Cardiovascular Diabetology

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Elevated whole blood viscosity is associated with an impaired insulin-stimulated myocardial glucose metabolism

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Abstract

Background Increased whole blood viscosity (WBV) was associated with impaired peripheral glucose metabolism, type 2 diabetes, and cardiovascular disease (CVD). Impaired myocardial glucose metabolism is a risk factor for CVD. Whether an increased WBV is associated with impaired myocardial glucose metabolism is still undefined.

Methods To elucidate this issue, we evaluated the association between WBV and myocardial glucose metabolic rate (MRGlu) in 57 individuals with different glucose tolerance status. Myocardial MRGlu was assessed using dynamic cardiac ^{18}F-FDG PET combined with euglycemic hyperinsulinemic clamp. WBV was calculated using a validated equation including hematocrit and plasma proteins: WBV = [0.12 × h] + [0.17 × (p − 2.07)], where h is the hematocrit (%) and p the plasma proteins (g/dl). The subjects were stratified into tertiles according to their myocardial MrGlu values.

Results As compared with individuals in the highest myocardial MrGlu tertile, those in the lowest tertile showed an age-adjusted increase in WBV (5.54 ± 0.3 cP vs. 6.13 ± 0.4 cP respectively; $P = 0.001$), hematocrit (39.1 ± 3.1% vs. 43.2 ± 3.7% respectively; $P = 0.004$), and total proteins (7.06 ± 0.3 g/l vs. 7.60 ± 0.3 g/l respectively; $P < 0.0001$). WBV was negatively correlated with myocardial MRGlu ($r = -0.416$, $P = 0.001$). In a stepwise multivariate regression analysis, including several cardiovascular risk factors, the only variables significantly associated with myocardial MrGlu were WBV (β −0.505; $P < 0.0001$), fasting insulin (β −0.346; $P = 0.004$), fasting plasma glucose (β −0.287; $P = 0.01$), and sex (β 0.280; $P = 0.003$) explaining the 69.6% of its variation.

Conclusions The current study showed a strongly association between an increase of WBV and an impaired myocardial glucose metabolism in individuals with a broad spectrum of glucose tolerance.

Keywords Blood viscosity, Myocardial glucose metabolism, Cardiovascular disease, Type 2 diabetes, Cardiac ^{18}F-FDG PET, Hematocrit, Insulin resistance

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Introduction

Blood viscosity is a measure of the intrinsic resistance of blood to flow in vessels, and is produced by the frictional interactions between the main blood components including plasma, plasma proteins, and red blood cells [1]. There is evidence indicating that raised whole blood viscosity (WBV) is associated with cardio-metabolic risk factors including dyslipidemia, prediabetes/type 2 diabetes (T2DM), hypertension, obesity, and metabolic syndrome [2–5], and target organ damage such as sub-clinical carotid atherosclerosis, vascular stiffness, reduced myocardial mechano-energetic efficiency and left ventricular hypertrophy [6–16] leading to higher risk of incident cardiovascular (CV) events [1, 17–21].

Impaired myocardial glucose metabolism is an early alteration observed in both individuals at increased risk of T2DM and in patients with overt T2DM [22–26]. Furthermore, myocardial insulin resistance is an independent predictor of CV events in individuals with coronary heart disease (CHD), and has been associated with early carotid, aortic and coronary atherosclerosis [27–30]. Previous studies have shown an association between increased WBV and impaired whole-body insulin sensitivity, assessed by euglycemic-hyperinsulinemic clamp technique [31–34] likely due to a reduced glucose and insulin delivery to metabolically active tissues. Whether an increased WBV is associated with impaired myocardial glucose metabolism is still undefined. To this purpose, we evaluated the relationship between WBV and insulin-stimulated myocardial glucose metabolic rate (MRGlu) assessed using cardiac dynamic PET with ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) combined with euglycemic-hyperinsulinemic clamp, in individuals with a broad spectrum of glucose tolerance.

Methods

Study participants

The study cohort comprised 57 subjects participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI), an ongoing observational study recruiting adult individuals with one or more cardio-metabolic risk factors recruited at a referral hospital of the University "Magna Graecia" of Catanzaro [29, 35]. Eligible subjects were recruited according to the following inclusion criteria: age between 30 and 70 years, and positivity for one or more cardio-metabolic risk factors including family history of diabetes, impaired fasting glucose, hypertension, dyslipidemia, and overweight/obesity. Exclusion criteria were type 1 diabetes, end-stage renal disease, previous CVD on the basis of medical history, resting electrocardiogram and stress test or myocardial scintigraphy for individuals with T2DM, history of atrial fibrillation or other arrhythmias, right and left bundle branch block, dyssynchrony in ventricular contraction, valvular heart disease, liver cirrhosis, history of malignant or autoimmune diseases, acute or chronic infections, history of alcohol or drug abuse and treatment with drugs known to influence glucose tolerance such as steroids and estro-progestins and medicaments affecting heart function including beta blockers and antiarrhythmic drugs. All subjects underwent anthropometrical evaluation including measurements of body mass index (BMI), waist circumference and body composition by bioelectrical impedance, and assessment of whole-body and cardiac insulin sensitivity. Readings of clinic blood pressure (BP) were measured at 3-min intervals using a standard sphygmomanometer, and BP values were the average of 3 measurements after a 10-min period of rest in the supine position. After an overnight fasting, biochemical determinations and a 75 g OGTT were performed in individuals with FPG < 126 mg/dl, HbA1c < 6.5% and no history of T2DM. According to the ADA criteria [36], individuals were classified as having normal glucose tolerance (NGT) when fasting plasma glucose was < 100 mg/dl (5.5 mmol/l), 2-h postload glucose < 140 mg/dl (< 7.77 mmol/l) and HbA1c < 5.7%, prediabetes when fasting plasma glucose was 100–125 mg/dl (5.5–6.9 mmol/l), 2-h postload glucose 140–199 mg/dl (7.77–11.0 mmol/l) or HbA1c 5.7–6.4%, T2DM when fasting plasma glucose was ≥ 126 mg/dl (> 7 mmol/l), 2-h post-load glucose was ≥ 200 mg/dl (> 11.1 mmol/l), HbA1c ≥ 6.5% or in treatment with antidiabetic drugs.

On the second day, after 12-h fasting, all subjects underwent ^{18}F-FDG PET scan combined with euglycemic hyperinsulinemic clamp.

The study was approved by the Ethics Committee (Comitato Etico Azienda Ospedaliera "Mater Domini"), and informed consent was obtained from each subject in accordance with principles of the Declaration of Helsinki.

^{18}F-FDG PET scan combined with euglycemic hyperinsulinemic clamp

Myocardial glucose metabolic rate (MrGlu) was measured by ^{18}F-FDG-PET acquired during an euglycemic hyperinsulinemic clamp as previously described [26, 37]. Subjects received a priming dose of insulin (100 UI/ml) (Humulin R; Eli Lilly) during the initial 10 min to raise the serum insulin concentration acutely (80 mU/m^2×min), and then it was maintained by continuous insulin infusion fixed at 40 mU/m^2×min [35]. The blood glucose level was maintained constant at 90 mg/dl for the next 120 min by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5-min intervals (mean coefficient of variation of blood glucose was < 4%). Glucose metabolized by the whole body (M) was calculated as the mean rate of glucose infusion measured during the last 60 min of the clamp examination

(steady state) and was expressed as milligrams per minute per kilogram fat-free mass (M_{FFM}).

The ^{18}F-FDG-PET imaging procedure was performed on a hybrid PET/CT scanner (GE Discovery ST8-2D PET scanner), starting 60 min after the insulin infusion. A 60-min dynamic acquisition was started simultaneously with the intravenous injection of 370 MBq^{18}F-FDG, according to the following time frame sampling: 8×15 s, 2×30 s, 2×120 s, 1×180 s, 6×300 s, 2×600 s [38]. PET images were reconstructed in a 128×128 matrix using a OSEM algorithm, and corrected for decay and attenuation based on co-registered CT. The insulin-glucose infusion continued during the entire PET acquisition. The estimation of myocardial MrGlu was performed by Patlak compartmental modelling [39], using the graphical tool specific for cardiac images analysis (PCARD) implemented in PMOD Software platform (Version 3.806) [39]. In PCARD, the full dynamic study is used for MRGlu calculation, and the arterial input function is extracted from a volume of interest (VOI) semi-automatically placed in the left ventricular cavity [40].

Whole blood viscosity

Whole blood viscosity (WBV) at 208 s−1 of shear rate was calculated by a previously validated equation that takes into account hematocrit and plasma proteins [10]: $WBV=[0.12\times h]+[0.17\times(p-2.07)]$, where h is hematocrit (%) and p is plasma protein levels (g/dl).

Laboratory determinations

Plasma glucose, total and HDL cholesterol, and triglycerides were assayed using enzymatic methods (Roche Diagnostics, Mannheim, Germany). HbA1c was measured with high performance liquid chromatography using an NGSP-certified automated analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy). Red blood cell count, haemoglobin, haematocrit and white blood cell count were analysed using an automated particle counter (Siemens Healthcare Diagnostics ADVIA® 120/2120 Haematology System). Serum insulin levels were determined by a chemiluminescence-based assay (Immulite®, Siemens Healthcare GmbH, Erlangen, Germany). Fibrinogen was measured by an automated nephelometric technology using the BNTMII System analyzer (Siemens Healthcare, Italy).

Statistical analyses

Triglycerides levels were natural log transformed for statistical analyses due to their skewed distribution. Continuous variables are expressed as means±SD. Categorical variables were compared by χ^2 test. Comparisons between women and men were performed using unpaired Student's t test. A general linear model with post hoc Bonferroni correction for multiple comparisons was used to compare differences of continuous variables between groups. Relationships between variables were determined by Pearson's correlation (r). Linear regression analysis was performed to determine the independent contributors to myocardial glucose metabolic rate. A stepwise multivariate regression analysis was performed to determine the independent contributors to myocardial glucose metabolic rate and whole blood viscosity. For all analyses a P value<0.05 was considered to be statistically significant. All analyses were performed using SPSS software Version 29 for Mac.

Results

The subjects in study were stratified into tertiles according to their myocardial MrGlu values.

Clinical characteristics of the three groups of individuals stratified into tertiles according to their insulin-stimulated myocardial MrGlu values are shown in Table 1. Of the 57 recruited individuals, 20 (35.1%) had NGT, 11 (19.3%) had prediabetes, and 26 (45.6%) had T2DM. All the subjects with T2DM were treated with metformin.

No differences were observed in sex distribution. Subjects in the lowest tertile of insulin-stimulated myocardial MrGlu were older and exhibited higher *BMI* than individuals in the highest tertile (32.5±5 kg/m^2 vs. 29.2±4 kg/m^2, P=0.02) (Table 1).

Cardiovascular risk factors and metabolic parameters in individuals stratified according to insulin-stimulated myocardial MrGlu values

As shown in Table 1, no differences between individuals in lowest myocardial MrGlu tertile as compared with those in the highest tertile were observed in waist circumference (108±12 cm vs. 101±10 cm; P=0.4), total cholesterol (186±37 mg/dl, vs. 185±29 mg/dl; P=0.7), HDL (45±10 mg/dl vs. 49±14 mg/dl; P=0.5) and LDL cholesterol (126±36 mg/dl vs. 118±28 mg/dl; P=0.9), triglycerides (164±74 mg/dl vs. 115±60 mg/dl; P=0.1), fasting plasma glucose (131±45 mg/dl vs. 100±27 mg/dl; P=0.054) diastolic blood pressure (79±11 mmHg vs. 75±10 mmHg; P=0.9) and fibrinogen (299±65 mg/dl vs. 269±82 mg/dl; P=0.2) (Table 1). Individuals in the lowest tertile showed an age-adjusted increase in *systolic blood pressure* (130±12 mmHg vs. 115±15 mmHg; P=0.03), *resting heart rate* (78±8 bpm vs. 68±4 bpm; P<0.0001), *fasting insulin* (18.8±10 mU/ml vs. 12.2±6.5 mU/ml; P=0.01) and *HbA1c* (7.1±1.2% vs. 5.8±1.1%; P=0.01), and a lower *whole-body insulin-stimulated glucose disposal* as compared with subjects in the highest tertile (3.16±1.8 vs. 8.4±7.7 mg/min×kg FFM; P=0.02) as compared with individuals in the highest tertile (Table 1). Furthermore, as compared with individuals in the highest tertile, a higher proportion of individuals in the lowest tertile had *prediabetes* or *T2DM* (P=0.001) and were

Table 1 Anthropometric and metabolic characteristics of study subjects stratified into tertiles according to myocardial MrGlu values

	Myocardial MrGlu tertile 1 Range 0.1–16.3 µmol/min/100 g (1)	Myocardial MrGlu tertile 2 Range 16.4–26.29 µmol/min/100 g (2)	Myocardial MrGlu tertile 3 Range 26.3–43 µmol/min/100 g (3)	*P* (1 vs. 2)[§]	*P* (1 vs. 3)[§]	*P* (2 vs. 3)[§]
Sex (F/M)	10/9	8/11	9/10	0.41	0.87	0.5
Age (years)	53 ± 10	50 ± 12	48 ± 11	0.9	0.08	0.09
BMI (kg/m^2)	32.5 ± 5	28.1 ± 4	29.2 ± 4	0.01	0.02	0.6
Waist circumference (cm)	108 ± 12	98 ± 11	101 ± 10	0.5	0.4	0.7
Systolic blood pressure (mmHg)	130 ± 12	124 ± 16	115 ± 15	0.5	0.03	0.1
Diastolic blood pressure (mmHg)	79 ± 11	75 ± 11	75 ± 10	0.9	0.9	0.7
Heart rate (bpm)	78 ± 8	68 ± 7	68 ± 4	< 0.0001	< 0.0001	0.4
Fasting plasma glucose (mg/dl)	131 ± 45	114 ± 35	100 ± 27	0.1	0.054	0.3
HbA1c (%)	7.1 ± 1.2	6.5 ± 1.1	5.8 ± 1.1	0.2	0.01	0.1
Total cholesterol (mg/dl)	186 ± 37	196 ± 47	185 ± 29	0.2	0.7	0.3
HDL cholesterol (mg/dl)	45 ± 10	48 ± 8	49 ± 14	0.3	0.5	0.8
LDL cholesterol (mg/dl)	126 ± 36	127 ± 36	118 ± 28	0.6	0.9	0.3
Triglycerides (mg/dl)	164 ± 74	119 ± 64	115 ± 60	0.2	0.1	0.7
Fasting insulin (mU/ml)	18.8 ± 10	11.03 ± 6	12.2 ± 6.5	0.005	0.01	0.9
NGT/prediabetes/T2DM (n)	1/4/14	6/6/7	13/1/5	0.005	0.001	0.2
Insulin-stimulated glucose disposal (mg/min × kg FFM)	3.16 ± 1.8	4.8 ± 3.1	8.4 ± 7.7	0.1	0.02	0.2
Fibrinogen (mg/dl)	299 ± 65	280 ± 49	269 ± 82	0.4	0.2	0.9
Glucose-lowering therapy (%)						
Meftormin (%)	70.6	33.3	26.3	0.02	0.01	0.8
Antihypertensive therapy (%)	58.3	35.3	16.7	0.4	0.06	0.1
Lipid-lowering therapy (%)	50	18.8	10.5	0.02	0.05	0.8

Data are means ± SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between the three groups were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons

BMI body mass index, *NGT* normal glucose tolerance, *T2DM* type 2 diabetes

[§]*P* values refer to results after analyses with adjustment for age

Table 2 Hemorheological parameters in subjects stratified according to insulin-stimulated myocardial MrGlu values

	Myocardial MrGlu tertile 1 Range 0.1–16.3 µmol/min/100 g (1)	Myocardial MrGlu tertile 2 Range 16.4–26.29 µmol/min/100 g (2)	Myocardial MrGlu tertile 3 Range 26.3–43 µmol/min/100 g (3)	*P* (1 vs. 2)[§]	*P* (1 vs. 3)[§]	*P* (2 vs. 3)[§]
White blood cells count (× 10^9/l)	7868 ± 1817	6072 ± 1510	6123 ± 917	0.01	0.006	0.02
Red blood cells count (× 10^2/l)	4.91 ± 0.5	4.84 ± 0.3	4.75 ± 0.3	0.5	0.2	0.6
Hematocrit (%)	43.2 ± 3.7	42.7 ± 4.2	39.1 ± 3.1	0.7	0.004	0.01
Total proteins (g/l)	7.6 ± 0.2	7 ± 0.2	7.06 ± 0.3	< 0.0001	< 0.0001	0.5
Whole blood viscosity (cP)	6.13 ± 0.4	5.97 ± 0.5	5.54 ± 0.3	0.2	0.001	0.8

Data are means ± SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between the three groups were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons.

[§]*P* values refer to results after analyses with adjustment for age

treated with *glucose-lowering* ($P=0.01$) and *lipid-lowering therapy* ($P=0.05$) (Table 1).

Hemorheological parameters in individuals stratified according to insulin-stimulated myocardial MrGlu values

Hemorheological parameters of the study individuals stratified into tertiles according to insulin-stimulated myocardial MrGlu values are shown in Table 2. As compared with individuals in the highest tertile, those in the lowest tertile showed an age-adjusted increase in *WBV* (5.54 ± 0.3 cP vs. 6.13 ± 0.4 cP respectively; $P=0.001$). These differences remained significant after further adjustment for glucose-lowering therapy and glucose tolerance status ($P=0.02$).

Moreover, as compared with individuals in the highest tertile, those in the lowest tertile showed an age-adjusted increase in *hematocrit* (39.1 ± 3.1% vs. 43.2 ± 3.7% respectively; $P=0.004$), *total proteins* (7.60 ± 0.3 g/l vs. 7.06 ± 0.2 g/l respectively; $P<0.0001$) and *white blood cells (WBC)* count ($7868 \pm 1817 \times 10^9$/l vs. $6123 \pm 917 \times 10^9$/l respectively; $P=0.006$) (Table 2). No difference between individuals in the lowest myocardial MrGlu tertile as

compared with those in the highest tertile was observed in red blood cell (RBC) count ($4.91\pm0.5\times10^2$/l vs. $4.75\pm0.3\times10^2$/l; $P=0.2$) (Table 2).

Differences in cardiovascular risk factors and metabolic and hemorheological parameters of men and women stratified into tertiles according to myocardial MrGlu values

Anthropometric, cardiovascular and hemorheological features of individuals stratified into tertiles according to myocardial MrGlu values according to sex are shown in Supplemental Table S1.

No sex-related differences in age, anthropometric, glycemic and insulinemic parameters, insulin-stimulated glucose disposal, lipid profile, fibrinogen and WBC count were observed across the tertiles, except for levels of HDL cholesterol which were significantly lower in men as compared with women in all myocardial MrGlu tertiles. Moreover, in the highest tertile of insulin-stimulated myocardial MrGlu men were *older*, and more likely to be treated with antihypertensive drugs ($P=0.04$) than women (Table S1).

In all myocardial MrGlu tertiles men exhibited significant higher values of *WBV* than women (Table S1). Additionally, in all myocardial MrGlu tertiles men showed significant higher values of *red blood cell count* and *hematocrit* as compared to women (Table S1).

Association between insulin-stimulated myocardial MrGlu, cardiovascular risk factors and hemorheological parameters

In a univariate analysis, WBV was negatively correlated with myocardial MRGlu (r=−0.416, $P=0.001$), whole-body insulin-stimulated glucose disposal (M_{FFM}) (r=−0.323, $P=0.01$), and positively correlated with fasting plasma glucose (r=0.302, $P=0.02$), waist circumference (r=0.414, $P=0.001$), systolic (r=0.406, $P=0.002$), and diastolic blood pressure (r=0.333, $P=0.01$) (Fig. 1).

Furthermore, in a univariate analysis divided by sex, myocardial MRGlu was negatively correlated with WBV (r=−0.416, $P=0.001$), waist circumference (r=−0.378, $P=0.004$), fasting plasma glucose (r=−0.354, $P=0.007$), HbA1c (r=−0.489, $P<0.0001$), hematocrit (r=−0.353, $P=0.007$), fibrinogen (r=−0.329, $P=0.01$), fasting plasma insulin (r=−0.353, $P=0.008$), and positively correlated with whole-body insulin-stimulated glucose disposal (r=0.441, $P=0.001$) (Fig. 2).

In order to evaluate the independent contributors to myocardial MrGlu, we performed a linear regression analysis in a model having myocardial MrGlu as dependent variable and including age, sex, BMI, waist circumference, blood pressure, lipid profile, fasting plasma glucose, HbA1c, WBV, fasting insulin, and fibrinogen as independent variables. The only variable significantly associated with myocardial MrGlu was whole blood viscosity (β −0.447; $P=0.01$) (Table 3). Moreover, in a stepwise multivariate regression analysis in a model having myocardial MrGlu as dependent variable and including the same risk factors above reported, the only variables significantly associated with myocardial MrGlu were whole blood viscosity (β −0.505; $P<0.0001$), fasting insulin (β −0.346; $P=0.004$), fasting plasma glucose (β −0.287; $P=0.01$), and sex (male) (β 0.280; $P=0.003$) explaining the 69.6% of its variation (Table 4).

Moreover, in order to evaluate the independent contributors to WBV, we performed a stepwise multivariate regression analysis in a model having whole blood viscosity as dependent variable and including several risk factors, including age, sex, BMI, waist circumference, blood pressure, lipid profile, fasting plasma glucose, HbA1c, fasting insulin, whole-body insulin sensitivity, myocardial glucose metabolism, white blood cells and fibrinogen as independent variables. Results of the regression analysis showed that the only variables significantly associated with whole blood viscosity were waist circumference (β 0.229; $P=0.003$), sex (male) (β 0.388; $P=0.004$) and myocardial MrGlu (β −0.400; $P=0.002$) explaining the 72.7% of its variation (Table 5).

Discussion

In this cross-sectional study, we showed that whole blood viscosity was negatively associated with a myocardial glucose metabolism, measured using cardiac dynamic ^{18}F-FDG-PET combined with euglycemic-hyperinsulinemic clamp, in individuals with different degrees of glucose tolerance and no history of coronary heart disease (r=−0.416, $P=0.001$). We found that individuals with lower myocardial glucose metabolic rate showed an age-adjusted increase in WBV as compared with individuals with higher myocardial glucose metabolism (6.13 ± 0.4 cP vs. 5.54 ± 0.3 cP respectively; $P=0.001$) and these differences remained significant also after further adjustment for glucose-lowering therapy and glucose tolerance status ($P=0.02$). These findings were strengthened by results of a stepwise multivariate regression analysis performed in order to investigate whether whole blood viscosity was associated with myocardial MrGlu independently of well-established cardio-metabolic risk factors including age, sex, BMI, waist circumference, blood pressure, lipid profile, fasting plasma glucose, HbA1c, WBV, fasting plasma insulin, and fibrinogen. We found that WBV was a major determinant of myocardial MrGlu independently of known cardiovascular risk factors explaining the 69.6% of its variation. In addition, a linear regression analysis confirmed that, among well-established cardio-metabolic risk factors, the only variable significantly associated with myocardial MrGlu was whole blood viscosity (β −0.447; $P=0.01$).

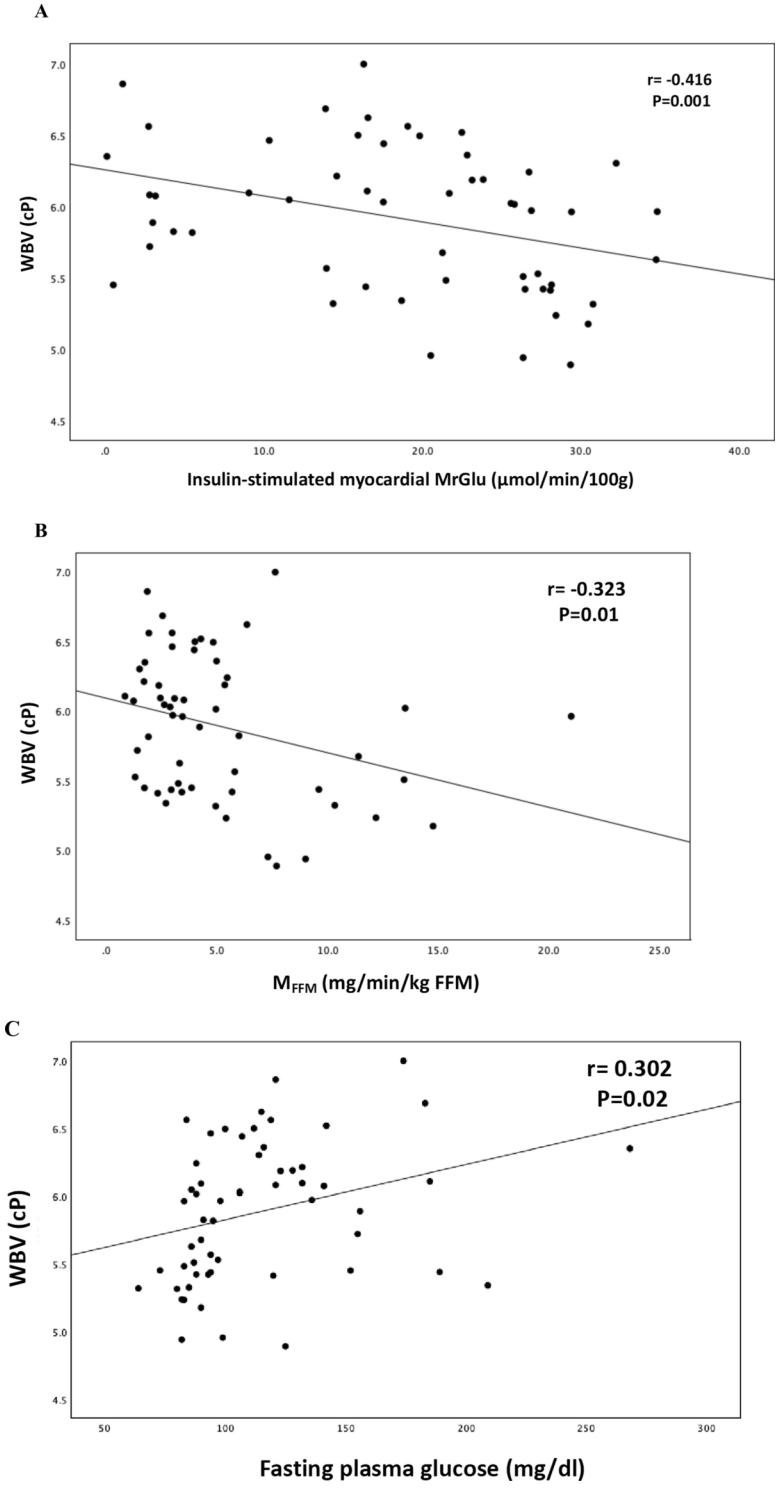

Fig. 1 Relationship between WBV and insulin-stimulated myocardial MrGlu (**A**), M_{FFM} (**B**), fasting plasma glucose (**C**), waist circumference (**D**), systolic blood pressure (**E**), diastolic blood pressure (**F**)

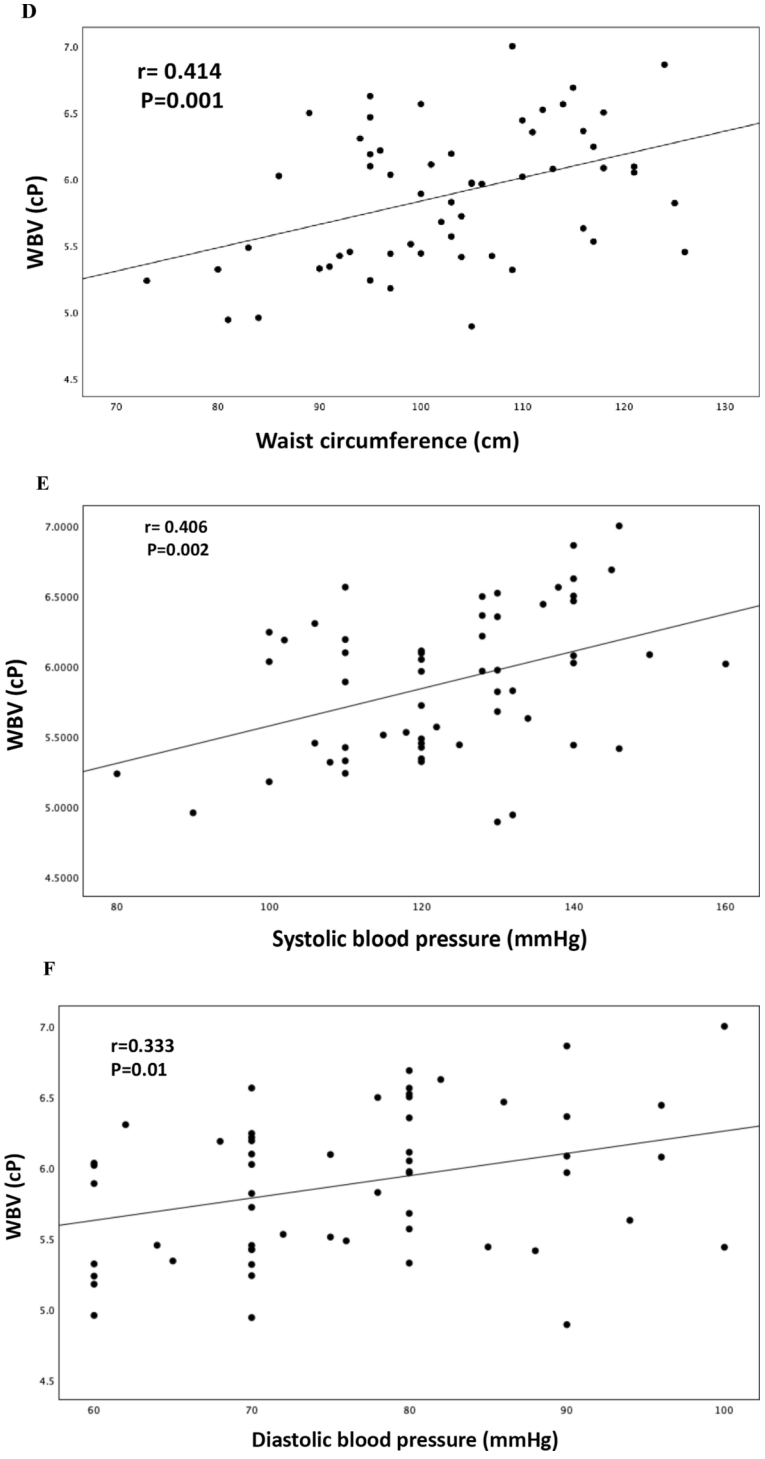

Fig. 1 (continued)

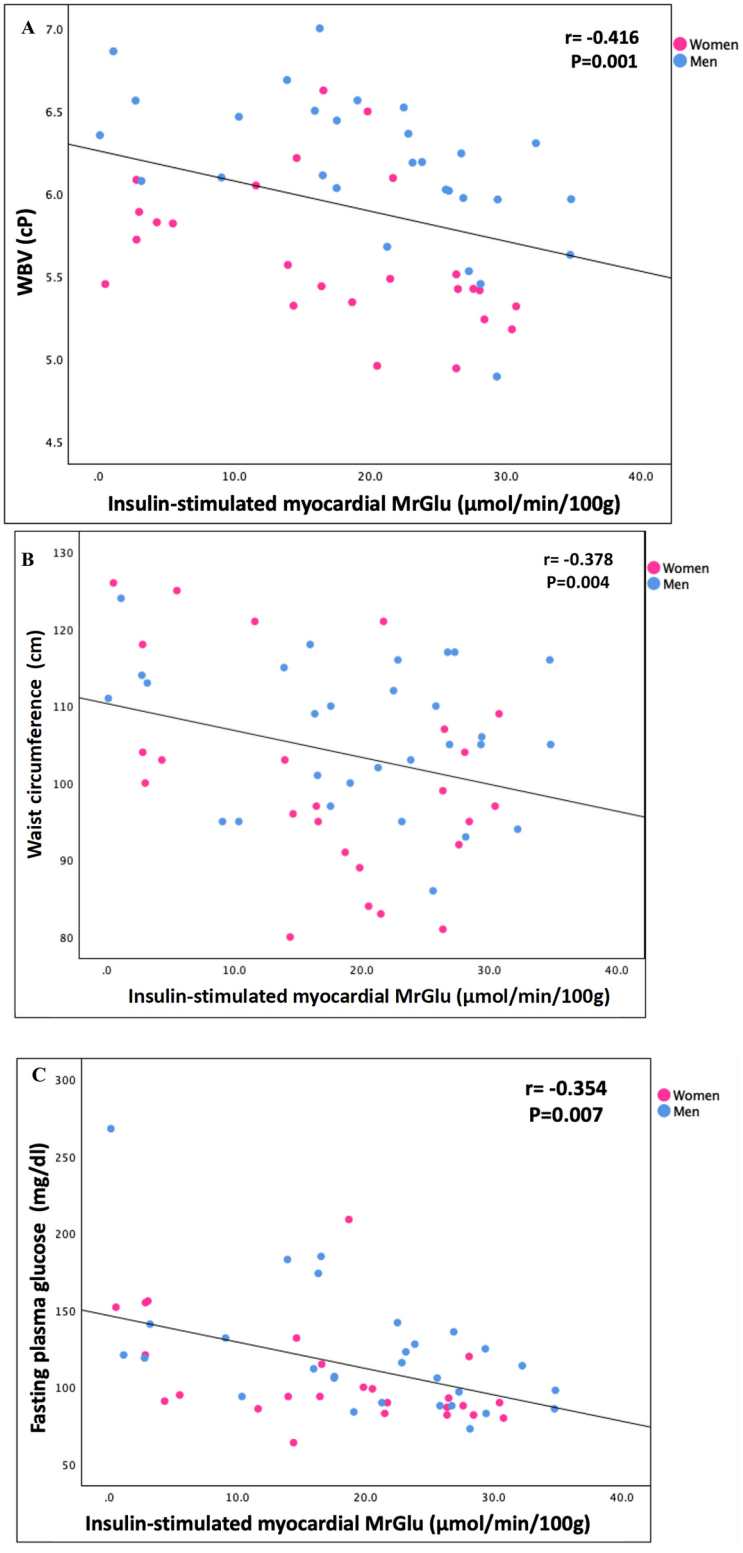

Fig. 2 Relationship divided by sex between insulin-stimulated myocardial MrGlu and WBV (**A**), waist circumference (**B**), fasting plasma glucose (**C**), hematocrit (**D**), fibrinogen (**E**), M_{FFM} (**F**)

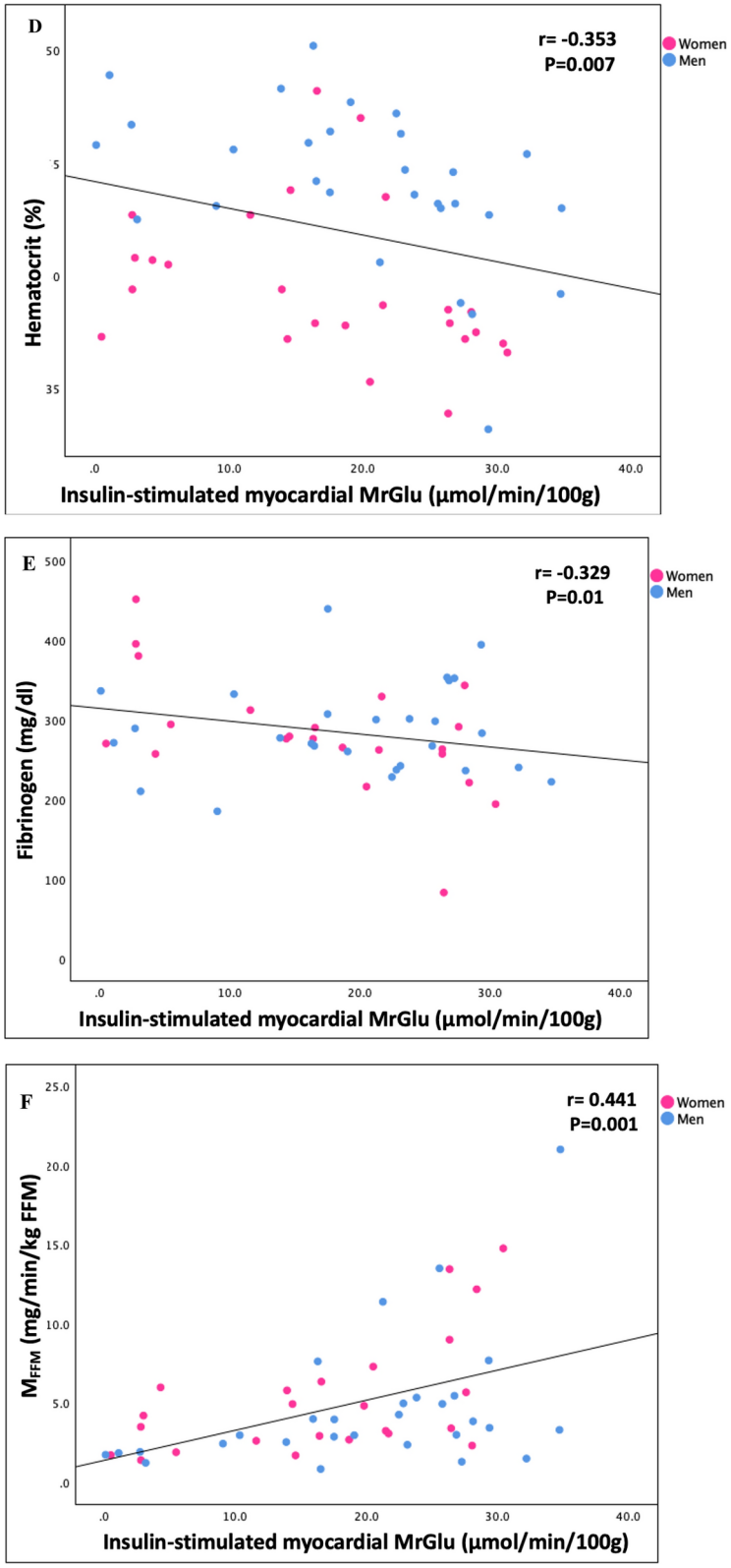

Fig. 2 (continued)

Table 3 Independent predictors of myocardial glucose metabolic rate after linear regression analysis

	Total r^2 (%)	*β*	*t*	*P*
Whole blood viscosity (cP)	74.1	−0.447	−2.732	0.01

Model including age, sex, BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, HDL, triglycerides, fasting plasma glucose, HbA1c, whole blood viscosity, fasting plasma insulin, fibrinogen

Table 4 Independent predictors of myocardial glucose metabolic rate after stepwise multiple regression analysis

	Total r^2 (%)	*β*	*t*	*P*
Whole blood viscosity (cP)	48.7	−0.505	−3.690	< 0.0001
Fasting insulin (mU/ml)	59.3	−0.346	−3.038	0.004
Fasting plasma glucose (mg/dl)	65.5	−0.287	−2.442	0.01
Sex (male)	69.6	0.280	2.159	0.03

Model including age, sex, BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, HDL, triglycerides, fasting plasma glucose, HbA1c, whole blood viscosity, fasting plasma insulin, fibrinogen

Table 5 Independent predictors of whole blood viscosity after stepwise multiple regression analysis

	Total r^2 (%)	*β*	*t*	*P*
Waist circumference (cm)	50.7	0.229	3.171	0.003
Sex (male)	62.9	0.461	4.010	< 0.0001
Myocardial MrGlu (μmol/min/100 g)	72.7	−0.400	−3.350	0.002

Model including age, sex, BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, HDL, triglycerides, fasting plasma glucose, HbA1c, fasting plasma insulin, Insulin-stimulated glucose disposal, myocardial glucose metabolism, white blood cells and fibrinogen

Our study extends previous findings showing an association between WBV and whole-body insulin resistance measured by either euglycemic-hyperinsulinemic clamp in small numbers of subjects [31–33] or proxy indices of insulin resistance in larger samples [3, 4, 41, 42]. However, to the best of our knowledge, the current study was the first to show an association between WBV and myocardial glucose metabolism in individuals with a broad spectrum of glucose tolerance.

There is evidence that increased blood viscosity is an independent predictor of ischemic heart disease and stroke in the general population [1]. Blood viscosity has been shown to be associated with target organ damage such as subclinical atherosclerosis, vascular stiffness, decrease of myocardial mechano-energetic efficiency, and left ventricular hypertrophy [6–16].

Myocardial insulin resistance is a condition related to an unfavorable cardiometabolic risk profile and early carotid, aortic and coronary atherosclerosis, and has been shown to be a predictor of CV events [27–30, 43]. Previous studies have shown that impaired myocardial glucose metabolism is associated with a reduced ejection fraction, a depressed myocardial mechano-energetic efficiency, and an increased cardiac workload, all strong predictors of heart failure [29, 36, 44, 45]. The relative contribution of free fatty acids (FFA) and glucose to energy provision for the human heart is 70% and 30%, respectively, but this proportion varies with the physiological state. Under normal state, cardiac ATP is predominantly derived from fatty acid oxidation, with glucose metabolism contributing less. Conversely, under stress conditions, fatty acid oxidation decreases, while glucose utilization increases [46]. These changes lead to mitochondrial dysfunction with a low energy production and, consequently, death of cardiomyocytes, alterations of mechano-energetic performance, mitochondrial dysfunction, left ventricular maladaptive changes, cardiac dysfunction, and therefore contribute to the development of heart failure and coronary heart disease [25–27, 29, 30, 47–50]. Taken together, these data support the idea that reduced myocardial glucose metabolism may represent one of the pathophysiologic mechanisms contributing to the increased risk of CV disease observed in individuals with increased WBV. The mechanism by which WBV negatively affect myocardial glucose uptake remains to be fully established. Elevated whole blood viscosity and high red blood cells and hematocrit, its main determinant, are associated to peripheral insulin resistance and impaired blood flow [4, 42, 51–54]. Decreased blood flow might affect myocardial glucose metabolism by limiting delivery of glucose and, consequently, myocardial glucose uptake [4, 42, 51].

On the other hand, a reduction of myocardial glucose metabolism could have an impact on whole blood viscosity. In a stepwise multivariate regression analysis, we found that myocardial glucose metabolism was an independent contributor of whole blood viscosity along with waist circumference and male sex explaining the 72.7% of its variation. The study of the pathophysiological mechanism linking impaired myocardial glucose uptake with increased whole blood viscosity is beyond the scope of this investigation. However, there is evidence that impaired insulin-stimulated myocardial glucose metabolism is strongly correlated with whole-body insulin resistance, which has been repeatedly reported to be associated with increased whole blood viscosity. Indeed, higher blood viscosity is associated with decreased flow, which, in turn, counteracts the transport of glucose to tissue [22, 27, 29]. A reduction in whole-body glucose uptake causes an increase in circulating glucose levels leading to increased insulin secretion and compensatory hyperinsulinemia. Hyperinsulinemia may cause vasoconstriction via sympathetic neural activation, which, in turn, would lead to hemoconcentration by increasing hematopoiesis, and hematocrit and, thereby, increased whole blood viscosity [42, 51].

Additionally, we found that men exhibited significantly higher values of hemorheological parameters, including WBV, hematocrit and RBC count as compared with women in all myocardial MrGlu tertiles. Accordingly, in the multivariate regression analysis male sex was an independent contributor of whole blood viscosity. Our results were in agreement with those of a previous study showing that male sex was the demographic variable most related to WBV, probably due to the higher hematocrit levels in men, but also influenced by sex-related differences in plasma volume regulation [10].

We also found an age-adjusted increase in hemorheological parameters, including hematocrit, total proteins and white blood cells count in subjects with low myocardial MrGlu. These findings are in line with results from prior studies showing a remarkable role of hemorheological parameters, including white blood cells count, in the development of insulin resistance, and type 2 diabetes [42, 51, 55]. White blood cells are independently associated with blood viscosity [3] and are an independent predictor of ischemic heart disease, both alone and along with viscosity [56].

This study has several strengths that merit considerations. A main strength is the use of gold standard methods to assess myocardial glucose metabolism by cardiac FDG PET combined with the euglycemic-hyperinsulinemic clamp technique, which allows the valuation of insulin-stimulated myocardial glucose uptake under uniform experimental conditions of euglycemia and physiological hyperinsulinemia [27, 57]. Moreover, glucose tolerance was accurately assessed using FPG, 2 h post-load glucose levels during an OGTT, and HbA1c according to ADA criteria thus excluding any potential misclassification of participants [36]. Additionally, all tests including anthropometric measures, OGTT, and ^{18}F-FGD PET scan combined with euglycemic hyperinsulinemic clamp were collected by skilled examiners after a standardized training, who were blinded to the clinical data of the study participants.

Nevertheless, some limitations should be taken into account. First, whole blood viscosity has not been directly measured by capillary viscometry. However, we estimated whole blood viscosity using an indirect measure that has been previously validated, and is suitable in clinical practice and large observational studies [10]. Furthermore, the consistency of the observed associations using routine haematological parameters may have useful implications for the clinical practice. Second, we have measured red blood cell count only before euglycemic hyperinsulinemic clamp, and therefore, we cannot account for possible variations induced by insulin infusion during clamp procedure. Moreover, this analysis includes only White individuals aging between 30 and 70 years with at least one cardiovascular risk factors attending a referral university hospital, thus limiting the generalizability of the present results to other ethnicities or to the general population. Furthermore, the cross-sectional design of the study precludes causal inferences, and, therefore, no conclusions regarding cause-effect relationships can be made. Additionally, the present findings were observed in an observational study, rather than in a randomized controlled trial thus the results may be subject to residual unknown confounding factors.

Conclusions

In conclusion, to the best of our knowledge, the current study showed an association between an increase of WBV and an impaired myocardial glucose metabolism in individuals with a broad spectrum of glucose tolerance. Indeed, whole blood viscosity was the main independent contributor of myocardial glucose metabolism. On the other hand, myocardial glucose metabolism was an independent contributor of whole blood viscosity along with waist circumference and male sex. These data support the idea that reduced myocardial glucose metabolism may represent one of the pathophysiologic mechanisms which could at least in part contribute to the increased risk of CV disease observed in individuals with increased WBV. On the other hand, a reduction of myocardial glucose metabolism could have an impact on whole blood viscosity. Clearly, our findings need to be confirmed by future prospective studies and should presently be considered as hypothesis generating.

Abbreviations

WBV	Whole blood viscosity
T2DM	Type 2 diabetes mellitus
CV	Cardiovascular
CHD	Coronary heart disease
MRGlu	Myocardial glucose metabolic rate
PET	Positron emission tomography
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
BMI	Body mass index
BP	Blood pressure
OGTT	Oral glucose tolerance test
FPG	Fasting plasma glucose
ADA	American Diabetes Association
NGT	Normal glucose tolerance
M_{FFM}	Insulin-stimulated glucose disposal corrected for fat-free mass
FFM	Fat-free mass
PCARD	Tool specific for cardiac images analysis
VOI	Volume of interest
WBC	White blood cells

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02513-7.

Additional file1

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Author contributions
E.S. designed the study, researched and analyzed data and wrote and edited the manuscript. P.Vi. and P.H.G. analyzed the data from the cardiac PET scans, F.C. performed cardiac PET scans. M.R., T.V.F., M.P., G.C.M., and A.S. researched data and reviewed the manuscript. P.Ve., G.L.C. and F.A. contributed to the discussion and reviewed the manuscript. G.S. designed the study, analyzed the data, and wrote and reviewed the manuscript. All authors reviewed the manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee (Comitato Etico Azienda Ospedaliera "Mater Domini"), and informed consent was obtained from each subject in accordance with principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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