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Longitudinal study on the effect of surgical weight loss on beat-to-beat blood pressure variability in patients undergoing bariatric surgery: a study protocol

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ABSTRACT

Introduction Alterations in linear and non-linear parameters of beat-to-beat blood pressure variability (BPV) have been shown to predict disease prognosis and distinguish between risk categories in various pathological conditions, independently of average blood pressure levels. Obesity places subjects at elevated risk of vascular diseases, including hypertension, resulting in serious cardiac, respiratory and cerebral events. However, little is known about the status of vascular dynamics in obese and morbidly obese adults.

Methods and analysis In this present quasi-experimental longitudinal study, changes in beat-to-beat BPV, using continuous, non-invasive blood pressure monitoring, in obese subjects undergoing bariatric surgery are characterised. The capacity of linear and non-linear measures of BPV to detect differences between hypertensive, prehypertensive and normotensive obese subjects prebariatric and postbariatric surgery are tested. Additionally, potential correlations between beat-to-beat BPV and age, body mass index, gender and comorbidities will be investigated. In parallel, the impact of the unsteady fluctuations of beat-to-beat blood pressure on the dynamic stresses imparted by blood flow on blood vessel walls will be explored. We expect to find altered BPV profiles in hypertensive and prehypertensive subjects as compared with normotensive subjects. We also expect to see differential normalisation in BPV profiles between hypertensive, prehypertensive and normotensive subjects over time.

Ethics and dissemination The study has been approved by the Institutional Review Board at the American University of Beirut (IRB ID: BIO-2018-0040). Study results will be made available to the public through publications in peer-reviewed journals and conference papers and/or presentations.

Strengths and limitations of this study

- This is a longitudinal study which accounts for intersubject differences and characteristics impacting beat-to-beat blood pressure variability (BPV).
- We use beat-to-beat BPV which allows for assessment of short-term changes mainly driven by autonomic control and vascular function reflecting in intraindividual differences.
- We employ both linear and non-linear parameters of beat-to-beat BPV which permits the characterisation of different profiles of BP fluctuations with different sensitivities and physiological determinants and/or correlates.
- One of the challenges we face during data collection is the ability to maintain the subject in an awake, yet motionless, state for 30 min, to avoid interference of sleep or movement on beat-to-beat BPV.

INTRODUCTION

Obese individuals are at increased risk of cardiovascular morbidity and mortality.[1] Indeed, weight gain has been associated with atherosclerosis, hypertension (HTN)[2] and vascular complications, that insidiously lead to cerebrovascular and respiratory vascular complications, including stroke and obstructive sleep apnoea (OSA).[3–5] Weight loss strategies ideally aim at reducing disease states associated with excess body fat. One of these strategies, bariatric surgery, was shown to have long-term positive outcomes on disease prognosis and complications.[6–10]

While increased average blood pressure (BP) has been established to be associated with deleterious effects, BP variability (BPV) has recently gained insight as a potential underlying mechanism for end-organ damage. BP varies on the long, short and very short term. Changes in BP can be observed from week-to-week, day-to-day and even from beat-to-beat.[11] The degree of change in BP values can be quantified using linear (conventional) and/or non-linear variability indices. Linear parameters quantify the degree of dispersion

in BP fluctuations and include the SD and coefficient of variation (CV); these have been shown to increase abnormally in different disease states. Non-linear parameters describe the complexity and degree of correlation in a time series[12 13] and include complexity analysis and detrended fluctuation analysis (DFA). Higher complexity is physiologically desirable.[14–17] Interestingly, studies have revealed the capacity of beat-to-beat BPV to detect premature changes in vascular structure and function, independently of average BP.[18–22] Additionally, researchers have been interested in studying the relative powers of linear and non-linear parameters in identifying pathological mechanisms and discriminating among groups with progressive vascular diseases.[14 16 23]

Characterisation of beat-to-beat BPV with respect to the status of blood vessels and end-organ damage in obese individuals, with or without concomitant HTN, remain scarce. The available studies investigate the status of beat-to-beat BPV in obese children in an attempt to study the early changes in vascular dynamics associated with obesity.[24 25] Whereas the results of one of the studies reflect a relatively intact pattern of beat-to-beat BPV in obese children,[24] results from another demonstrate early detrimental autonomic processes.[25] Moreover, adult subjects with abdominal obesity-associated HTN demonstrated an increase in daytime and night BPV positively correlated with body mass index (BMI).[26] However, these results were only published as an abstract. Additionally, while the ameliorative effect of bariatric surgery has been previously demonstrated on heart rate (HR) variability in a patient population of obese diabetics,[27 28] the responsiveness of beat-to-beat BP dynamics to metabolic improvements associated with bariatric surgery remains ill defined.

Rationale

In this longitudinal study, the aim is to describe the profile of beat-to-beat time series in obese and morbidly obese patients undergoing elective bariatric surgery. Particularly, the relative capacity of linear and non-linear variability parameters to differentiate among hypertensive, prehypertensive and non-hypertensive obese patients preoperation will be tested. Additionally, the responsiveness of beat-to-beat BP dynamics to surgical weight loss-induced metabolic amelioration over time will be studied. The potential outcome of bariatric surgery on beat-to-beat BP dynamics will be investigated. In parallel, the impact of unsteady BP dynamics on the normal and shear stresses imparted by blood flow on the vascular wall will be characterised to identify possible underlying end-organ damage related to increased vascular injury.

Objectives

1. To determine the longitudinal effect of weight loss through bariatric surgery on BP complexity and fluctuation measures among no-HTN, pre-HTN and HTN subjects over time over time (from preoperation to 3, 6 and 12 months postoperation).
2. To compare BPV metrics among no-HTN, pre-HTN and HTN subjects.
3. To assess the use of the new BPV metrics (complexity and DFA) alone or in combination with conventional BPV measures for discriminating between no-HTN and HTN patients.
4. To quantify the impact of the unsteady dynamics of the observed beat-to-beat pressure on the dynamic stresses imparted by the blood flow on the walls of the blood vessels

METHODS AND ANALYSIS

Study design

This is a single-centred, longitudinal, quasi-experimental study taking place at the American University of Beirut Medical Center (AUBMC), Lebanon in the Metabolic and Bariatric Unit.

Participants

The target population is obese and morbidly obese (BMI ≥30) subjects who are scheduled for bariatric surgery (Laparoscopic Sleeve Gastrectomy or Roux-en-Y Gastric Bypass) at the AUBMC.

Recruitment methods and study procedures

Candidates for bariatric surgery are first approached and introduced to the study by their treating physician and then by the research assistant on their preoperation visit. Consent is then obtained. During this visit, beat-to-beat BP is monitored. Later, BP monitoring sessions take place at 3, 6 and 12 months postbariatric surgery, during postoperation follow-up clinic appointments (figure 1).

Preoperation and postoperation beat-to-beat BPV monitoring

After their preoperation appointment, patients are seated in a comfortable chair next to a desk. Based on the patient's choice among a number of relaxing videos, a 30 min video is played on a desktop screen facing the patient. Continuous BP monitoring is carried out by plethysmography using a FINAPRES NOVA finometer (Finapres Medical Systems, Amsterdam, the Netherlands). The finger cuff is fitted based on a finger circumference ruler provided by the manufacturer. Notably, the finger cuff comes in three sizes: small, medium and large. For 30 min, the subject is asked to remain quiet and abstain from moving. 5 min after the start of beat-to-beat BP monitoring, after a stable signal is obtained, brachial calibration is done using an arm cuff (sphygmomanometer) as per the manufacturer's recommendation. Finger BP signal is calibrated according to the average of two acquired brachial BP values to obtain reconstructed BP values. After this time, BP monitoring is paused for 1 min at 10 and 20 min to allow the finger to rest from continuous pressure. This process is repeated at three time points, which are 3, 6 and 12 months after the bariatric surgery.

Inclusion and exclusion criteria

All patients 18 years old and above who are scheduled for bariatric surgery at AUBMC will be approached for

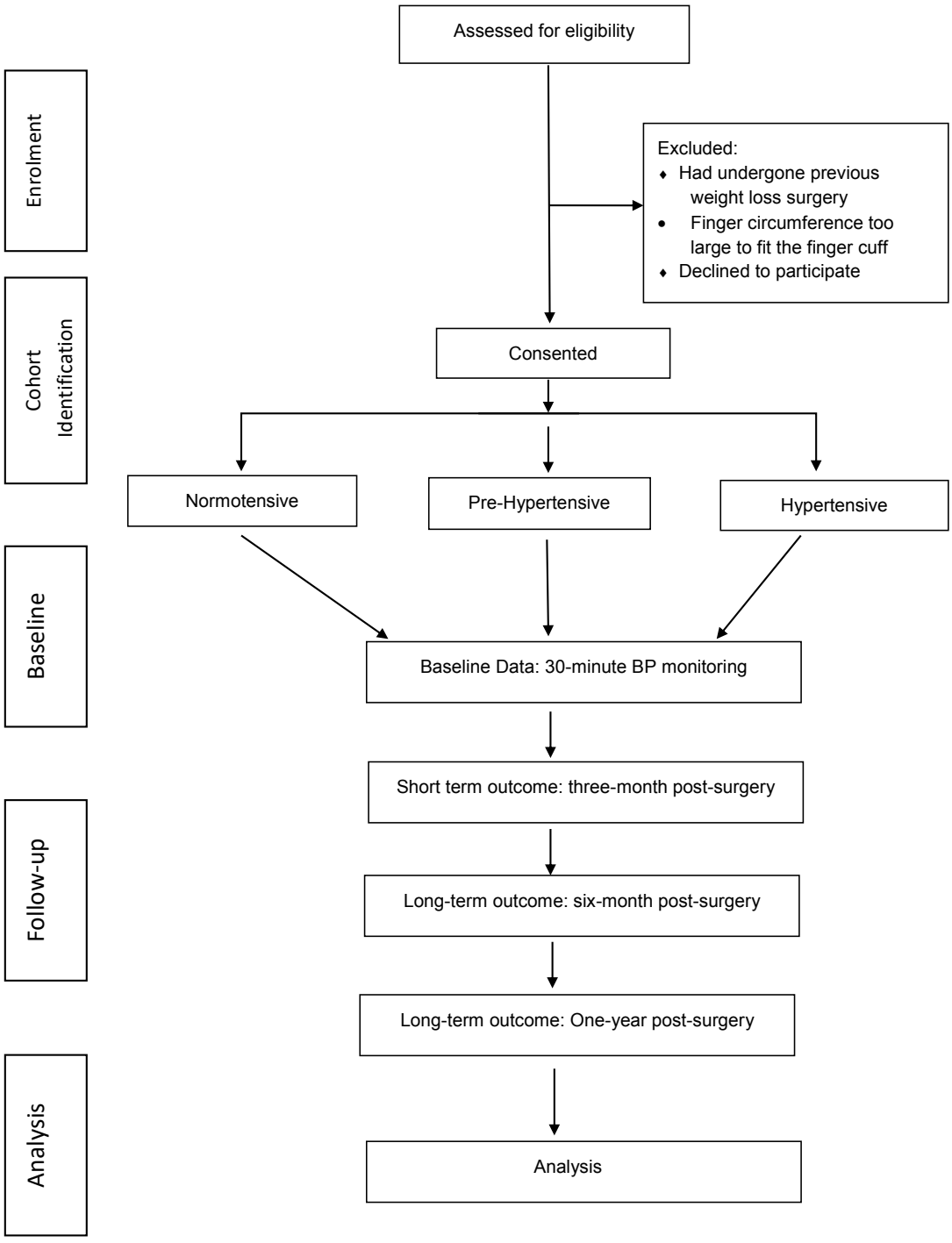

Figure 1 Flow of participants diagram which illustrates participants enrolment throughout the study.

this study. HTN, pre-HTN and normotensive subjects will be approached; HTN status is previously confirmed by the referring physician and will be retrieved from the patients' medical records. To avoid confounding factors and false negatives, patients who had undergone previous weight loss surgeries are excluded. Additionally, those whose arm or finger circumference is/are too large to fit the arm or finger cuffs available at the company are also excluded from the study.

Measures

Outcomes

The study outcomes are the variability parameters derived from the beat-to-beat BP time series described in the Plan of analysis section.

Other variables

From the beat-to-beat time series, the following measures will be derived: Systolic BP, diastolic BP, mean arterial

pressure and HR. We will also collect other variables including: Sociodemographics: age (in years), weight (in kg), gender, education (none, high school or less, college), marital status (single, married, divorced, widowed); life-style habits: Cigarette smoking (yes, no), narguile smoking (yes, no), alcohol consumption (yes, no), exercise (yes, no); Patient history of: heart disease, dyslipidaemia, diabetes, kidney, thyroid, OSA (yes, no); Family history of: heart disease, HTN, diabetes (yes, no) and classes of antihypertensive medication, if any.

Sample size calculation

We based our power analysis on the aim of determining the effect of weight loss through bariatric surgery on BP complexity and fluctuation measures among no-HTN, pre-HTN and HTN subjects. Since we found no previous studies similar to ours, we computed effect sizes based on available studies comparing entropy measures and DFA exponent between independent/dependent groups. Those effect sizes were moderate to high (f=0.20–0.75 in independent samples[14 29 30]). To remain on the conservative side, we assumed a moderate effect size (f=0.25) in our sample size calculation. Power analysis for a between-group repeated measures design indicate that with three time point comparison to baseline (3 months, 6 months and 12 months), a sample size of 102 patients would have 80% power to detect a medium effect size of 25% at α=0.05, assuming a medium correlation between the repeated measures ρ=0.5. Since this a longitudinal study, we assumed a 20% attrition rate, therefore, we aim to recruit a total of 129 subjects (43 in every group). The average yearly number of bariatric surgeries at AUBMC is around 231. GPower V.3.0.10 was used for sample size determination.

Plan of analysis

Conventional/linear variability analysis

SD and CV will be calculated.

Complexity analysis

Complexity analysis consists of measures that quantify the irregularity of biological signals, called entropy measures. Sample entropy (SampEn) is a measure of the self-similarity in a time series. It depends on two parameters: a dimension m which is the number of consecutive data points in a pattern and a tolerance r within which the m points are considered a self-match. SampEn is the negative natural logarithm of the conditional probability that sequences within r for the m consecutive data points remain within r for the next point. SampEn is related to approximate entropy (ApEn), but unlike it, SampEn eliminates self-counting of matches and as a result minimises the dependency of this complexity index on the length of the time series. Using SampEn will thus remove this bias introduced by ApEn. A Matlab code to compute SampEn, available on Physionet (http://www.physionet.org/physiotools/sampen/c/) was used in our previous study.[31]

Detrended fluctuation analysis

DFA has been developed to detect the correlations of varying ranges (short and long range) embedded in a time series using the fractal property. As used previously, DFA can be analysed in two ways: a single slope α for the whole time series, and double slopes, one for short-term correlations (α_S) and one for long-term correlation (α_L) based on an a priori cut-off (n=10). DFA scaling exponents α, α_S and α_L are measures of the smoothness of a time series, higher correlations indicate increased predictability or smoother series. A Matlab (MathWorks, Natick, Massachusetts, USA) code to derive α, α_S and α_L was implemented by the research team and used in our previous study.[31]

Quantification of haemodynamic forces (aim 4)

The dynamic forces imparted by the blood flow on the blood vessels caused by the mechanical loading- the observed beat-to-beat BP- will be quantified using a physically based computational model. This will be accomplished as follows. A model construction tool (Simpleware) will be used to construct a 3D model form medical images (CT Scans, MRI, etc). A computational mesh is then generated from the geometrical model. The blood flow will then be dynamically simulated in space (3D) and time using a physically based computational tools (OpenFOAM or ANSYS) that numerically solve the system of coupled partial differential equations governing the fluid/solid continuum behaviour. The observed (or properly scaled) beat-to-beat pressure history will act as the forcing to the problem. In addition to the mesh and the forcing, well-established stress/strain and stress/rate of strain models for the tissue and blood will be employed.

Statistical analysis

We will perform descriptive statistics to determine and compare the subject group characteristics including demographics and medical history. For aim 1, we will use linear mixed models to assess the changes in the variability metrics (as determined by SD, CV, SampEn, α, α_S and α_L) over time among study subjects. For aim 2, we will use one-way analysis of variance to compare the BPV metrics between no-HTN, pre-HTN and HTN subjects. For aim 3, we will build a discriminant linear function of the variability indices in order to classify the subjects. Baseline data will be used for aims 2 and 3. Algorithms for computing entropies and the alpha exponents are implemented in MATLAB. All tests will be two-tailed and a $p<0.05$ will be considered significant. The statistical analyses will be conducted using STATA V.13 and SPSS V.24 for Windows.

Patient and public involvement

Patients and the public were not involved in the design of the study. Patients are recruited on a visit-to-visit basis. No research-specific visits are required. Study results will be made available to the public through publications in

peer-reviewed journals and conference papers and/or presentations.

Ethics and dissemination

Approached subjects have an identification number (ID). Those who meet the inclusion criteria and are willing to participate have a documented name linked to their ID number and their name will appear on all consent forms. Documents with participants' names are kept in a locked drawer in the principal investigator's office. Only the principal investigator has access to that drawer. The study protocol is approved by the Institutional Review Board (IRB) at the American University of Beirut (IRB ID: BIO-2018-0040). Additionally, the research team members are certified by the Collaborative Institutional Training Initiative (CITI).

Results of the study are going to be submitted for publication in peer-reviewed, refereed scientific journals and presented in national and international conferences. Additionally, the results will be shared at the Vascular Medicine Programme at AUBMC to promote the importance and significance of beat-to-beat BPV profile characterisation among patients.

Study status at the time of manuscript submission

The subjects' recruitment started in October 2019 and was delayed due to several reasons including COVID-19 lockdown and civil unrest in the country. After initiation of the study and before the lockdown, we recruited 11 patients preoperative and 2 patients at 3 and 6 months postoperative follow-up visits. The average age of the first seven recruited subjects is 42.43 years, and the average BMI is 41.07. Three subjects were females, 5 on HTN medication and all subjects had comorbidities; BPV parameters of these subjects are presented in table 1.

DISCUSSION

Previous studies investigated the effect of autonomic control on beat-to-beat BPV[21 32 33] and showed that an increased sympathetic activity could result in changes in BPV related to increased vascular resistance.[32] This is particularly important in obese individuals who are known to have altered sympathovagal balance.[34] In fact, the latter has been shown to be a determinant of short-term variability.[35] While the status of HR variability in obese individuals has been previously described, few studies characterise changes in beat-to-beat BPV, particularly in terms of complexity and self-correlation of BP signal in obese and morbidly obese subjects. Additionally, to the best of our knowledge, the responsiveness of altered BP dynamics, that is, variability, to surgical weight loss has not been previously assessed.

In our study, we expect to observe altered BPV profiles, reflected by increased linear fluctuations and self-correlation as well as decreased complexity of beat-to-beat BP time series, in HTN and pre-HTN individuals as compared with their normotensive counterparts. We also expect that BPV profiles will improve with weight loss after bariatric surgery, although differentially across the different HTN categories. Our study is also speculated to establish a relationship between beat-to-beat BPV, body weight and average BP.

We acknowledge the fact that in the obese hypertensive group, antihypertensive treatment regimens might differentially influence beat-to-beat dynamics.[36 37] Some drug classes were associated with positive outcomes with respect to control BPV; while others had negative outcomes on variability.[38] However, such results were derived from intermittent BP monitoring and thus, unlike our present study, variability measures were calculated based on

Table 1 Preoperation linear and non-linear BPV parameters of study subjects

Subject	Series	Average (Brachial)	No of beats	Linear		Non-linear		
				SD	CV	SampEn	ApEn	DFA α
1	SBP	155	1620	11.56	7.74	0.95	0.98	0.93
	DBP	98		7.61	9.69	1.02	1.09	0.98
2	SBP	130	1792	5.81	4.38	1.45	1.38	0.75
	DBP	91		6.43	7.4	0.83	0.93	0.88
3	SBP	160	2722	15.24	9.56	1.33	1.35	1.00
	DBP	83		8.74	9.95	1.38	1.36	1.07
4	SBP	133	2301	21.19	14.11	0.37	0.43	1.12
	DBP	75		12.89	13.61	0.53	0.60	1.12
5	SBP	139	1994	17.48	13.09	0.60	0.71	1.03
	DBP	94		12.47	13.96	0.71	0.83	0.97
6	SBP	168	1714	16.62	10.95	1.08	1.03	1.07
	DBP	78		5.30	7.48	0.76	0.79	0.98
7	SBP	156	2155	8.48	6.12	1.35	1.25	0.94
	DBP	98		5.29	6.13	0.82	0.90	0.85

ApEn, approximate entropy; BPV, blood pressure variability; CV, coefficient of variation; DBP, diastolic blood pressure; DFA, detrended fluctuation analysis; SampEn, sample entropy; SBP, systolic blood pressure.

non-continuous BP. We, therefore, aim at soliciting drug therapy-related information from patient charts.

Two additional factors are worth inspecting and are indeed taken into account. Those are gender differences and family history of cardiovascular disease. Indeed, offspring of hypertensive parents were found to present with an altered profile of beat-to-beat BPV in response to an autonomic challenge, like a cold pressor test, when compared with offspring of normotensive parents.[22] Finally, gender-specific differences in adaptation to metabolic and cardiovascular insults and responsiveness to abrupt ameliorative interventions are worth discovering especially in light of previous studies.[39 40]

Our study will be the first to look at fairly novel measures of BPV among obese and morbidly obese subjects undergoing bariatric surgery and their relationship with body weight and average BP. Application of continuous, non-invasive BP monitoring for characterisation of BP complexity and self-correlation may be helpful in providing insight into the early deteriorating mechanisms of cardiovascular control.

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Contributors Conceptualisation, SF and KB; methodology, SF, N-MZB and RA; software, SF; validation, SF and N-MZB; formal analysis, SF, N-MZB, RA, IL and KB; investigation, SF, N-MZB, RA, IL and KB; data curation, SF and N-MZB; writing—original draft preparation, SF and N-MZB; writing—review and editing, SF, N-MZB, IL and KB; visualisation: SF; supervision: SF; project administration: SF; funding acquisition: SF. All authors have read and agreed to the published version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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