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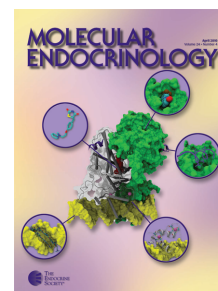
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The impact of GH/IGF-I axis and nocturnal breathing disorders on cardiovascular features of adult patients with Prader-Willi Syndrome

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Running title: GHD, sleep apnea and cardiovascular risk in PWS

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Abstract

Context Adult patients with Prader-Willi syndrome (PWS) are prone to develop obesity, GH deficiency (GHD) and their related complications, with cardiopulmonary failure explaining over half of PWS fatalities.

Objective and study participants This study was undertaken to examine the effect of GHD and sleep breathing disorders on cardiovascular risk factors and heart features of 13 PWS (age 26.9 ± 1.2 yr) and 13 age-, gender- and BMI-matched obese individuals (age 26.2 ± 0.8 yr).

Results Compared to controls, PWS patients had lower GH response to Arginine+GHRH, IGF-I levels, triglycerides, total- and LDL-cholesterol, insulin and HOMA-IR. DXA and abdominal CT scans revealed a greater fat mass, similar abdominal fat but greater sleep breathing disorders in PWS than obese subjects. Echocardiography showed no systolic or diastolic alteration, although PWS had lower left ventricle mass (LVM) (135.7 ± 7.7 vs. 163.5 ± 8.4 g, $p < 0.05$) and nonsignificantly lower values of LV end-diastole diameter ($p = 0.08$) compared to obese controls. Baseline radionuclide angiography documented comparable values of systolic and diastolic values between groups. However, adrenergic stimulation with dobutamine caused a lower increase of LV ejection fraction (LVEF, 71.9 ± 1.9 vs. $76.3 \pm 1.2\%$, $p < 0.05$) and heart rate (103 ± 6.9 vs. 128 ± 2.8 bpm, $p < 0.05$) in PWS than obese individuals. By multivariate analysis, nocturnal oxygen desaturation and IGF-I levels were main significant predictors of LVM and heart rate in PWS patients.

Conclusions PWS differs from simple obesity by a healthier metabolic profile, impaired nocturnal breathing, decreased heart geometry and systolic and chronotropic performance. GHD and the predictive role of IGF-I on structural and functional heart parameters suggest a GH/IGF-I-mediated control of cardiac risk in PWS.

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder bearing dysmorphogenetic abnormalities, restricted longitudinal growth and behavioral disorders (1). Hypothalamic-pituitary dysfunction is a recognized cause of compulsive appetite leading most PWS patients to develop morbid obesity, and also explains body temperature instability, hypogonadism and altered GH secretion (1-3). Typically, PWS patients present with decreased lean body mass and increased fat/lean mass ratio not only if compared to lean subjects, but also in relation to simple obese patients (4). Although fat accumulation accounts for 44-53% of body weight in PWS adults (5), the identification of an atypically reduced visceral fat depot in obese PWS females has been hypothesized to explain a healthier lipid profile and insulin sensitivity compared to matched obese population (6,7).

Regardless of their metabolic advantages, however, adult PWS patients demise prematurely for complications conventionally related to obesity, such as diabetes mellitus, arterial hypertension, sleep apnea and cardiopulmonary disorders (1,8-10). This circumstance prompted many investigators to recommend strict preventive measures for uncontrolled weight accrual in PWS (1), but an awareness is rising that critical illnesses and sudden death of PWS patients may not be entirely caused by obesity alone. Retrospective studies estimated mortality rates in PWS to be 3% a year across all ages and 7% a year in patients aged over 30 years, with several cardiovascular fatalities described as unrelated to obesity (11-15). It is currently unclear if poor health outcomes of PWS are influenced by GH deficiency (GHD) (16-19), an

independent cause of central adiposity, unfavorable lipid profile, endothelial dysfunction, impaired diastolic and systolic functions and increased risk of ischemic heart disease in hypopituitary populations (20-22).

Based on these data, we sought to explore the occurrence of cardiovascular alterations and the potential influence of GHD, sleep breathing disorders and regional fat distribution on heart morphology and function in a group of obese PWS adults matched by an age-, gender- and BMI-comparable control group.

Subjects and Methods

All subjects were Caucasian and aged over 18 years. The patients' group consisted of 13 PWS adults (6 females and 7 males, age 26.9 ± 1.2 yr, BMI 46.3 ± 1.6 kg/m²), showing typical PWS clinical phenotype (1). Cytogenetic analysis was performed in all patients and revealed interstitial deletion of the proximal long arm of chromosome 15 (15q11-q13) in all but two subjects with uniparental disomy. All patients suffered from childhood obesity and were undergoing strict parental guidance for control of feeding obsession. Two patients suffering from arterial hypertension were receiving therapy with ACE-inhibitor plus Ca-antagonist (n=1) and loop diuretics (n=1), while another patient was treated with low-dose β -blocker due to past episode of ventricular arrhythmia. One hypertensive patient also suffered from type-2 diabetes mellitus and was insulin-treated. No other patient had previously manifested signs/symptoms or undergone treatment for cardiovascular disorders. Two of 3 PWS women with primary amenorrhea were undergoing sex steroid substitutive therapy, 2 of 3 untreated females

suffered from oligomenorrhea while the remaining suffered from secondary amenorrhea. Five patients had previously undergone GH treatment, withdrawn in all cases 1-4 years before enrollment in the current study. Five PWS patients were receiving treatments with neuroleptics. As controls, 13 age-, sex- and BMI-matched otherwise healthy individuals (6 females, 7 males, age 26.2 ± 0.8 yr, BMI 43 ± 1.2 kg/m²) were selected from patients admitted to our Institution for evaluation and cure of obesity and its complications, and accepted to participate to the study.

All participants reported stable body weight in the previous 2 months, none had impaired renal or hepatic function nor had been previously subjected to weight-reducing gastric surgery or was undergoing weight-reducing medical treatments. Two PWS patients and 2 controls were cigarette smokers. Subjects were enrolled in this study after approval of institutional Ethic Committee and written consent, under parental guidance for PWS patients.

Anthropometric measurements and hormonal testing Physical examination included determination of height and weight in fasting conditions and after voiding. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in centimeters (kg/cm²). Waist was measured as halfway between the costal edge and the crista. Hip was measured as the greatest circumference around the nates. Dual-energy x-ray absorptiometry (DXA) was used for measurements of fat body mass (FBM, %) (GE-Lunar, Madison, WI). Intra-abdominal (visceral, VAT) and subcutaneous abdominal fat (SAT) were measured by 6-mm single-slice L₄-level computed tomography using GE Hi-Speed DX/I with 6.4 CT scanner software (General Electric

Medical Systems, Milwaukee, WI). Intra-abdominal fat was separated from retroperitoneal fat by drawing a line to the pericolic gutters. Sagittal diameter was measured as the anterior-to-posterior distance in millimeters at the disk level. A single image was obtained during suspended respiration. The within-subject variation for repeated analyses of fat measurement in our laboratory is <1%. Pituitary GH secretion was evaluated by dynamic testing with Arginine+GHRH. Arginine (SALF, Bergamo, Italy) was administered at a dose of 0.5 g/kg up to a maximal dose of 30 g infused slowly in 0-30 min; GHRH (1-29) (Ferring, Milan, Italy) was given at a dose of 1 µg/kg as an i.v. bolus at 0 min. Blood sample were taken basally before arginine and GHRH infusion, respectively, and then at 15 min intervals from 0 to 90 min. According to recent studies assessing the GH cutoff for GHD diagnosis in lean and obese subjects, GHD was classified according to a GH response to Arginine+GHRH as <4.1 µg/l (23).

Cardiovascular examinations M-mode, two-dimensional and pulsed Doppler echocardiographic studies were performed with commercially available ultrasound systems (Hewlett-Packard Sonos 2500, Andover, MA) using a 2.5 MHz transducer, during 3-5 consecutive cardiac cycles. Records were obtained by one investigator (EE), unaware of patients' characteristics and medical history. All subjects were studied in left lateral recumbent position after a 10 min resting period according to the recommendations of the American Society of Echocardiography (24). The following measurements were recorded on M-mode tracing: interventricular septum thickness (IST, mm), left ventricular (LV) posterior wall thickness (LVPWT, mm) and end-diastole diameter (LVEDD, mm); calculation of the LV mass (LVM, g) was made using the

Devereux's formula according to the Penn convention with the following regression-corrected cube formula (25): $LVM = 1.04 [(IST + LVEDD + LVPWT)^3 - (LVEDD)^3] - 14 \text{ g}$, as well as after correction for body surface area ($LVMi, \text{g/m}^2$), $\text{height}^{2.7}$ ($LVM/h^{2.7}$) or percent fat mass ($LVM/FM, \text{g\%}$). None of the present series suffered from LV hypertrophy, considered as $LVMi$ values $\geq 135 \text{ g/m}^2$ in males and $\geq 110 \text{ g/m}^2$ in females. Doppler studies provided indices of ventricular filling that were derived from the mitral flow velocities curves, i.e. maximal early diastolic flow velocity ($E, \text{cm/s}$), maximal late diastolic flow velocity ($A, \text{cm/s}$), peak E/A wave velocity ratio (normal value ≥ 1) and the deceleration time of early filling (DT, ms). Estimated pulmonary artery systolic pressure ($PASP, \text{mm Hg}$) was derived from the amount of tricuspid regurgitation using the modified Bernoulli equation, in addition to the estimated right atrial pressure (normal $\geq 25 \text{ mm Hg}$).

Equilibrium radionuclide ventriculography was performed, after *in vivo* red blood cells labeling (1100 MBq of ^{99m}Tc), at rest and during dobutamine infusion, an inotropic β_1 -adrenergic agent that stimulates myocardial contractility at lower doses and elicits chronotropic effect at higher doses. Acquisitions were obtained with patients in supine position in the left anterior oblique "best septal" view with a large field-of-view camera (Apex 409, Elcsint, Haifa, Israel) equipped with a parallel-hole high sensitivity collimator, as previously reported (26). Data were collected in mini-list mode to compensate for heart variability during acquisition; 32 frames were acquired in a 64×64 array, excluding extrasystolic and post-extrasystolic beats. Dobutamine infusion was performed in 5-minute steps; image acquisition was obtained during the last 3 minutes of each step. A total of 5.0×10^6 counts were collected for each study. Electrocardiography was

continuously monitored and measurement of systolic (SBP) and diastolic blood pressure (DBP) by cuff sphygmomanometer was performed at each step. Indices of LV and right ventricle (RV) function were derived by analysis of the background-corrected time-activity curve, which was constructed by a semiautomated edge-detection method with a variable region of interest. LV ejection fraction (LVEF, %) was computed on the basis of relative end-diastolic and end-systolic counts. In all participants, framing rate was sufficiently high to allow calculation of diastolic parameters. Accordingly, peak filling rate (PFR) was computed from the first derivative of a third-order polynomial function fitted to the first two thirds of the diastolic portion of the LV time-activity curve by a least squares technique, normalized for end-diastolic volume (EDV) and expressed as EDV per second (EDV/s). As normal, the following values were taken in consideration: LVEF $\geq 50\%$ in basal conditions with $\geq 5\%$ increments during dobutamine; RVEF $\geq 45\%$ in basal condition with $\geq 5\%$ increments during dobutamine; PFR ≥ 2.5 EDV/s.

Polysomnography study All participants underwent an adaptation night and then a full-night polysomnography in a dedicated laboratory in a quiet room. Subjects were allowed to maintain their usual sleep habits and timing. The following parameters were recorded: EEG using C3-A2, C4-A1, O2-A1, O1-A2 derivations integrated by bipolar montages Fp2-F4, F4-C4, C4-P4, P4-O2; Fp1-F3, F3-C3, C3-P3, P3-O1; Fz-Cz, Cz-Pz of the 10-20 international placement system; electro-oculogram (bipolar montage: right ocular cantus-left ocular cantus); electrocardiogram; respiratory effort by thoracic and abdominal strain gauges, nasal air-flow by nasal cannula, snoring nose by a microphone, arterial oxyhaemoglobin (SaO₂) using a pulse oximeter with finger probe;

submental and tibialis anterior muscles electromyogram. Respiratory parameters included in the present study were: apnea-hypopnea index (AHI) and duration, basal oxygen saturation (basal SaO₂), lowest oxygen saturation (lowest SaO₂), time in minutes spent at oxygen saturation below 90% (SaO₂ <90%), average minimum SaO₂ during desaturations (desat SaO₂), number of desaturations/hours of sleep (desat SaO₂/h).

Hormone assays All measurements were performed using commercially available kits. GH levels were measured by chemiluminescence (Immulin 2000 Analyzer, DPC, Los Angeles, CA) calibrated against WHO 1st IRP 80/50, having a sensitivity of 0.01 µg/l and intra- and inter-assay coefficients of variation (CVs) of 2.9-4.2% and 4.2-6.5%, respectively. Total IGF-I levels were assayed by chemiluminescence IGF-I immunoassay by Liaison (Nichols Advantage, San Juan Capistrano, CA), having a sensitivity of 6 µg/l, intra-assay and inter-assay CVs of 4.8% and 6.7%, respectively. Serum insulin levels were measured by chemiluminescence (Immulin 2000). Enzymatic methods (Boehringer-Mannheim, Mannheim, Germany) were employed for determination of blood glucose; total-, HDL- and LDL-cholesterol; and triglycerides. The total/HDL-cholesterol ratio was also calculated as an indicator of severe cardiovascular risk in GHD patients (27). Insulin resistance was measured by homeostatic model approach (HOMA-IR), calculated as insulin (µU/ml) x blood glucose (mmol/l)/22.5 (28). Ultrasensitive C-reactive protein was measured by CRP (latex) HS Roche kit, having sensitivity of 0.003 mg/dl, intra-assay CVs of 5.35% at 0.05 mg/dl, 2.51% at 0.17 mg/dl and 4.25% at 0.193 mg/dl; inter-assay CVs of 5.79% at 0.0481 mg/dl and 4.25% at 0.193 mg/dl. For conversion from metric to SI units: leptin, µg/l x

0.0625 = nmol/l; insulin, $\mu\text{U/ml} \times 7.175 = \text{pmol/l}$; glucose, $\text{mg/dl} \times 0.05551 = \text{mmol/l}$; cholesterol, $\text{mg/dl} \times 0.02586 = \text{mmol/l}$.

Data analysis

Results are presented as mean $\pm$ S.E.M. Two-tailed unpaired Student's T test was used for comparison among groups equally obese. Relationships between variables were analyzed using Pearson's correlation analysis. Independent variables influencing cardiovascular parameters were tested by multiple linear regression analysis. Based on significant regressions obtained from a variety of iterative (stepwise, forward and backward selections) model-building strategies, three multivariate models analyzing the cardiovascular effects of independent variables [age, peak GH and IGF-I levels (model A); percent fat mass, SAT, VAT and VAT/SAT ratio (model B); AHI, AHI/h, desat SaO_2 and $\text{SaO}_2 < 90\%$ (model C)] in each group separately and in both as a whole, a multiple model estimated the regression of each of LVM, LVEDD, E/A, baseline and dobutamine-stimulated LVEF, PFR and heart rate in comparison to peak GH, IGF-I, VAT, SAT, VAT/SAT ratio, AHI and $\text{SaO}_2 < 90\%$ as independent variables. Analyses were performed using SPSS 10.0 (SPSS, Inc., Chicago, IL) and Prism (Graphpad Software, Inc., San Diego, CA). Significance was set at $p < 0.05$.

Results

At study entry, PWS patients had comparable age, gender distribution and BMI but shorter stature compared to obese controls (Table 1). The metabolic profile was more advantageous in PWS than obese controls and consisted of lower insulin and HOMA-IR indices of insulin resistance ($p<0.05$ for both), lower total-cholesterol, LDL-cholesterol and triglycerides levels ($p<0.05$ for all); determination of atherogenic risk by total/HDL-cholesterol ratio ($p<0.05$) and proinflammatory protein C-reactive protein, although nonsignificantly lower ($p<0.085$), confirmed previous findings. A significantly greater total body fat was found by DXA in PWS patients, despite similarities between groups in abdominal fat distribution assessed by waist-to-hip ratio and CT scans. No differences were documented between PWS males and females for values of SAT (713 ± 27 vs. 701 ± 67 cm²), VAT (129 ± 12 vs. 168 ± 34 cm²), VAT/SAT ratio (0.18 ± 0.02 vs. 0.24 ± 0.02) as well as percent fat mass (55.9 ± 0.9 vs. $56.2\pm2.7\%$).

By Arginine+GHRH test, mean GH peak levels were lower in PWS patients than obese controls ($p<0.05$), and the observed peak GH secretion was <4.1 µg/l in 5 PWS (38%) and 2 obese controls (15%). IGF-I levels were also significantly lower in PWS than in obese controls ($p<0.01$).

Polysomnography revealed a greater prevalence of sleep breathing disorders in PWS compared to obese subjects, consisting of greater apnea-hypopnea index ($p<0.05$) and lower oxygen saturation during nocturnal sleep, a longer time spent at oxygen saturation below 90%, lower average minimum SaO₂ during desaturations as well as higher number of desaturations/hours of sleep ($p<0.01$ for all) (Table 1).

Echocardiography No PWS patients or controls showed abnormalities in regional wall motion, valve function or cardiac chambers structure. However, PWS patient, when compared to obese controls, had lower absolute values of LVM ($p<0.05$) caused by specific reduction of LVPWT ($p<0.05$), with a trend toward lower values of LVEDD ($p=0.08$) (Table 2). Significant differences were also noted when LVM was indexed by fat mass ($p<0.01$) but not when indexed by body surface area or height^{2,7}. Doppler analysis did not detect systolic or diastolic abnormalities and recorded comparable values in LVEF, E/A ratio, PASP and DT between PWS and obese controls. Where an adequate measurement was obtained, PASP was ≥ 25 mmHg in 8 of 9 PWS (88%) and 6 of 8 simple obese subjects (75%). No patient or control showed abnormalities in right ventricle function. Similarities in echocardiographic and Doppler parameters occurred in the PWS state when patients were stratified by peak GH values at Arginine+GHRH test (data not shown). At odds with obese controls, gender-based analysis revealed that PWS men had higher values of LVM (149.2 ± 9.7 g vs. 120 ± 9.2 g, $p<0.05$) and LVEDD (53.5 ± 3 mm vs. 41.3 ± 2.5 mm, $p<0.01$) than women.

Radionuclide angiography At baseline, there were no differences between PWS and obese controls in heart rate, diastolic or systolic blood pressure, LVEF, RVEF and PFR (Table 2 and Fig. 1). Two PWS (15%) and 1 obese subject (7%) had lower than normal LVEF. A slight impairment of RVEF and PFR was also noted in 5 PWS (38%) and 6 obese (46%), and 4 PWS (30%) and 3 obese subjects (23%), respectively.

In 1 PWS patient treated with β -blockers dobutamine test was not performed. Mean peak dobutamine doses did not differ between PWS and obese subjects (22.7 ± 2.7

vs. 28 ± 2.3 μ /kg/min) and, with the exception of mild transient nausea experienced at the end of infusion in a limited number of cases, the compound was generally well tolerated. No subject developed clinically relevant arrhythmias, angina, electrocardiographic signs of ischemia or severe hypertension necessitating termination of the test. A blunted chronotropic response during dobutamine infusion was documented in PWS patients when compared to obese controls ($p < 0.01$) and in 5 PWS patients (38%) the heart rate increased $< 50\%$ (Fig. 1). No changes were observed during dobutamine infusion in diastolic and systolic arterial pressure. During dobutamine infusion (Table 2, Fig. 1 and 2), LVEF increased $\geq 5\%$ in all subjects ($p < 0.01$ vs. baseline for both groups) but one 26-year old PWS female. Peak LVEF was, on average, significantly lower in PWS than obese subjects ($p < 0.05$); however, the rest-peak increments were comparable between groups. No differences were also observed between groups in dobutamine-stimulated and rest-peak increments of RVEF and PFR. Similarities in cardioscintigraphic parameters occurred in the PWS state when patients were stratified by peak GH values at Arginine+GHRH test (data not shown).

Correlation studies Bivariate analysis was performed in each group as illustrated in Table 3. Multivariate analysis in PWS patients revealed that LVM was best predicted by $\text{SaO}_2 < 90\%$ ($t = 4.37$, $P = 0.007$), IGF-I ($t = 3.40$, $p = 0.019$) and, negatively, by VAT ($t = -2.69$, $p = 0.040$); significant regression coefficients were also found between basal heart rate and IGF-I ($t = -3.41$, $p = 0.019$), AHI ($t = 3.38$, $p = 0.019$) and $\text{SaO}_2 < 90\%$ ($t = -2.81$, $p = 0.037$); between basal PFR and IGF-I ($t = 2.77$, $p = 0.038$); and between LVEDD and $\text{SaO}_2 < 90\%$ ($t = 2.74$, $p = 0.040$). Only nonsignificant regression slopes were

recorded in the obese groups. By merging data from both groups, significant regression coefficients were obtained between basal LVEF and IGF-I ($t=3.85$, $p=0.003$) and AHI ($t=-2.71$, $p=0.02$), as well as between basal PFR and IGF-I values ($t=2.62$, $p=0.02$).

Discussion

Life expectancy is reduced in PWS and adult patients are prone to premature death from cardiopulmonary problems traditionally related to obesity (1,2,7,13-20). An alternative hypothesis suggests the existence of an intrinsic clinical fragility predisposing PWS patients to cardiovascular complications independently of obesity (20). A number of cardiac abnormalities have been described in PWS children with chromosome 15 defects including microdeletions of genes essential for proper angiogenesis and heart development, such as NR2F2 and ACTC (29-31). Indeed, cases of dilated cardiomyopathy have also been reported in PWS infants and adults independent of the loss of genes critical for cardiac morphology (13,14). Overall, irreversible critical illnesses are frequent causes of unexpected death in obese as well as in lean PWS patients due to ischemic and non-ischemic cardiovascular disease in as many as 40-60% of cases (12,13).

In the current study, the cardiovascular features of PWS patients were examined relatively to fat accumulation, GH secretory status and sleep breathing disorders. Fat body mass accounted for 45-64% of body weight in PWS compared to 36-55% of obese patients, with similar proportions of abdominal subcutaneous and visceral fat between populations. By combining DXA and CT scans results, PWS patients showed a greater fat

accumulation in the extra-abdominal areas. PWS adults also exhibited a significantly healthier metabolic profile than obese subjects. Our results thus agree with similar previous metabolic and anthropometric studies (4,5,7) and partly vary from whole-body MRI studies showing a selective reduction of visceral fat in adult PWS females PWS after adjustment for total adiposity (6). Assessment of GH/IGF-I axis showed a lower GH response to Arginine+GHRH, decreased IGF-I levels and shorter stature in PWS than in obese controls. According to recent GH cutoff normative data obtained under Arginine+GHRH test in lean and obese subjects (23), biochemical criteria for GHD were fulfilled by 38% of our PWS and 15% of obese individuals, while previous collective data inferred that 40-100% of PWS patients fulfill diagnostic criteria of GHD by using a variety of dynamic tests (23). Furthermore, our polysomnography study complimented Literature evidence of increased apneic episodes and hypercapnic arousal thresholds in PWS (10,33), and demonstrated a significantly higher number of apnea-hypopnea episodes and greater nocturnal desaturation in PWS than obese controls.

Of greater importance, PWS patients exhibited signs suggestive of a modification of heart geometry, due to a 17% decrease of left ventricle mass and nonsignificantly lower values of end-diastolic diameter. These differences were abrogated when left ventricular mass was indexed by body surface area or by height^{2.7}, but persisted if indexed by body fat, suggesting that this methodology may also be feasible in the obese setting of PWS. Unlike previous studies in larger subsets of uncomplicated obese subjects (34,35), our investigation showed no signs of left ventricle hypertrophy or diastolic dysfunction by echocardiography, while an impairment of peak filling rate and right ventricle ejection fraction was documented in comparable proportions of PWS and

obese controls by radionuclide angiography, an imaging approach less operator-dependent than echocardiography. These abnormalities however disappeared under dobutamine stimulus, a predominant β_1 -receptor agonist simulating the effect of exercise that allowed to circumvent common drawbacks associated with the PWS state, i.e. obese phenotype, muscle hypotonia and scant propensity to exercise. Interestingly, such methodology showed that left ventricle ejection fraction was normal at baseline but peaked at significantly lower levels in PWS than obese individuals, although the rest-peak increments were comparable between groups. Inversely, the lower chronotropic response obtained in PWS subjects may reflect an initial derangement of cardiac output under adrenergic stimulation; this finding, however, remains of uncertain prognostic relevance. Dobutamine increases heart rate dose-dependently via α_1 -receptors and this response is blunted in condition of increased vagal tone (36). A disturbance in sympathovagal tone has been implicated in the development of arrhythmia and sudden death in different patients groups (37), and a decrease of heart rate partakes in the hypokinetic syndrome of GHD (22), although initial findings of abnormal parasympathetic activity studies in PWS (38) have not been reproduced in subsequent studies performed in resting conditions and under autonomic challenges (39).

One potential contributor to cardiovascular alterations in PWS is sleep apnea, that is mixed in most patients and includes a central component caused by a defect in the central ventilatory drive response to hypercarbia, as well as a peripheral obstructive component caused by deficient faringeal patency associated with obesity (10). The significant correlations herein obtained between nocturnal breathing and cardiovascular features in PWS patients are, thus, of potential interest and claim for a tight relationship

between sleep breathing disorders and either left cardiac mass and output or heart rate. In the general population, sleep apnea is an independent risk factor for arrhythmias, sympathetic hyperactivity, hypertension, diastolic and systolic dysfunction, pulmonary congestion and cardiac hypertrophy (40). Although sleep apnea-related hypoxia is acknowledged as a cause of cor pulmonale in PWS (13,14), the cardiovascular characteristics of PWS appear to be better explained by the hypotrophic hypokinetic syndrome associated with GHD (22). It is known that hypopituitary patients with GHD are at high risk for coronary artery disease and impaired cardiac function leading to a 2-fold greater cardiovascular mortality than in the general population (20-22). Childhood- and adulthood-onset GHD patients present with a reduced left ventricle mass and diameter proportionately to the duration of GHD or to IGF-I levels (22,41,42), while radionuclide angiography investigations documented impaired cardiac performance at rest and peak exercise and abnormal diastolic filling (22). In large cohorts, cardiac dysfunction occurs proportionately to the severity of GHD, with systolic and diastolic abnormalities affecting 45-78% of GHD patients (43). Although our study failed to discriminate the effect of GHD severity on cardiovascular features of PWS likely due to the patients sample size and the confounding effect of obesity on GH secretion (44), left ventricular mass and peak filling rate in PWS were positively predicted by IGF-I, a more reliable marker of GHD in obesity (45).

In conclusion, this is the first comparative study assessing cardiovascular features in obese individuals with and without PWS, sharing identical racial background and similar gender distribution. We are inclined to interpret current results as supporting the hypothesis that PWS does not entirely reflect the cardiovascular characteristics of

obesity, as obese PWS adults differed from obese controls by a healthier metabolic profile, greater non-abdominal fat accumulation, higher severity of sleep apnea, decreased cardiac mass and lower chronotropic response to an adrenergic stimulus. Cardiovascular characteristics seem to resemble those seen in GHD despite the absence of other features typical of GHD like abdominal adiposity and metabolic alterations (20). In this view, the potential effect of gonadal steroid replacement or inborn constitutional abnormalities remains to be elucidated. Demonstration that GH intervention helps to improve body composition, sleep quality and pulmonary function in PWS (19,46), may contribute to anticipate the potential effects of GH treatment on cardiovascular features. Their relevance, however, remains to be fully established in conditions of critical illnesses and warrants appropriate surveillance.

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Table 1: Anthropometric, biochemical, body composition and polysomnography studies in PWS and obese controls (for conversion factors, see *Patients and Methods*).

Parameters	PWS patients	Obese
Age (yrs)	26.9±1.2	26.2±0.8
M/F	6/7	6/7
Body weight (kg)	108.5±4	125.4±3.3 ^c
Height (cm)	153.2±2	169.2±2.4 ^c
Body mass index (kg/m ²)	46.3±1.6	43±1.2
Waist/hip	0.93±0.02	0.91±0.02
Peak GH (μg/l)	6.8±0.9	14.9±2.9 ^a
IGF-I (μg/l)	94.5±13.3	155.3±13 ^b
Leptin (μg/l)	44.6±3.6	56.1±7.3
Blood glucose (mg/dl)	84.2±5.7	85.7±3.1
Insulin (mUI/ml)	6.2±2.4	15.6±2 ^a
HOMA-IR	1.9±0.3	3.3±0.5 ^a
Triglycerides (mg/dl)	102±12.8	172.4±27.8 ^a
Total-cholesterol (mg/dl)	181.1±10.9	215.5±13.3 ^a
LDL-cholesterol (mg/dl)	118.8±8.4	148.2±10.6 ^a
HDL-cholesterol (mg/dl)	50.7±3.7	45.6±2.6
Total-/HDL-cholesterol	3.7±0.3	4.9±0.3 ^a
C-reactive protein (mg/dl)	1±0.2	1.6±0.6
Fat mass (%)†	56.1±1.3	46±1.6 ^b
SAT (cm ²)‡	707±32.8	675.5±33.6
VAT (cm ²)‡	147.3±15.3	150.1±24.8
VAT/SAT	0.21±0.02	0.24±0.06
Abdominal AP diameter (cm)‡	29.3±6	30.1±6
Apnea-hypopnea index	5.4±1.4	1±0.4 ^a
Apnea-hypopnea duration (sec)	14.3±1.7	8.9±1.5
Basal SaO ₂ (%)	93.2±0.6	99±0.4 ^c
Lowest SaO ₂ (%)	86.2±1	91.1±0.5 ^b
SaO ₂ <90% (min)	52.3±9	11.1±2.7 ^b
Desat SaO ₂ (%)	71.7±1.7	86.4±0.7 ^b
Desat SaO ₂ /h	16.3±3.2	1.7±0.5 ^b

Significance is indicated as *a* (p<0.05), *b* (p<0.01) or *c* (p<0.001).

Abbreviations: HOMA-IR, homeostatic model approach-insulin resistance; SAT and VAT, abdominal subcutaneous and visceral adipose tissue; AP, anteroposterior; basal SaO₂, basal oxygen saturation; lowest SaO₂, lowest oxygen saturation; SaO₂ <90%, time spent at SaO₂ <90%; desat SaO₂, average minimum SaO₂ during desaturations, desat SaO₂/h, number of desaturations/hour of sleep.

†, as determined by total-body DXA

‡, as determined by abdominal CT scans

Table 2: Results obtained at echocardiography and radionuclide angiography at baseline and under progressively escalating doses of dobutamine (DOB) in PWS and obese adult subjects.

Parameters	PWS patients	Obese controls
Echocardiography		
LVPWT (mm)	9±0.4	10.1±0.3 ^a
IVST (mm)	9.6±0.4	9.4±0.3
LVM (g)	135.7±7.7	163.5±8.4 ^a
LVMi (g/m ²)	67.1±3.2	70.6±3.1
LVM/h (g/h ^{2.7})	42.7±1.9	39.5±1.9
LVM/FM (g%)	2.4±0.2	3.7±0.3 ^b
LVEDD (mm)	43.6±1.3	47±1.2
LVEF (%)	63.1±1.4	60.6±1
E/A	1.6±0.1	1.5±0.1
PASP (mm Hg)	29.5±1.7	31.6±1.5
DT (ms)	181±7.6	175.4±4.5
Radionuclide angiography		
LVEF (%)	56.7±1.7	58.6±1.6
LVEF Dob (%)	71.9±1.9	76.3±1.2 ^a
ΔLVEF (%)	27.2±3.5	31.2±3.4
RVEF (%)	43.5±1.4	42.4±2.7
RVEF Dob (%)	61.1±1.6	57.2±3.3
ΔRVEF (%)	42.6±4.1	37.4±8
PFR (EDV/s)	2.6±0.2	2.9±0.2
PFR Dob (EDV/s)	4.2±0.3	4.5±0.3
ΔPFR (%)	70.2±22	56.2±8
HR (bpm)	63.2±3.5	68.3±3
HR Dob (bpm)	103±6.9	128±2.8 ^a
ΔHR (%)	57.3±9.1	92.9±10 ^a
DBP (mmHg)	75.5±2.3	78.5±2
DBP Dob (mmHg)	75.9±2.2	83.1±3.1
SBP (mmHg)	117±2.9	125.8±3.9
SBP Dob (mmHg)	131.4±7.2	145.4±9

Significance is indicated as *a* (p<0.05) or *b* (p<0.01).

Abbreviations: LV and RV, left and right ventricles; PWT, posterior wall thickness; IVT, interventricular septum thickness; LVM, left ventricle mass; LVMi, LVM indexed by body surface area; LVM/h, LVM indexed by height^{2.7}; LVM/FM, LVM indexed by percent fat mass; LVEDD, LV end-diastole diameter; LVEF, LV ejection fraction; E/A, early-to-late mitral peak flow velocity; PASP, pulmonary artery systolic pressure; DT, deceleration time; PFR, peak filling rate; HR, heart rate; DBP and SBP, diastolic and systolic blood pressures.

Table 3: Results obtained by bivariate correlation analysis between the main hormonal/anthropometric/polysomnography parameters and indices of left ventricle mass, diastolic and systolic functions and heart rate.

<i>Parameter</i>	PWS patients							
	<i>GH</i>	<i>IGF-I</i>	<i>SAT</i> ‡	<i>VAT</i> ‡	<i>V/S</i> ‡	<i>%FM</i>	<i>AHI</i>	<i>SaO₂</i>
LVM	-0.22	0.54 ^a	-0.06	-0.10	-0.01	-0.30	0.61 ^a	0.55 ^a
LVEDD	0.39	0.40	-0.12	-0.18	-0.16	-0.75 ^b	0.24	0.46
E/A	0.05	0.16	-0.43	-0.45	-0.31	-0.18	-0.42	-0.59 ^a
LVEF	0.21	0.50	-0.32	-0.09	0.12	-0.38	-0.17	-0.24
LVEF Dob	-0.14	-0.003	-0.23	0.33	0.56 ^a	-0.52	-0.14	0.07
PFR	-0.19	0.54 ^a	-0.39	-0.10	0.19	-0.32	0.24	0.12
PFR Dob	-0.23	-0.14	0.01	0.11	0.21	0.05	-0.43	-0.16
HR	-0.55 ^a	-0.46	-0.11	0.53	0.67 ^b	0.60 ^a	-0.15	-0.18
HR Dob	-0.51	-0.50	-0.23	0.58 ^a	0.71 ^b	-0.19	-0.24	0.11
Obese controls								
LVM	-0.01	-0.25	-0.38	0.29	0.29	-0.21	0.21	0.41
LVEDD	0.10	-0.18	-0.23	-0.24	-0.13	0.27	-0.35	0.11
E/A	0.29	0.27	-0.59 ^a	0.17	0.27	-0.13	0.28	0.36
LVEF	0.35	0.38	-0.50	-0.01	0.13	-0.18	0.30	-0.22
LVEF Dob	0.27	0.09	-0.12	0.39	0.33	-0.26	0.50	-0.07
PFR	0.08	-0.16	-0.21	-0.03	-0.01	-0.1	-0.03	-0.40
PFR Dob	0.43	-0.09	-0.45	-0.07	0.02	0.23	0.37	0.10
HR	-0.16	0.03	0.34	0.31	0.15	-0.08	-0.02	-0.59
HR Dob	0.35	-0.20	0.21	-0.35	-0.43	0.45	-0.71 ^b	-0.53

Data are indicated as Pearson's r. Significance is indicated as *a* (p<0.05) or *b* (p<0.01).

Abbreviations: SAT and VAT, abdominal subcutaneous and visceral adipose tissue; V/S, VAT/SAT ratio; %FM, percent fat mass; AHI, apnea-hypopnea index; SaO₂ <90%, time spent at SaO₂ <90%; LVM, left ventricle mass; EDD, end-diastole diameter; E/A, early-to-late mitral peak flow velocity; EF, ejection fraction; Dob, dobutamine; PFR, peak filling rate; HR, heart rate;

‡, as determined by abdominal CT scans

†, as determined by total-body DXA

Legend to figures

Fig. 1: Individual baseline and dobutamine-stimulated values of left ventricle (LV) ejection fraction (upper panel), peak filling rate (medium panel) and heart rate (lower panel) in PWS patients (left column) and obese controls (right column). For significance: ★, $p < 0.01$ vs. baseline values; ★★, $p < 0.01$ vs. baseline and $p < 0.05$ vs. PWS.

Fig. 2: Percent dobutamine-stimulated variation (% delta values, Mean $\pm$ SEM) over baseline values of LV ejection fraction (upper panel), peak filling rate (medium panel) and heart rate (lower panel) in PWS patients (left open column) and obese controls (right closed column). For significance: ★, $p < 0.01$ vs. PWS.

Fig. 1

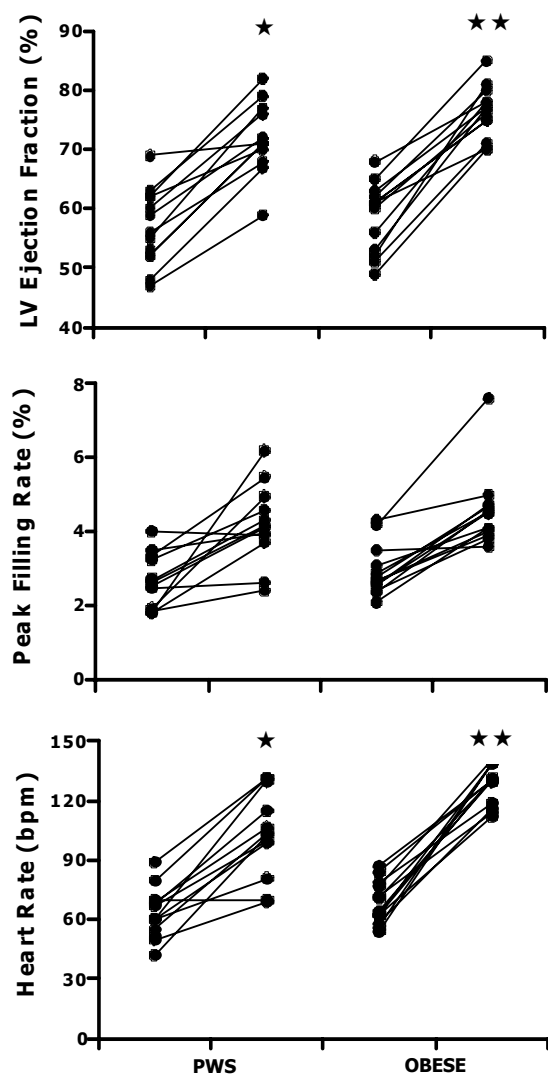


Fig. 2

