STUDY PROTOCOL

Official Title: RIGID-TyG: Arterial stiffness and its association with triglyceride–glucose-based metabolic indices and morning blood pressure patterns

Institution: Faculdade de Medicina de São José do Rio Preto (FAMERP), Brazil

Ethics Approval (CAEE): 57703722.7.0000.5415

Setting: Specialized Cardiovascular Diagnostic Center / Hypertension Clinic of the São José do Rio Preto School of Medicine

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TEXT

RIGID-TyG: assessment of arterial stiffness and its association with metabolic indices based on triglycerides and glucose

1. ABSTRACT

Systemic arterial hypertension remains one of the main causes of cardiovascular morbidity and mortality worldwide, and its evaluation should not be restricted to mean blood pressure (BP) levels. Vascular and metabolic markers have expanded the understanding of cardiovascular risk, particularly carotid–femoral pulse wave velocity (cfPWV), considered the gold standard for the assessment of arterial stiffness, and the triglyceride–glucose (TyG) index, recognized as an indirect marker of insulin resistance.

Evidence suggests that insulin resistance, central adiposity, and vascular dysfunction share common pathophysiological mechanisms, including endothelial dysfunction, low-grade inflammation, sympathetic activation, and arterial remodeling. These mechanisms may contribute both to increased arterial stiffness and to alterations in circadian blood pressure regulation, particularly in the morning period, when a physiological rise in blood pressure levels occurs. When exaggerated, this phenomenon, known as morning blood pressure surge (MBPS), is associated with increased cardiovascular risk.

The present study aims to evaluate the association between carotid–femoral pulse wave velocity (cfPWV) and metabolic indices, including the TyG index and its derived metrics (TyG-WC, TyG-BMI, and TyG-WHtR), as well as composite indices such as the body roundness index (BRI), the metabolic score for insulin resistance (METS-IR), and the cardiometabolic index (CMI). Additionally, morning blood pressure and MBPS will be investigated across different metabolic profiles.

This is an observational, cross-sectional study with prospective collection of clinical, anthropometric, laboratory, and hemodynamic data in individuals referred for ambulatory blood pressure monitoring (ABPM). The results are expected to contribute to the integration of accessible metabolic markers with arterial stiffness parameters and morning hemodynamic load, improving cardiovascular risk stratification in individuals with suspected hypertension or untreated hypertension.

2. OBJECTIVES

2.1 Primary objective

To evaluate the association between arterial stiffness measured by carotid–femoral pulse wave velocity (cfPWV) and the triglyceride–glucose index.

2.2 Secondary objectives

To evaluate the association between derived metrics of the triglyceride–glucose index, including TyG-WC, TyG-BMI, and TyG-WHtR, and cfPWV values.

To evaluate the association between composite metabolic indices, including METS-IR and CMI, and cfPWV.

To evaluate the relationship between metabolic indices (TyG, TyG-WC, TyG-BMI, TyG-WHtR, METS-IR, and CMI) and morning blood pressure and MBPS.

To compare the performance of different metabolic and anthropometric indices in identifying individuals with increased arterial stiffness and higher morning hemodynamic load.

3. THEORETICAL BACKGROUND

Systemic arterial hypertension remains one of the main determinants of cardiovascular morbidity and mortality at a global level, showing a continuous and progressive relationship with adverse events, including myocardial infarction, stroke, and heart failure [1]. Evidence from large population-based studies demonstrates that even modest increases in blood pressure (BP) are associated with a significant increase in cardiovascular risk, reinforcing the need for more comprehensive risk stratification strategies beyond conventional office BP measurements [2–3].

In this context, the incorporation of vascular markers has enabled a better understanding of cardiovascular pathophysiology. Arterial stiffness (AS), particularly assessed by carotid–femoral pulse wave velocity (cfPWV), is considered the gold standard for the non-invasive evaluation of aortic stiffness and shows a strong independent association with cardiovascular events and mortality [4]. Increased cfPWV reflects structural and functional alterations of the arterial wall, including elastin fragmentation, increased collagen content, vascular calcification, and endothelial dysfunction, representing an integrated marker of cumulative vascular damage [5–6].

In parallel, insulin resistance plays a central role in the pathophysiology of cardiometabolic diseases. This metabolic state is associated with reduced nitric oxide bioavailability, increased sympathetic nervous system activity, chronic low-grade inflammation, and vascular remodeling, mechanisms directly involved in the development of arterial stiffness [7–8]. The triglyceride–glucose (TyG) index, derived from widely available laboratory parameters, has been validated as a reliable surrogate marker of insulin resistance, showing consistent associations with type 2 diabetes mellitus, subclinical atherosclerosis, and cardiovascular events [9–10].

In addition to the TyG index alone, derived metrics that incorporate anthropometric parameters, such as the triglyceride–glucose index combined with waist circumference (TyG-WC), the triglyceride–glucose index combined with body mass index (TyG-BMI), and the triglyceride–glucose index combined with the waist-to-height ratio (TyG-WHtR), have been proposed with the aim of more comprehensively capturing the interaction between metabolism and adiposity, particularly central adiposity, which is recognized as an important determinant of cardiovascular risk [11–13]. However, other composite indices have been developed to integrate multiple pathophysiological domains.

In this context, the body roundness index (BRI), derived from waist circumference and height, provides a geometric estimate of body fat distribution and has been associated with visceral adiposity and cardiometabolic alterations [14]. Complementarily, the metabolic score for insulin resistance (METS-IR), which integrates fasting glucose, triglycerides, body mass index, and HDL-cholesterol, allows for a more comprehensive assessment of insulin resistance [15], while the cardiometabolic index (CMI), based on the waist-to-height ratio and lipid profile, reflects the interaction between central adiposity and dyslipidemia [16].

These indices may provide incremental value over isolated markers by integrating multiple pathophysiological pathways involved in vascular dysfunction. Central adiposity, insulin resistance, and lipid abnormalities are associated with endothelial dysfunction, increased sympathetic activity, chronic low-grade inflammation, and vascular remodeling, mechanisms directly related to increased arterial stiffness [5]. In this context, higher values of BRI, METS-IR, and CMI may be associated with increased cfPWV, reflecting greater impairment of arterial compliance.

Another relevant dimension of cardiovascular pathophysiology is the circadian variability of blood pressure. The awakening period is characterized by a physiological increase in BP, mediated by sympathetic activation, increased catecholamine release, and hormonal changes, including cortisol. When exaggerated, this phenomenon, known as morning blood pressure surge (MBPS), has been associated with a higher incidence of cardiovascular events, particularly stroke and coronary events [17–21].

From a hemodynamic perspective, arterial stiffness (AS) may amplify this morning BP increase, since less compliant arteries have a reduced capacity to buffer the pulse wave, resulting in greater transmission of pulsatile pressure to the peripheral and microvascular circulation. In addition, metabolic dysfunction may interfere with autonomic regulation and baroreflex sensitivity, contributing to alterations in the circadian control of BP [22–23].

Despite the biological plausibility and clinical relevance of these interactions, the integrated relationship between metabolic indices derived from insulin resistance, anthropometric markers of central adiposity, arterial stiffness, and morning BP parameters remains insufficiently explored. Understanding these mechanisms may provide new insights

into the pathophysiology of hypertension in its early stages and contribute to the identification of phenotypes at higher cardiovascular risk, even in apparently normotensive individuals.

Therefore, the present study aims to evaluate the association between arterial stiffness, measured by cfPWV, and metabolic and anthropometric indices, including TyG and its derived metrics, BRI, METS-IR, and CMI, as well as to investigate their relationship with morning BP and MBPS, integrating metabolic, structural, and functional dimensions of cardiovascular pathophysiology.

4. JUSTIFICATION

The assessment of cardiovascular risk needs to go beyond traditional blood pressure (BP) measurements, incorporating markers that reflect early structural and metabolic changes. Arterial damage, assessed by cfPWV, is a well-established marker of subclinical vascular damage, while the TyG index and its derived analyzes represent simple and accessible alternatives for estimating insulin resistance and metabolic dysfunction. Despite the wide availability of metabolic indices, their relationship with direct markers of arterial stress is still not fully established, especially when multiple derived and composite indices are included within the same analytical model. In addition, the interaction between these markers and the hemodynamic load during the morning period, a critical phase of the circadian cycle associated with a higher incidence of cardiovascular events, remains poorly explored.

Prospective data collection allows greater control over measurement quality, standardization of protocols, and reduction of biases inherent to secondary analyses. This design makes it possible to integrate, in a simultaneous and systematic manner, clinical, laboratory, and hemodynamic variables, bringing the results closer to real-world clinical practice conditions. Therefore, the present study is justified by the need to investigate, in an integrated manner, the relationship between metabolic dysfunction, arterial impairment, and morning blood pressure behavior, contributing to the development of more precise cardiovascular risk stratification strategies.

5. METHODS

5.1 Study design and data sources

This is an observational, cross-sectional study with a prospective component. The study will use data derived from two complementary sources: (1) data previously collected in a research project approved by the Research Ethics Committee of the Faculdade de Medicina de São José do Rio Preto – FAMERP – SP in 2022 (CAEE 57703722.7.0000.5415) and (2) data obtained prospectively according to the standardized protocol established in the present study. The previously collected data refers to participants evaluated within the context of the prior protocol approved by the Research Ethics Committee and will be used secondarily, with assurance of confidentiality and anonymization of the information.

Additionally, new participants will be prospectively included, with collection of clinical, anthropometric, laboratory, and hemodynamic data performed according to the protocol described in this study, after signing the informed consent form. The study population will consist of adults referred for ambulatory blood pressure monitoring (ABPM) in a specialized center for the diagnosis and follow-up of cardiovascular diseases.

Data collection will be performed within the clinical care setting, concurrently with routine clinical evaluation, including office blood pressure measurements, anthropometric measurements, 24-hour ABPM, cfPWV measurement, and the acquisition of laboratory parameters required for the calculation of metabolic indices. To ensure comparability between previously collected data and prospectively obtained data, equivalent methodological criteria will be adopted, including standardized protocols for blood pressure measurement, assessment of arterial stiffness by cfPWV, and uniform definition of clinical and laboratory variables.

5.2 Study setting and clinical context

Participants will be evaluated in a specialized center for the diagnosis and follow-up of cardiovascular diseases, within the context of clinical diseases referral for ambulatory blood pressure monitoring. This setting includes individuals referred by the attending physician for diagnosis clarification of arterial hypertension, investigation of elevated office BP, or better characterization of the 24-hour blood pressure profile.

5.3 Study population

Adults aged 18 to 65 years, of both sexes, will be included, who undergo ABPM as part of routine clinical evaluation and who are not using antihypertensive medication at the time of inclusion. The focus on untreated individuals aims to reduce the potential confounding effect of antihypertensive treatment on arterial stiffness, morning blood pressure, and indices derived from ABPM.

5.4 Inclusion and exclusion criteria

Individuals who meet all of the following criteria will be included in the study:

- Age between 18 and 65 years;
- Both sexes;
- Referral for ambulatory blood pressure monitoring (ABPM) as part of clinical evaluation;
- Not using antihypertensive medication at the time of inclusion;
- Availability of complete office blood pressure data and valid ABPM recordings;
- Undergoing arterial stiffness assessment by carotid–femoral pulse wave velocity (cfPWV);
- Availability of laboratory tests including fasting glucose and triglycerides for calculation of the triglyceride–glucose (TyG) index;
- Agreement to participate in the study by signing the informed consent form (for prospective participants).

Individuals presenting any of the following conditions will be excluded from the study: Current use of antihypertensive medication;

• Cardiac arrhythmias that compromise the accuracy of blood pressure measurements or cfPWV;

- ABPM recordings with inadequate quality or an insufficient number of valid measurements;
- Clinical conditions that prevent or compromise adequate cfPWV measurement;
- Severe vascular diseases or anatomical alterations that preclude pulse wave analysis;
- Absence of essential data for calculation of metabolic indices or evaluation of the primary outcomes;
- Refusal to participate in the study or absence of a signed informed consent form (for prospective data collection).

5.5 Clinical data collection

Demographic and clinical data routinely recorded during the initial evaluation will be used, including age, sex, relevant clinical history, and cardiovascular history. These variables will be used both for sample characterization and as potential covariates in the analytical models.

5.6 Anthropometric assessment and calculation of derived indices

Anthropometric measurements will include weight, height, and waist circumference, obtained according to a standardized protocol. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m^2).

Waist circumference will be used as a marker of central adiposity and will be measured at the midpoint between the last rib and the iliac crest. Additionally, the body roundness index (BRI) will be calculated as a derived marker of body adiposity and central fat distribution, using the following formula: $BRI = 364.2 - 365.5 \times \sqrt{[1 - ((WC / 2\pi)^2 / (0.5 \times height)^2)]}$, where WC represents waist circumference in meters and height in meters [14].

BRI will be included in the analyzes as a continuous variable and may also be categorized into quartiles for the evaluation of its association with arterial stiffness parameters and morning blood pressure variables.

5.7 Office blood pressure measurement

Office blood pressure will be measured by a trained professional using a validated automatic device (Microlife BP3AC1-1PC, Shenzhen, China), in an appropriate environment and after a period of rest. Three consecutive measurements will be obtained, performed on the same arm and under standardized conditions, and the mean of these measurements will be used for baseline blood pressure description and for the initial clinical characterization of the participants, in accordance with international recommendations for blood pressure measurement in humans [24].

5.8 Ambulatory blood pressure monitoring

All participants will undergo 24-hour ambulatory blood pressure monitoring (ABPM) using a validated device (Dyna-MAPA monitor, Cardios, São Paulo, Brazil), with an appropriately sized cuff and preferably on the non-dominant arm. The device will be programmed to perform measurements every 20 minutes during the daytime period and every 30 minutes during the nighttime period. Daytime and nighttime periods will be defined based on the schedules reported by the participants in a sleep and activity diary. Only recordings with adequate quality will be considered valid, according to accepted criteria in guidelines and position statements on ABPM [25,26].

Blood pressure classification by ABPM will be based on the 24-hour mean, with ambulatory hypertension defined as a mean 24-hour BP ≥130/80 mmHg. Based on this classification, participants will be stratified into normotensive and untreated hypertensive groups for comparative and interaction analyses.

5.9 Definition of morning blood pressure parameters

Morning systolic blood pressure (mSBP) and morning diastolic blood pressure (mDBP) will be calculated as the mean of the measurements obtained during the first two hours after awakening. Only recordings with at least two hours of valid measurements after awakening will be considered eligible for the calculation of morning parameters.

Sleep-through morning blood pressure surge (ST-MBPS) will be defined as the difference between mSBP and the lowest systolic blood pressure during the sleep period, considering this value and its adjacent readings, according to standardized definitions in the literature [17–19].

The prewaking morning blood pressure surge (PW-MBPS) will be defined as the difference between mSBP and the mean systolic blood pressure during the two hours preceding awakening. These two indices will be analyzed as complementary measures of morning blood pressure behavior.

5.10 Arterial stiffness assessment

AS will be assessed by carotid–femoral pulse wave velocity (cfPWV) using the Complior Analyze device (ALAM Medical, Paris, France), with the participant in the supine position after at least 10 minutes of rest. Measurements will be performed in accordance with current recommendations for arterial stiffness research and clinical practice [27].

At least three consecutive measurements will be obtained per participant. For analysis, the mean of the closest measurements will be used, provided that the difference between them is equal to or less than 0.5 m/s, ensuring greater reproducibility and quality control of the assessment.

5.11 Laboratory assessment and acquisition of biochemical data

All patients included in the study must present laboratory tests previously performed as part of the clinical evaluation requested by the attending physician responsible for referral for ABPM. Biochemical tests will be performed after a fasting period of at least 8 hours, according to routine clinical practice, and will mandatorily include measurements of fasting glucose and plasma triglycerides.

Laboratory results will be obtained through reports presented by the participants at the time of evaluation. There is no direct intervention by the researchers in the request, selection of the laboratory, or performance of the tests, characterizing these data as originating from routine clinical practice, which may include both previously collected data and prospectively obtained data. This aspect reinforces the observational nature of the study and brings the findings closer to real-world conditions. Laboratory tests will be performed in certified clinical laboratories, following standardized diagnostic methods.

Laboratory and anthropometric parameters will be used for the calculation of metabolic indices associated with insulin resistance and cardiometabolic risk. The triglyceride–glucose (TyG) index will be calculated according to the following formula: TyG = Ln [TG (mg/dL) × fasting glucose (mg/dL) / 2]. From TyG, the following indices will be derived: TyG-WC = TyG × waist circumference (cm); TyG-BMI = TyG × body mass index (kg/m²); TyG-WHtR = TyG × [waist circumference (cm) / height (cm)] [9–13].

Additionally, composite metabolic indices independent of TyG will be calculated: METS-IR (metabolic score for insulin resistance): METS-IR = Ln [(2 × fasting glucose (mg/dL)) + TG (mg/dL)] × BMI (kg/m²) / Ln [HDL-C (mg/dL)] [15]; CMI (cardiometabolic index): CMI = [waist circumference (cm) / height (cm)] × [TG (mmol/L) / HDL-C (mmol/L)] [16].

All indices will be analyzed as continuous variables and will also be categorized into quartiles for the evaluation of their association with arterial stiffness parameters and morning blood pressure variables.

5.12 Study variables

The main exposure variable will be represented by the TyG index and its derived metrics. The main vascular variable will be cfPWV. Secondary hemodynamic outcomes will include mSBP, mDBP, ST-MBPS, and PW-MBPS. Potentially confounding clinical variables, such as age, sex, BMI, waist circumference, mean 24-hour BP, and hypertension status, will be considered in the analytical models according to their pathophysiological relevance.

5.13 Sample size calculation

The sample size calculation based on the primary objective, referring to the association between carotid–femoral pulse wave velocity and the triglyceride–glucose index, indicates a minimum requirement lower than the final planned sample. However, considering the secondary objectives of the study, which include the evaluation of morning blood pressure and morning blood pressure surge across quartiles of metabolic indices, with additional stratification between normotensive and untreated hypertensive individuals, a more robust sample size was chosen.

5.14 Statistical analysis

Continuous variables will be described as mean and standard deviation or median and interquartile range, according to data distribution, while categorical variables will be presented as absolute frequencies and proportions. Normality will be assessed using appropriate methods prior to the selection of comparative tests.

For the analysis of secondary objectives, participants will be distributed into TyG quartiles. Comparisons between quartiles will be performed using analysis of variance (ANOVA) or the corresponding test, with calculation of p for trend when appropriate. Analyzes may be repeated after stratification by hypertension status, in order to evaluate differential behavior of morning parameters between normotensive and untreated hypertensive individuals.

The association between cfPWV and TyG, as well as between TyG and morning BP parameters, will be evaluated using univariable and multivariable linear regression models. Covariates will be selected a priori based on biological plausibility and prior evidence, including age, sex, BMI, mean 24-hour systolic and diastolic BP, hypertension status, and other clinically relevant variables. Interaction terms will also be explored, particularly between TyG metrics and hypertension status.

Considering the analytical tradition of the group in arterial stiffness studies, additional methods of agreement and bias assessment may be employed to explore relationships between continuous variables when appropriate, including Lin's concordance correlation coefficient and Bland–Altman analysis. The level of statistical significance will be set at 5% in two-tailed tests.

5.15 Ethical aspects

The present study will be conducted in accordance with the ethical principles established by the Brazilian National Health Council, in compliance with Resolution CNS No. 466/2012.

The use of previously collected data will be carried out under the original ethical approval (CAEE: 57703722.7.0000.5415), and specific authorization for its use in the present protocol will be requested from the Research Ethics Committee.

This is an observational study with a prospective component, involving the collection of clinical, anthropometric, laboratory, and hemodynamic data within the context of routine clinical practice. Previously collected data will be used secondarily, with assurance of confidentiality and anonymization of the information. Participants included prospectively will be invited to voluntarily participate in the study and must agree to the informed consent form (ICF) prior to inclusion. Participation in the study will not imply any modification of usual clinical management.

The procedures performed, including ambulatory blood pressure monitoring, assessment of arterial stiffness by cfPWV, and laboratory tests, are part of routine clinical care and will be used for research purposes in a non-interventional manner.

Collected data will be stored in a secure database with restricted access to the researchers involved and will be anonymized or pseudonymized whenever applicable, in accordance with the Brazilian General Data Protection Law (Law No. 13.709/2018). Participants may withdraw their consent at any time without any impact on their clinical follow-up. The study will only begin after approval by the Research Ethics Committee of the responsible institution.

6. RISKS AND BENEFITS

The risks associated with participation in this study are considered minimal. As this is an observational study, without therapeutic or experimental intervention, participants will be subjected only to procedures already indicated within the clinical care context, such as blood pressure measurement, ABPM, and cfPWV assessment.

Possible discomforts may be related to the use of the ABPM device, including a sensation of pressure in the arm during measurements or mild interference with sleep. These effects are transient and widely described in clinical practice. There is also a potential risk related to the confidentiality of the information.

To minimize this risk, strict data protection measures will be adopted, including secure storage, restricted access, and anonymization of the data whenever applicable. There are no guaranteed direct benefits to participants. However, participation in the study may contribute to a more detailed assessment of the cardiovascular profile, potentially aiding in the identification of subclinical alterations.

Indirect benefits include the generation of relevant scientific knowledge regarding the integration between metabolic markers and morning blood pressure behavior, with potential impact on improving cardiovascular risk stratification and clinical practice.

7. REFERENCES

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