Risk (%)	7.3±1.3
Arterial hypertension n (%)	103 (40.1)
Type 2 diabetes n (%)	76 (29.6)

Dyslipidaemia n (%)	62 (24.1)
OSAS n (%)	51 (19.8)
Hypothyroidism n (%)	44 (17.1)
Hyperuricemia n (%)	9 (6.2)
Arthropathy n (%)	78 (30.4)
Depression n (%)	24 (9.3)

*Table 1. Characteristics of the population (n=257) and prevalence of the main comorbidities associated with obesity before bariatric surgery. BMI: body mass index; OSAS: obstructive sleep apnea syndrome; 10-Year ASCVD Risk (%): quantitative estimation of absolute risk of atherosclerotic cardiovascular disease at 10 years; Optimal 10-Year ASCVD Risk (%): The 10-year risk estimate for "optimal risk factors" (individual of the same age, sex and race and Total cholesterol of ≤ 170 mg/dL, HDL-cholesterol of ≥ 50 mg/dL, untreated systolic blood pressure of ≤ 110 mm Hg, no diabetes history, and not a current smoker); * data available on 146 patients.*

4.2 Comparison between patients with obesity and healthy subjects

The control group consisted of 17 healthy subjects without obesity (mean BMI 20.7±8.3), with a mean age of 40.9±10.1 years, of which 70.6% (n=12) were females. Comparisons of functional parameters between PwO and HS are displayed in table 2.

Table 2. Comparison between patients with obesity and healthy subjects.

	PwO	HS	p
BMI (kg/m^2)	43.9±6.4	20.7±8.3	<0.0001
Age (years)	45.5±10.1	40.9±10.1	0.087
SBPrest (mmHg)	126.8±13.3	112.2±9.3	<0.0001
DBPrest (mmHg)	77.9±9.8	67.7±7.8	<0.0001
SBPsubmax (mmHg)	143.4±18.5	126.5±14.2	<0.0001
DBPsubmax (mmHg)	78.2±10.6	69.1±11.1	0.002

METssubmax	3.0±0.66	7.5±2.6	<0.0001
SBPpeak (mmHg)	177.8±23.0	157.1±14	<0.0001
DBPpeak (mmHg)	71.3±14.3	64.1±16.2	0.071
METsmax	8.2±2.6	15.6± 3.2	<0.0001
SBPrecovery (mmHg)	126.5±11.3	121.5±8.6	0.093
DBPrecovery (mmHg)	73.7±9.8	67.2±9.4	0.017
HRrest (bpm)	83±13.5	66.1±11.6	<0.0001
HRsubmax (bpm)	119±15.7	115.4±26.9	0.517
HRpeak (bpm)	157.0±18.0	176.8±11.6	<0.0001
HRpeak % of predicted	89.8±8.7	99.1±5.0	<0.0001
HRrecovery (bpm)	98.7±13.3	93.1±15.3	0.149
W-SBPsubmax	9.0±10.7	2.3±2.1	<0.0001
W-SBPpeak	8.0±5.1	3.1±0.9	<0.0001

Table 2: represents comparisons of clinical and CPET parameters between PwO before bariatric surgery and HS. SBP/DBPrest: systolic and diastolic blood pressure at rest; SBP/DBPsubmax: systolic and diastolic blood pressure at submaximal exercise intensity; METssubmax: intensity of exercise at submaximal stage; SBP/DBPpeak: systolic and diastolic blood pressure at the peak of exercise; METsmax: intensity of exercise at peak of effort; SBP/DBPrecovery: systolic and diastolic blood pressure at the end of the recovery phase; HRrest, submax, peak, recovery: heart rate at rest, at submaximal exercise, at exercise peak, at the end of the recovery phase. HRpeak % of predicted: percentage of age-predicted heart rate reached at exercise peak. W-SBPsubmax: workload-indexed systolic blood pressure at submaximal intensity; W-SBPpeak: workload-indexed systolic blood pressure at exercise peak.

PwO had a reduced functional capacity (VO_2/Kg 19.5±3.5 vs 39.6±6.9 mL/min/Kg; p<0.0001) and a lower exercise tolerance. Systolic blood pressure (Figure 1a; table 2) was significantly higher in PwO than in HS both at rest (p<0.0001) and during submaximal and maximal exercise (both p<0.0001), the systolic blood pressure at the end of the recovery phase was the only exception resulting statistically similar between the two groups. The

diastolic blood pressure (Figure 1b; table 2) was significantly higher in PwO at rest and during submaximal exercise (p<0.0001 and p=0.002, respectively), but this difference loose statistical significance at peak of exercise and at the end of the recovery phase. Accordingly, there is a clear and statistically significant difference in terms of W-SBP both at submaximal and at peak of exercise (table 2).

Figure 1. Blood pressure during maximal exercise testing.

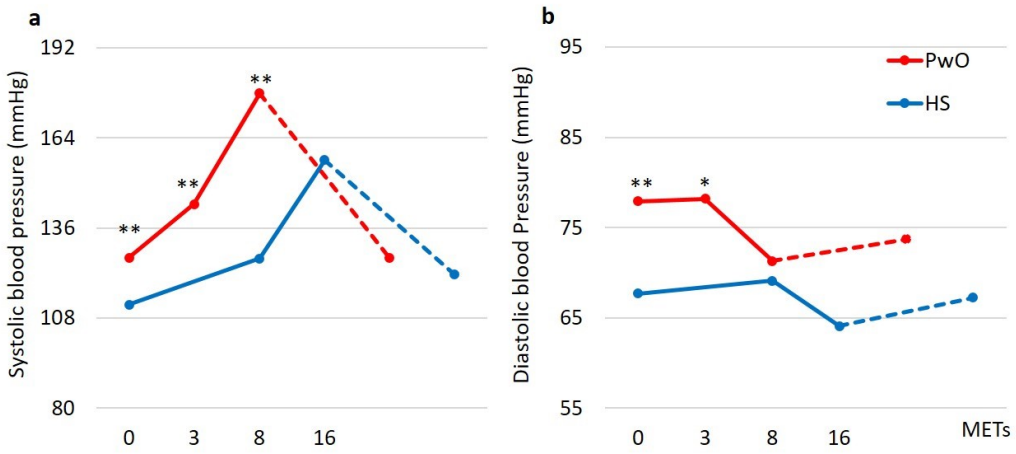

Figure 1: represents the behavior of systolic (a) and diastolic (b) blood pressure during exercise (solid line) and the recovery phase (dashed line) in PwO (red) and HS (blu). Significant differences between PwO and HS of blood pressure recorded in the same phase of exercise testing are expressed as *<0.005 and **<0.0001. As visible, despite reaching a lower exercise intensity PwO showed greater blood pressure than HS.

4.3 Comparisons before and after bariatric surgery

A statistically significant reduction in BMI (32.5±5.2 vs 43.9±6.4 kg/m^2; p<0.001), body weight (89.4±17.8 vs 120.8±23.2 kg; p<0.001) and waist circumference (106.0±15.0 vs 130±16 cm; p<0.001) was observed after bariatric surgery (figure 2a). A weight loss of -31.5±10.2 Kg occurred corresponding to a percent weight loss of -25.9±6.2 %; a ΔBMI of -11.4±3.4 Kg/m^2 and a ΔBMI% of -26±6.4%. Comorbidities also significantly improved

after bariatric surgery with 22.2% (n= 52) of the subjects with hypertension; 18.3% (n= 47) type 2 diabetes and 17.9% (n=46) dyslipidemia (figure 2b). After bariatric surgery the prevalence of obstructive sleep apnea syndrome (OSAS) was 13.2% (n= 34) and that of arthropathy 26.1% (n= 67). 4.8% (n= 7 out of 146) had hyperuricemia, 16.3% (n= 42) hypothyroidism and 8.6% (n= 22) depression all with significant reduction. Finally, the 26.1% reduced or stopped anti-hypertensive drugs after bariatric surgery.

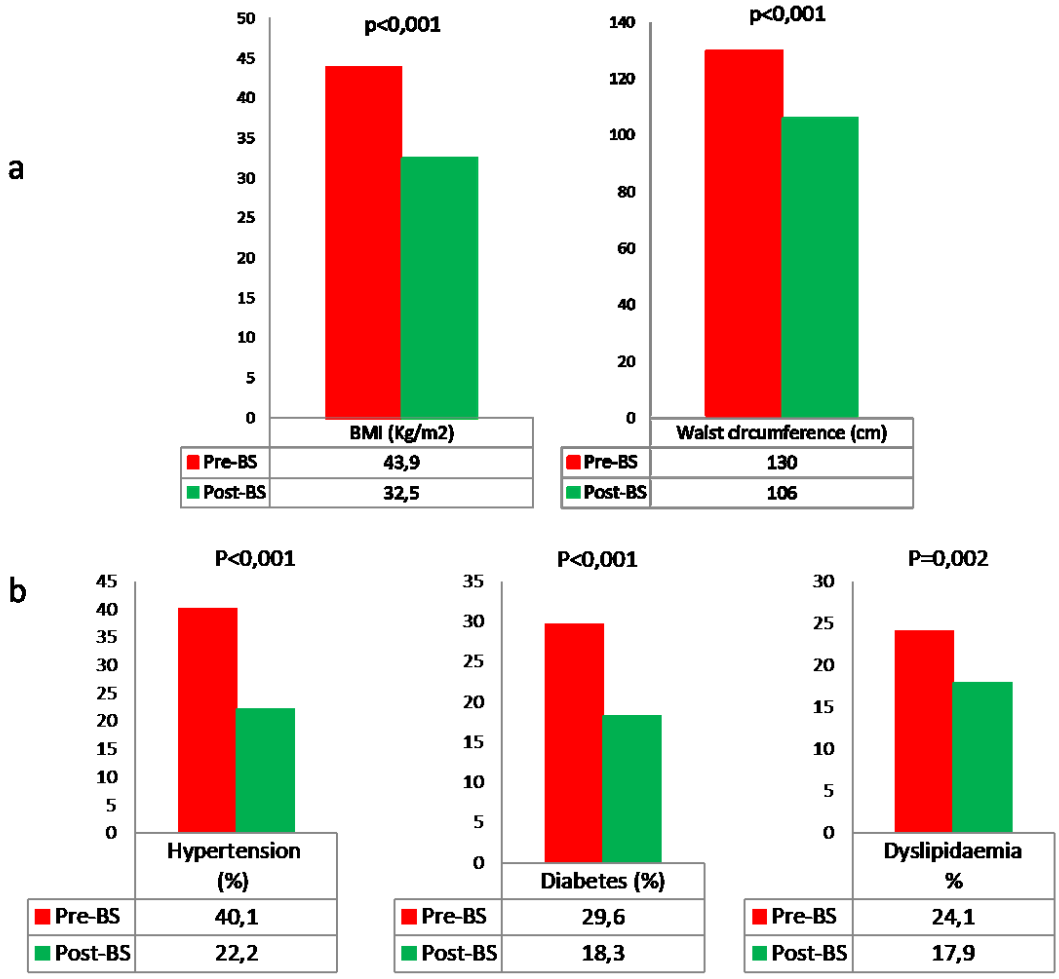

Figure 2. a) variation of BMI and waist circumference after bariatric surgery in patients with severe obesity; b) Prevalence before and after bariatric surgery of the main obesity comorbidities associated with cardiovascular risk (chi square test with McNemar correction).

As expected functional capacity and exercise tolerance significantly improved in PwO after bariatric surgery (i.e. +3.9±0.22 mL/min/Kg and +2.1±1.5 METs, respectively; both

p<0.0001). With regard to resting blood pressure, a reduction of both systolic pressure (-10.2±15.8 mmHg and -7.4±12.3%; p<0.0001) and diastolic pressure (-2.5±11.6 mmHg and 5.7±15.0%; p<0.0001) was observed. As well as a reduction in both systolic (-15.0±19.7 mmHg and -9.6±13.0%; p<0.0001) and diastolic (-4.5±10.9 mmHg -4.4±16.4%; p<0.0001) submaximal pressure was observed. Submaximal intensity was similar before and after bariatric surgery (0.06±0.43; p=0,05). Similarly, also blood pressure at peak of exercise was lower after bariatric surgery both for systolic (-10.3±25.1 mmHg and -5.0±14.0%; p<0.0001) and diastolic pressure (-2.0±15.1 mmHg and -4.4±16.4%; p=0.025), despite the significant increase in exercise intensity reached at peak of exercise after bariatric surgery. Additionally, at the end of the recovery phase systolic and diastolic blood pressure were significantly lower (SBPrecovery -7.5±11.5 mmHg and DBPrecovery -3.3±9.6 mmHg) after bariatric surgery (figure 3; table 3).

Figure 3. Systolic and diastolic blood pressure during exercise test before and after bariatric surgery.

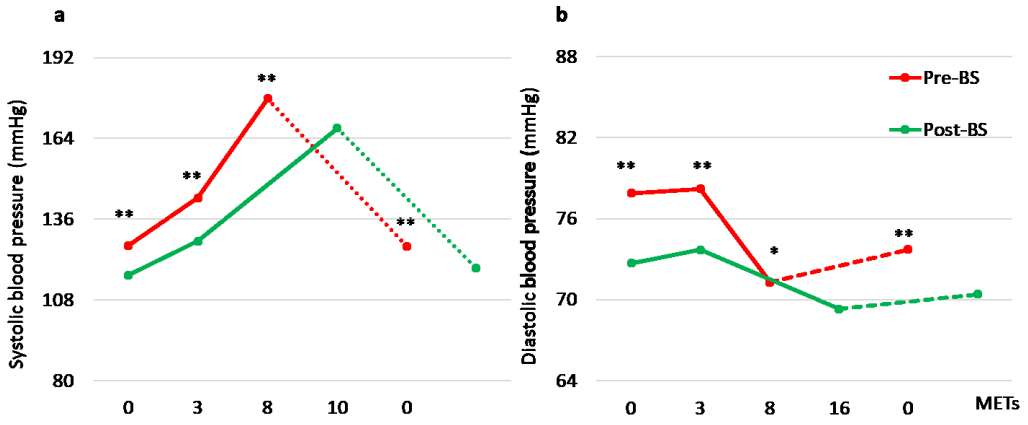

Figure 3. represents the behavior of systolic (a) and diastolic (b) blood pressure during exercise (solid line) and the recovery phase (dashed line) in PwO before (red) and after bariatric surgery (green). Significant differences of blood pressure recorded in the same phase of exercise testing between PwO before and after bariatric surgery are expressed as *<0.05 and **<0.0001. As visible, despite reaching a higher exercise intensity after bariatric surgery PwO showed a lower blood pressure than before.

There was also a reduction in resting, submaximal and peak heart rate ($p<0.0001$; $p<0.0001$ and $p=0.023$, respectively). The percentage of the maximum age-predicted heart rate at peak of exercise was similar before and after bariatric surgery. All these data are displayed in table 3. Respiratory Exchange Ratio at peak of exercise was significantly increased after bariatric surgery (1.19 ± 0.1 vs 1.13 ± 0.1; $p<0.0001$).

Table 3. Cardiopulmonary parameters before and after bariatric surgery

		Pre	**Post**	**p**
Functional capacity	METsmax	8.2±2.6	10.3±2.5	<0.0001
	VO_2peak/Kg (ml/min/Kg)	19.5±3.5	23.4±5.3	<0.0001
Rest	SBPrest	126.8±13.3	116.6±14.1	<0.0001
	DBPrest	77.9±9.8	72.7±10.2	<0.0001
	HRrest	83±13.5	67±10.7	<0.0001
Submaximal exercise	SBPsubmax	143.4±18.5	128.4±17.4	<0.0001
	DBPsubmax	78.2±10.6	73.7±10.2	<0.0001
	HRsubmax	119±15.7	96±14.9	<0.0001
Exercise peak	SBPpeak	177.8±23.0	167.5±24.2	<0.0001
	DBPpeak	71.3±14.3	69.3±14.9	0.025
	HRpeak	157±18.0	155±19.2	0.023
	HRpeak % predicted	89.8±8.7	88.8±9.4	0.05
Recovery phase	SBPrecovery	126.5±11.3	119.0±11.0	<0.0001
	DBPrecovery	73.7±9.86	70.4±8.9	<0.0001
Workload-indexed blood pressure	WSBPsubmax	9.0±10.7	6.0±7.6	<0.0001
	WSBPpeak	8.0±5.2	6.0±3.2	<0.0001

Table 3: represents comparisons of CPET parameters of PwO before and after bariatric surgery. SBP/DBPrest: systolic and diastolic blood pressure at rest; SBP/DBPsubmax: systolic and diastolic blood pressure at submaximal exercise intensity; METssubmax: intensity of exercise at submaximal stage; SBP/DBPpeak: systolic and diastolic blood pressure at the peak of exercise; METsmax: intensity of exercise at peak of effort; SBP/DBPrecovery: systolic and diastolic blood pressure at the end of the recovery phase; HRrest, submax, peak, recovery: heart rate at rest, at submaximal exercise, at exercise peak, at the end of the recovery phase. HRpeak % of predicted: percentage of age-

predicted heart rate reached at exercise peak. W-SBPsubmax: workload-indexed systolic blood pressure at submaximal intensity; W-SBPpeak: workload-indexed systolic blood pressure at exercise peak.

Finally, both W-SBPsubmax (-3.0±12.2 mmHg/METs; p=0.0001) and W-SBPpeak (-2.1±4.8 mmHg/METs; p<0.0001) were significantly reduced. The percentage reduction in W-SBPpeak after bariatric surgery was equal to 4.95±13.9%. The prevalence of PwO that presented a W-SBPpeak ≥10 mmHg/METs was equal to 21.8% (n=61), while after bariatric surgery this number was halved representing the 10.1% (n=26). Patients who after bariatric surgery showed a W-SBPpeak ≥10 mmHg/METs were characterized by a higher percentage of hypertension (73% vs 37%; p <0.0001) and a higher percentage of subjects that reduced or stopped anti-hypertensive drugs after bariatric surgery (54% vs 23%; p=0.001). Furthermore, these subjects showed a lower VO_2/Kg before bariatric surgery, a lower percentage of BMI and weight loss and higher age, 10y-ASCVD risk, BMI before surgery, triglycerides, and glycemia. No significant difference was found for sex, diabetes, dyslipidemia, smoking status, waist circumference, variation in functional capacity, lifetime cardiovascular risk, blood lipids, SBPrest and its variation after surgery. In addition, W-SBPsubmax and W-SBPpeak of PwO after bariatric surgery were significantly different from HS (p=0.018 and p<0.0001, respectively), while absolute values of systolic and diastolic blood pressure were similar at rest, at submaximal and maximal intensity and at the end of the recovery phase. A stepwise logistic regression analysis showed that determinants of the probability to have W-SBPpeak ≥10 mmHg after bariatric surgery were high age (p=0.019), high W-SBPpeak before bariatric surgery (p=0.021), and low VO_2peak/kg before bariatric surgery (p=0.013), independently from SBPrest and BMI before and their percent variation after bariatric surgery.

5. DISCUSSION

The aim of this work was to investigate the blood pressure response to exercise assessed via cardiopulmonary exercise test in a population of patients with severe obesity compared with healthy subjects and before and after sleeve gastrectomy. In particular, we explored the workload-indexed pressure.

It is well established that hypertension and obesity often coexist. It is also known that patients with severe obesity without hypertension show higher blood pressure values when compared with normal weight and non-hypertensive subjects [30]. In addition, an exaggerated pressure response during exercise increases the risk of cardiovascular events regardless of resting blood pressure and may suggests the presence of masked hypertension in patients with normal office blood pressure values [92,115]. The present study shows that patients with severe obesity have higher blood pressure values than those with normal weight but similar for gender and age. This difference can be seen both at rest and during exercise. Especially during exercise, it may be noticed a significant difference in terms of workload-indexed blood pressure that represents the pressure response to a given workload. This index seems the most suitable to compare the pressure responses of different populations and be able to evaluate the hemodynamic response [122]. As can be seen from the present work, those with severe obesity reach lower workload than those with normal weight, but develop greater pressures, although they rarely present real hypertensive responses during exercise. As known, these trend of blood pressure during exercise correspond to an increase in the overall risk of cardiovascular disease and mortality added to the already present risk, due to other co-morbidities of obesity such as diabetes mellitus, dyslipidemia and OSAS [32,108]. Interestingly, the difference in blood pressure during the recovery phase was not significant between PwO and HS. A recent paper highlighted that obesity did not affect

post exercise hypotension, confirming the beneficial effect of physical activity in patients with obesity also with hypertension [37,127].

Moreover, the present study showed that six months after bariatric surgery blood pressure is significantly reduced at rest, during all stages of the maximal exercise test and at the end of the recovery phase. The reduction in resting systolic blood pressure of about 10 mmHg recorded in this population of PwO is not only statistically, but also clinically relevant considering the evidences about the significant relative risk reduction of cardiovascular events that already starts from 5 mmHg systolic blood pressure lowering obtained with pharmacological treatment [128]. A further strength of these results is that this variation in blood pressure after bariatric surgery is observable despite 26% of these subjects had reduced or suspended anti-hypertensive therapy. While many studies have already shown a significant effect of bariatric surgery in lowering resting blood pressure levels [129,130], few investigated the effect on arterial pressure during exercise [131] and by considering also blood pressure recorded at submaximal exercise. This is one of the first studies that demonstrates a statistically significant reduction in submaximal blood pressure after bariatric surgery. In the study conducted by Ben-Dow et al. [131], authors demonstrated a reduction in blood pressure during exercise for all exercise intensities considered (low, moderate and high). However, this study was based on a relatively limited population (n=19, of which only 4 were male). Nevertheless, their findings were in line with our observations thus supporting the validity of the present work. In previous literature, the clinical and prognostic value of submaximal blood pressure has been demonstrated also independently from resting blood pressure. Blood pressure recorded at submaximal exercise is representative of the chronic hemodynamic load for the cardiovascular system during the normal activities of daily living and is closer to the 24-hours blood pressure [132]. An increased pressure response to submaximal exercise can also predict the future onset of hypertension [117,133], as well as cardiovascular events

and mortality [115]. This parameter is also associated with hypertension-related markers of organ damage such as left ventricular hypertrophy [116], endothelial dysfunction, and arterial stiffness [134]. The study of submaximal blood pressure could therefore have a clinical relevance in identifying subjects at higher risk of masked hypertension and not optimal control of blood pressure values. Our study also observed a reduction in the prevalence of the major comorbidities associated with obesity affecting cardiovascular risk, such as diabetes mellitus, dyslipidemia and OSAS. This result is consistent with current scientific evidence [135]. Also functional capacity and exercise tolerance significantly improved after bariatric surgery, as previously reported [136]. It is known that relatively small improvements in cardiorespiratory fitness (such as 1 MET) have been associated with considerable reductions in mortality [137].

The current study has also demonstrated a statistically significant reduction of the Workload-indexed Blood Pressure, both for submaximal and maximal intensities. To the best of our knowledge, this is the first work that introduces this parameter in the study of blood pressure during exercise in subjects with severe obesity. Currently, the gold standard for diagnosis and management of arterial hypertension is the 24-hours ambulatory blood pressure monitoring (ABPM). This instrument is more indicated than the office blood pressure and home blood pressure monitoring in describing blood pressure profile, the daytime/nighttime pattern, blood pressure variability and the real blood pressure control [138], but it does not provide any specific data regarding the response to the exact intensity during activities of daily living. The workload-indexed Blood Pressure may represent an innovative parameter for clinical practice and more accurate tool for clinical research. This parameter relates blood pressure values to the intensity of exercise measured in METs, by assuming the linear relationship between exercise intensity and cardiac output increase [106]. The workload-indexed blood

pressure may thus indicate more accurately the real hemodynamic load experienced by patients throughout a specific task [122].

However, workload-indexed Blood Pressure needs to be explored also in prospective studies that confirm its real and independent predictive power on cardiovascular events. Hedman et al. showed that workload-indexed Blood Pressure assessed at maximal exercise intensity, has a higher predictive power of cardiovascular events and mortality than the absolute systolic pressure at peak of exercise [108]. In addition, in previous literature, data about submaximal workload-indexed Blood Pressure are scarce and prevent to gain prognostic conclusions. In the present study, the significant reduction of the workload-indexed Blood Pressure is documented also when considering the number of subjects with a W-SBPpeak ≥10 mmHg/METs before and after bariatric surgery. This value is considered by the current guidelines as the physiological response to exercise [83], but in the study of Hedman et al. this limit corresponds to un upper limit when considering the risk of mortality even in a group of subjects with low cardiovascular risk [108]. Actually, in our population, subjects that after bariatric surgery continue to have W-SBPpeak ≥10 mmHg/METs presents also a higher cardiovascular risk profile, a smaller weight loss percentage as well as a lower cardiorespiratory fitness. Moreover, independent determinants of the probability to have a high (≥10 mmHg) W-SBPpeak are age, the W-SBPpeak and VO_2peak/kg before bariatric surgery. Cardiac and vascular remodeling occurring with obesity and also with age may explain the permanent high blood pressure response to exercise. In fact, it is documented that after bariatric surgery ventricular geometry, arterial stiffness and diastolic dysfunction improves.[135] However, it is possible that in some people the cardiovascular changes induced by age, hypertension and obesity become permanent damage. Furthermore, it is known that VO_2max is inversely related with arterial stiffness and in particular with the proximal aortic stiffness as expression of central arterial distensibility [135].

Another interesting feature is that, despite the difference with HS was very marked both before and after bariatric surgery, PwO experienced a clear reduction of the workload-indexed Blood Pressure after bariatric surgery, but the mean value is similar to that measured by Headman et al. in a group of subjects with high cardiovascular risk. Further studies are essential to understand the prognostic values of these findings. Moreover, in the clinical practice is highly recommended to perform a close and continuous surveillance of blood pressure values in these patients also after the required adjustments of pharmacological treatment [139]. Additionally, we emphasize the importance of the execution of a CPET and the evaluation of submaximal and maximal blood pressure in patients with severe obesity. This stress test may unmask poor pressure control not visible at rest or a case of masked hypertension. Furthermore, workload-indexed Blood Pressure could also play an important role in the planning of a structured exercise prescription after bariatric surgery. The current diagnostic, therapeutic and assistance pathway for patients with severe obesity in the Veneto Region provides, after bariatric surgery, the development of a structured physical exercise prescription aimed to improve the weight reduction and reduce the total metabolic and cardiovascular risk. The determination of workload-indexed Blood Pressure may help to provide a more tailored prescription in order to prevent adverse events and to maximize the benefit related to exercise training. The present work has also found that the percent reduction in body weight is not an independent determinant of high workload-indexed Blood Pressure. This result appears in agreement with previous literature, which show a pressure reduction that goes beyond the weight loss. In addition, a temporal dissociation between blood pressure reduction and the weight loss has been also previously described. In fact, the lowering of the pressure values appears from days immediately after surgery and even before a evident drop in body weight [129]. This early effect has been attributed to an improvement in hemodynamic mechanisms, such as reduction of intravascular volume and an

improvement of pressor natriuresis, which are important mechanisms underlying hypertension in obesity [140]. Furthermore, the ability of sleeve gastrectomy to modify metabolic and neuro-humoral parameters has been well described [135,141]. After sleeve gastrectomy, a marked reduction in circulating levels of leptin and ghrelin, an attenuation of sympathetic and renin-angiotensin-aldosterone axis hyperactivity, and an increase in insulin sensitivity can be observed [142].

The present study has been conducted in a clinical setting, therefore this condition limits the execution of experimental protocols totally dedicated to the recording of blood pressure during exercise. Moreover, the measurement of blood pressure during exercise is limited at the methodological level, as the main instruments available in clinical contexts are not referred primarily to the measurement during exercise. In addition, the formulas dedicated to the measurement of the workload-indexed blood pressure assume a linear relationship between pressure and intensity, but while this correlation is established for cardiac output, it is not certain for blood pressure. Nevertheless, the relationship between external load and pressure should be studied in more depth and in different populations considering also the role of other factors in determining arterial pressure (i.e. arterial function). It would be interesting also to conduct a study using invasive pressure measurement to clarify the actual pressure trend during exercise and compare the different responses of different populations. Moreover, in this study it was not possible to compare the pressure values during exercise with the values recorded by the 24-hour ambulatory blood pressure monitoring. This could enrich current results by clarifying the relationship between workload-indexed blood pressure and 24-hour blood pressure.

6. CONCLUSIONS

1. PwO show increased blood pressure values compared to normal weight subjects both at rest and during exercise. This difference is mitigated in the recovery phase, confirming the acute effect of exercise in blood pressure lowering also in this population. Workload-indexed blood pressure is significantly higher in PwO when compared with HS.

2. After bariatric surgery there is a marked reduction of all blood pressure values, both at rest and during all stages of physical exercise, despite a gain in exercise tolerance and in maximal intensity reached at peak of exercise. In particular, workload-indexed blood pressure during exercise is significantly reduced after bariatric surgery.

3. PwO who even after bariatric surgery show a workload-indexed blood pressure at peak of exercise ≥10 mmHg have also higher cardio-metabolic risk profile and a lower percent weight loss.

4. In this population, main independent determinants of high workload-indexed blood pressure at peak of exercise after bariatric surgery are VO_2/Kg before bariatric surgery, W-SBPpeak before bariatric surgery and age.

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