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Whole blood viscosity is associated with reduced myocardial mechano-energetic efficiency in nondiabetic individuals

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Abstract

Introduction: This cross-sectional study aimed to investigate the association between myocardial mechano-energetic efficiency (MEE) and whole blood viscosity (WBV) in nondiabetic adults participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study.

Methods: 1143 participants underwent an oral glucose tolerance test and an echocardiogram for myocardial MEE per gram of left ventricular mass (MEEi) measurement. WBV was measured as: $[0.12 \times h] + [0.17 \times (p\text{-}2.07)]$, where h is haematocrit and p is plasma protein levels.

Results: Study population includes 595 males and 548 females with a mean age of 46 ± 12 years and a mean BMI of 30.0 ± 6.2 kg/m^2. Individuals with normal glucose tolerance were 63%, while those with impaired fasting glucose, impaired glucose tolerance and or the combination of both were 14.3%, 13% and 9.7%, respectively. A univariate analysis showed that MEEi was significantly associated with sex, age, smoking, BMI, waist circumference, total cholesterol, HDL, triglycerides, fasting glucose, fasting insulin, HOMA-IR index, glucose tolerance, C-reactive protein, haematocrit, haemoglobin, plasma protein and WBV. In a multivariable regression model including variables that were significantly associated with MEEi in univariate analysis, MEEi was associated with HOMA-IR ($\beta = -0.144$, $p < .001$), age ($\beta = -0.140$, $p < .001$), WBV ($\beta = -0.129$, $p < .001$) and glucose tolerance ($\beta = -0.064$, $p = .04$). The independent association between WBV and MEEi remained statistically significant ($\beta = -0.122$, $p < .001$) when antihypertensive therapy and lipid-lowering therapy were included in the model.

Conclusion: WBV is associated with decreased myocardial MEE independently of other cardiovascular risk factors.

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KEYWORDS
cardiac energetics, cardiovascular disease, CATAMERI, haematocrit, left ventricular function

1 | INTRODUCTION

There is increased evidence that abnormalities in myocardial energetics characterized by reduced left ventricular (LV) mechanical efficiency and elevated oxygen consumption are involved in the development of cardiovascular (CV) disease.[1–10]

Cardiac work relies on energy derived almost entirely from aerobic oxidation, and requires the coupling between myocardial oxygen consumption (MVO_2) and LV function.[8] The myocardial mechano-energetic efficiency (MEE) of the left ventricle can be defined as the ratio between the energy employed to generate external work (i.e., stroke work) and the amount of oxygen consumed during each contraction.[1–3,5] Specific assessment of MVO_2 requires invasive techniques such as coronary sinus catheterization[11] or expensive and time-consuming techniques such as noninvasive positron emission tomography,[12] two methods unsuitable in large epidemiological studies based on routine examinations.[8] To overcome this problem, a simple, noninvasive, ultrasound-based method to measure myocardial MEE has been validated. This method is based on the calculation of the ratio between LV stroke work, assessed as stroke volume (SV) × systolic blood pressure (SBP), and MVO_2 estimated by the double product, that is, SBP multiplied by heart rate (HR).[2,3]

Pathophysiological mechanisms causing impaired myocardial MEE have not been elucidated so far. Amongst others, whole blood viscosity may be a plausible candidate. Whole blood viscosity is a measure of the intrinsic resistance of blood to flow and is generated by the frictional interactions between the main blood components, such as plasma, plasma proteins and red blood cells.[13] Prior studies have shown a relationship between increased blood viscosity and CV risk factors, including smoking habit, dyslipidaemia, insulin resistance, prediabetes/type 2 diabetes, hypertension and obesity.[14–23] Moreover, whole blood viscosity has been associated with both organ damage such as LV hypertrophy, sub-clinical carotid atherosclerosis and vascular stiffness, and CV events, including cerebral infarction, ischemic heart disease and CV mortality.[24–35] However, the impact of increased whole blood viscosity on myocardial MEE has not been explored yet. To this end, we examined the association between myocardial MEE per gram of left ventricular mass (MEEi) and whole blood viscosity in a cohort of nondiabetic adults participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study.

2 | MATERIALS AND METHODS

2.1 | Study population

The CATAMERI study is an ongoing observational study consecutively recruiting Caucasian adults who are screened for one or more cardio-metabolic risk factors including dysglycaemia, overweight/obesity, dyslipidaemia and hypertension at the 'Magna Graecia' of Catanzaro University hospital as previously described in details.[36,37] In the present study, 1143 participants were analysed after the exclusion of subjects with type 1 and type 2 diabetes, a history of malignant or autoimmune diseases, end-stage renal disease, hepatic failure, anaemia, hemoglobinopathies, haemolytic disease, gastrointestinal affections associated with bleeding or malabsorption, eating disorders or any other cause of malnutrition, acute or chronic infectious diseases, chronic or acute pancreatitis, accumulation diseases such as amyloidosis and hemochromatosis, self-report drug abuse or alcohol consumption of >20 g/day, positivity for antibodies to hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg), and treatment with corticosteroids, antiplatelet and anticoagulant drugs. A study flowchart describing enrolment is reported in the (Figure S1). All participants were visited in the morning, after an overnight fast. During the first visit, information regarding medical history, smoking status, drug use and alcohol consumption was gathered, anthropometrical parameters including body mass index (BMI), waist circumference and clinic blood pressure were recorded, and a sample of venous blood was drawn for laboratory measurements. A 75 g oral glucose tolerance test (OGTT) was performed for glucose tolerance assessment.

The study was approved by the local ethics committee (Comitato Etico Azienda Ospedaliera 'Mater Domini'), and every participant provided written informed consent in accordance with the principles of the Helsinki Declaration.

2.2 | Analytical determinations

Haemoglobin, haematocrit and white blood cell count were analysed using an automated particle counter (Siemens Healthcare Diagnostics ADVIA® 120/2120 Haematology System). Fasting plasma glucose, triglycerides, total and high-density lipoprotein (HDL) cholesterol levels were assessed by enzymatic methods (Roche). High-sensitivity C-reactive protein (hsCRP) levels were

analysed by an automated device (CardioPhase® 144 hsCRP). Plasma insulin concentrations were measured with chemiluminescence-based assay (Immulite®, Siemens Healthcare GmbH).

2.3 | Echocardiographic measurements

All participants underwent echocardiographic investigation performed by a single skilled examiner using a VIVID-7 Pro ultrasound machine (GE Technologies, Milwaukee, WI) with an annular phased array 2.5-MHz transducer. Measurements of interventricular septal (IVS) thickness and LV internal diameter were done at end diastole. LV end-diastolic (LVEDV) and end-systolic volume (LVESV) were assessed according to the Simpson method and indexed for body surface area (BSA).[38] Left ventricular mass (LVM) was calculated using the Devereux formula[39] and normalized by BSA [LVMI]).[40] SV was calculated as the difference between LVEDV and LVESV. External myocardial work was evaluated as stroke work calculated as SBP × echocardiographic SV. MVO2 was measured by the 'double product' of HR × SBP. Therefore, MEE was calculated as SBP × SV/SBP × HR = SV/HR where HR was expressed in seconds (HR/60). Because MEE is highly related to LVM, MEE was normalized to LVM to attain a measure of the amount of blood ejected in 1 second by each gram of LVM (i.e., indexed MEE, MEEi, ml/s per g).[2,3,41]

2.4 | Calculations

The homeostasis model assessment index of insulin resistance (HOMA-IR) was defined as fasting insulin × fasting glucose/22.5.[42]

Whole blood viscosity at 208 s^{-1} of shear rate was calculated by a previously validated equation that takes into account haematocrit and plasma proteins[13]: whole blood viscosity = [0.12 × h] + [0.17 × (p-2.07)], where h is haematocrit (%) and p is plasma protein levels (g/dl).

Estimated glomerular filtration rate (eGFR) was calculated by using the CKD-EPI equation[43]: eGFR = 141 × min(Scr/k, 1) α × max(Scr/k, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1).

Glucose tolerance state was established according to the ADA criteria, based on OGTT using both fasting and 2 h post-challenge glucose levels.[44] All individuals were categorized as having normal glucose tolerance (NGT) when fasting plasma glucose was <100 mg/dL (5.6 mmol/L) and 2 h post-load glucose was <140 mg/dL (7.8 mmol/L), isolated impaired fasting glucose (IFG) when fasting plasma glucose was 100–125 mg/dL (5.6–6.9 mmol/L) and 2 h post-load glucose was <140 mg/dL (<7.8 mmo/l), isolated impaired glucose tolerance (IGT) when fasting plasma glucose was <100 mg/dL (5.6 mmol/L) and 2 h post-load glucose was 140–199 mg/dL (7. 8–11.0 mmol/L), and combined IFG/IGT when fasting plasma glucose was 100–125 mg/dL (5.6–6.9 mmol/L) and 2 h post-load glucose was 140–199 mg/dL (7.8–11.0 mmol/L).

2.5 | Statistical analysis

Normality of continuous variables was assessed by kurtosis and skewness measures and normal probability plots. Non-normally distributed variables including triglycerides, HOMA-IR and hsCRP were log transformed to achieve normality before statistical analyses. Continuous data are expressed as means ± SD. As for study design, only subjects with all data available were included in the analysis. Correlations between normally distributed variables were determined by Pearson's correlation coefficient. Correlations between categorical variables were determined b Spearman's correlation coefficient. The independent association between myocardial MEEi and whole blood viscosity was tested by multiple regression analysis, including the variables significantly associated with myocardial MEEi in a univariate analysis. Variables that are incorporated into the formulas of the whole blood viscosity such as haematocrit and plasma protein levels and variables used to calculate myocardial MEEi were not computed in the regression model to avoid potential collinearity. Variation inflation factor (VIF <2) and condition index and (<15) were applied to demonstrate the absence of multicollinearity between variables comprised in the multiple linear regression model.[45] A p-value ≤0.05 was considered statistically significant. All statistical analyses were performed by SPSS software program version 27 for Windows (IBM CORP).

3 | RESULTS

The study population includes 595 males and 548 females with a mean age of 46 ± 12 years (range 18–64 years), a mean BMI of 30.0 ± 6.2 kg/m^2 (range 17 to 63 kg/m^2) and a mean waist circumference of 101 ± 15 cm (range 62–165 cm).

The main anthropometric and metabolic characteristics of the study population are shown in Table 1. Six-hundred and thirty (55.1%) of the 1143 participants, are categorized as never smokers, 264 (23.1%) as current smokers and 249

TABLE 1 Anthropometric and metabolic characteristics of the study population ($N = 1143$).

Variables	Mean ± SD
Sex (male/female)	595/548
Age (years)	46 ± 12
BMI (kg/m^2)	30.0 ± 6.2
Waist circumference (cm)	101 ± 15
Smoking status (never smokers/current smokers/ex-smokers)	630/264/249
Heart rate (beats/min)	71 ± 10
Systolic blood pressure (mmHg)	128 ± 17
Diastolic blood pressure (mmHg)	80 ± 11
Total cholesterol (mg/dL)	201 ± 39
HDL-C (mg/dL)	51 ± 14
Triglycerides (mg/dL)	128 ± 79
Fasting plasma glucose (mg/dL)	93 ± 10
Fasting plasma insulin (μU/mL)	13.6 ± 8.6
NGT/ IFG/ IGT/ IFG-IGT	720/163/149/111
HOMA-IR	3.13 ± 2.01
hsCRP (mg/L)	3.5 ± 4.1
Creatinine (mg/dl)	0.78 ± 0.16
eGFR (ml/min/1.73m^2)	130 ± 37
Haematocrit (%)	42 ± 4
Haemoglobin (g/dL)	14.1 ± 1.2
Total plasma proteins (g/dL)	7.26 ± 0.44
Whole blood viscosity (cP)	5.96 ± 0.44
Antihypertensive therapy, yes (%)	43.1
ACE inhibitors (*n*)	183
ARBs (*n*)	185
Beta blockers (*n*)	189
Calcium channel blockers (*n*)	150
Diuretics (*n*)	163
Lipid-lowering therapy, yes (%)	10.1

Note: Data are means ± SD. Triglycerides, HOMA-IR and hsCRP were natural log transformed for statistical analyses, but values in the table represent back transformation to the original scale.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; GT, impaired glucose tolerance; NGT, normal glucose tolerance.

(21.8%) as ex-smokers. Individuals with NGT were 63% of the whole population, those with IFG were 14.3%, while those with IGT or IFG/IGT combined were 13% and 9.7%, respectively (Table 1). In the whole study group, mean haematocrit was 42 ± 4%, mean total plasma proteins concentration was 7.26 ± 0.44 g/dL, and mean whole blood viscosity was 5.96 ± 0.44 cP. Echocardiographic parameters are shown in Table 2.

TABLE 2 Left ventricular geometry, systolic and diastolic function and mechano-energetic performance in the study subjects ($N = 1143$).

Variables	Mean ± SD
LV end-systolic volume (mL)	35 ± 17
LV end-diastolic volume (mL)	122.1 ± 37.2
LVM (g)	197 ± 63
LVM index (g/m$^{2.7}$)	103 ± 28
Stroke volume (mL)	87.1 ± 25.2
Stroke work (mmHg*ml)	11,211 ± 3786
Myocardial oxygen consumption (mmHg × bpm)	9066 ± 1832
Myocardial MEEi (mL/sec/g)	0.395 ± 0.108

Note: Data are means ± SD.

Abbreviations: LV, left ventricular; LVM, left ventricular mass; LVMI, left ventricular mass index; MEEi, myocardial mechano-energy efficiency per gram of left ventricular mass.

Next, we sought to examine the association between myocardial MEEi and whole blood viscosity. As shown in Table 3, in a univariate analysis, myocardial MEEi was significantly associated with sex, age, smoking status, BMI, waist circumference, total cholesterol, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, HOMA-IR, eGFR, glucose tolerance status, hsCRP, haematocrit, haemoglobin, total plasma protein levels and whole blood viscosity.

In addition, whole blood viscosity was significantly associated with sex, age, smoking status, waist circumference, total cholesterol, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, HOMA-IR, eGFR, glucose tolerance status, haemoglobin, systolic and diastolic blood pressure, heart rate, stroke work and myocardial oxygen consumption.

To estimate the independent contribution of whole blood viscosity to myocardial MEEi, we built a multivariable regression model including variables that were significantly associated with MEEi in a univariate analysis, that is, sex, age, smoking status, BMI, total and HDL cholesterol, triglycerides, hsCRP, eGFR, glucose tolerance status and HOMA-IR. Comparison of standardized coefficients allowed the determination of the relative strength of each trait association with MEEi (listed from strongest to weakest): age ($\beta = -0.146$, $p < .001$), HOMA-IR ($\beta = -0.145$, $p < .001$), whole blood viscosity ($\beta = -0.130$, $p < .001$) and glucose tolerance status ($\beta = -0.064$, $p = .04$) (Table 4). The independent association between whole blood viscosity and MEEi remained statistically significant ($\beta = -0.125$, $p < .001$) when HOMA-IR was replaced by fasting plasma glucose and insulin levels in the regression model (Model 2; Table 4). Moreover, the independent association between whole blood viscosity and MEEi remained statistically significant ($\beta = -0.122$, $p < .001$) when antihypertensive

TABLE 3 Correlations between myocardial MEEi, whole blood viscosity and anthropometric and metabolic variables.

	Myocardial MEEi		Whole blood viscosity	
Variables	***r***	***p***	***r***	***p***
Sex	−.161	<.001	.587	<.001
Age (years)	−.177	<.001	.077	.009
Smoking status	−.066	.025	.210	<.001
BMI (kg/m^2)	−.152	<.001	.035	.243
Waist circumference (cm)	−.163	<.001	.170	<.001
Total cholesterol (mg/dL)	−.082	.005	.102	<.001
HDL-C (mg/dL)	.166	<.001	−.266	<.001
Triglycerides (mg/dL)	−.210	<.001	.263	<.001
Fasting plasma glucose (mg/dL)	−.147	<.001	.139	<.001
Fasting plasma insulin (μU/mL)	−.203	<.001	.129	<.001
HOMA-IR	−.241	<.001	.157	<.001
Glucose tolerance status	−.181	<.001	.099	<.001
hsCRP (mg/L)	−.099	0001	−.049	.109
eGFR (ml/min/1.73m^2)	.165	<.001	−.408	<.001
Haematocrit (%)	−.193	<.001	-----	------
Haemoglobin (g/dL)	−.234	<.001	.859	<.001
Total plasma proteins (g/dL)	−.131	<.001	-----	------
Whole blood viscosity (cP)	−.210	<.001	-----	-------
Systolic blood pressure (mmHg)	-----	------	.229	<.001
Diastolic blood pressure (mmHg)	-----	------	.217	<.001
Heart rate (beats/min)			.064	.03
Stroke work (mmHg*ml)	-----	-------	.264	<.001
Myocardial oxygen consumption (mmHg × bpm)	-----	-------	.200	<.001

Abbreviations: BMI, body mass index; C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HDL-HOMA-IR, homeostasis model assessment index of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

therapy and lipid-lowering therapy were included in the regression model (Model 3; Table 4). Finally, the independent association between whole blood viscosity and MEEi remained statistically significant ($\beta = -0.133$, $p = .006$) when the regression analysis was restricted to the individuals having a value of HOMA-IR ≥2.5 ($n = 616$).

4 | DISCUSSION

The main result of the present study is that myocardial MEEi, as estimated by an indirect validated method,[2] is significantly associated with whole blood viscosity in a large cohort of nondiabetic individuals. This finding was strengthened by results of a multivariate linear regression that investigated whether whole blood viscosity was associated with reduced myocardial MEEi independently of well-established cardio-metabolic risk factors including age, sex, smoking status, BMI, total cholesterol, HDL, triglycerides, glucose tolerance status, hsCRP and HOMA-IR index of insulin resistance. We found that whole blood viscosity was a major determinant of myocardial MEEi independently of cardiovascular risk factors known to be associated with MEEi.[46–49] It has been shown that antihypertensive treatments may regulate blood viscosity: Diuretics by stimulating diuresis may cause haemoconcentration, while other classes of antihypertensive treatments have been shown to decrease blood viscosity, likely, by reducing blood pressure and pressure-dependent renal filtration.[50–53] We found that the association between whole blood viscosity and myocardial MEEi remained statistically significant even after adjustment for antihypertensive therapy. This makes unlikely that antihypertensive therapy contributed to the observed association between whole blood viscosity and MEEi.

There are several potential pathophysiological mechanisms underpinning the relationship between elevated whole blood viscosity and impaired capability of the left ventricle to convert chemical energy into stroke work. Stroke volume is determined by the interaction between the preload, the contractile state of the heart and the postload forces. According to Poiseuille's law, a rise in whole blood viscosity, causing a decrease in blood flow rate results in a physiologic compensatory increase in blood pressure or vasodilation.[54] Thus, we found that whole blood viscosity was positively associated with systolic and diastolic blood pressure suggesting a compensatory blood pressure increase in response to raised blood viscosity. This compensatory elevation in blood pressure may constitute an extra circulatory workload for the heart. A cartoon displaying the assumed pathophysiological mechanisms of the association between MEEi and whole blood viscosity is reported in Figure 1.

Impaired insulin sensitivity and compensatory hyperinsulinemia may represent additional pathophysiological mechanisms linking increased whole blood viscosity and depressed MEEi. It has been reported that a higher degree of insulin resistance, estimated by the HOMA-IR index, is associated with a reduction in myocardial MEEi,[41] and that an impairment in insulin-stimulated myocardial glucose metabolism, measured by dynamic positron emission tomography with 18F-fluorodeoxyglucose combined with euglycemic–hyperinsulinemic clamp, is associated with reduced myocardial MEEi in individuals with different degrees of glucose tolerance.[55] There is also substantial

TABLE 4 Multiple regression analysis evaluating the association between whole blood viscosity, anthropometric and metabolic variables and myocardial MEEi as dependent variable.

	Dependent variable: myocardial MEEi				
	Independent contributors	Standardized coefficient β	Unstandardized Coefficient B (95% CI)	p	VIF
Model 1 includes sex, age, smoking status, BMI, total cholesterol, HDL-C, triglycerides, hsCRP, glucose tolerance status, HOMA-IR, eGFR and whole blood viscosity.	Age	−0.146	−0.001 (−0.002 to −0.001)	<.001	1.442
	HOMA-IR	−0.145	−0.026 (−0.039 to −0.013)	<.001	1.510
	Whole blood viscosity	−0.130	−0.032 (−0.050 to −0.014)	<.001	1.561
	Glucose tolerance status	−0.064	−0.007 (−0.013 to −0.0002)	.04	1.165
Model 2 includes sex, age, smoking status, BMI, total cholesterol, HDL-C, triglycerides, hsCRP, glucose tolerance status, fasting plasma glucose, fasting plasma insulin, eGFR and whole blood viscosity.	Age	−0.169	−0.031 (−0.002 to −0.001)	<.001	1.579
	Fasting plasma insulin	−0.146	−0.002 (−0.003 to −0.001)	<.001	1.403
	Whole blood viscosity	−0.125	−0.031 (−0.49 to −0.013)	<.001	1.569
	Glucose tolerance status	−0.100	−0.010 (−0.018 to −0.003)	.006	1.487
Model 3 includes sex, age, smoking status, BMI, total cholesterol, HDL-C, triglycerides, hsCRP, glucose tolerance status, HOMA-IR, eGFR, antihypertensive therapy, lipid-lowering therapy and whole blood viscosity.	HOMA-IR	−0.140	−0.025 (−0.038 to −0.012)	<.001	1.516
	Whole blood viscosity	−0.123	−0.030 (−0.048 to −0.012)	<.001	1.573
	Age	−0.118	−0.001 (−0.002 to −0.0004)	.002	1.617
	Antihypertensive therapy	−0.070	−0.015 (−0.029 to −0.001)	.04	1.269
	Glucose tolerance status	−0.061	−0.006 (−0.013 to −0.0001)	.05	1.168

Abbreviations: BMI, body mass index; C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HDL-HOMA-IR, homeostasis model assessment index of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

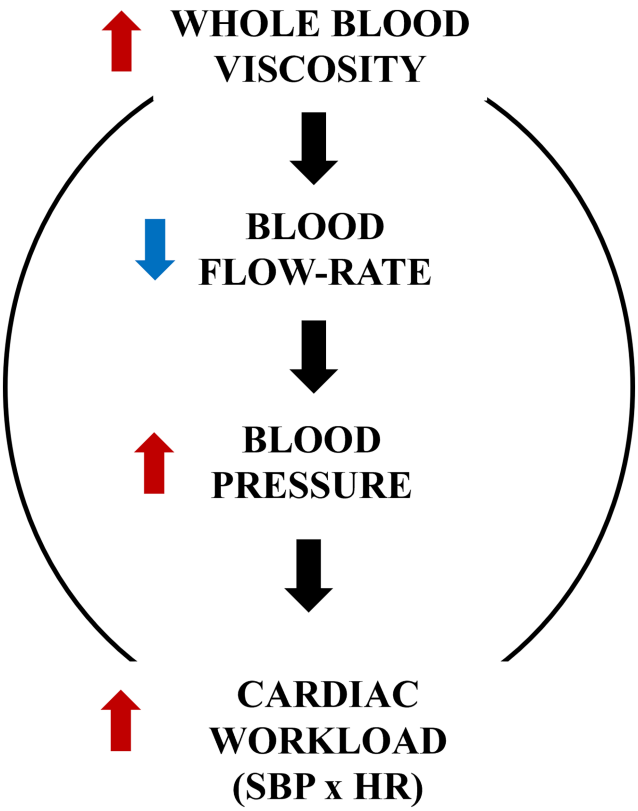

FIGURE. 1 Pathophysiological mechanism of the association between MEEi and whole blood viscosity. HR, heart rate; SBP, systolic blood pressure.

evidence showing that impaired insulin sensitivity is associated with higher values of haematocrit, the main determinant of blood viscosity, increased blood viscosity and higher erythrocyte aggregability.[56–59] An increase in blood viscosity is associated with decreased flow, which, in turn, may lead to a decreased delivery of glucose to the skeletal muscle.[60] These changes lead to an increase in blood glucose levels which promotes insulin secretion and compensatory hyperinsulinemia. Moreover, hyperinsulinemia may induce vasoconstriction via sympathetic neural activation, which, in turn, would lead to increased blood pressure and cardiac workload.[61] Taken together, these data support the idea that insulin resistance and compensatory hyperinsulinemia may represent a pathophysiological mechanism linking whole blood viscosity to myocardial MEEi. Although we observed that whole blood viscosity was positively correlated with both HOMA-IR index, and fasting plasma glucose and insulin levels, the findings that whole blood viscosity remained associated with myocardial MEEi even after adjustment for fasting plasma glucose and insulin levels or HOMA-IR index argue against the possibility that these factors might have contributed to the association of whole blood viscosity with myocardial MEEi.

There is evidence of a significant association between elevated blood viscosity and CV morbidity and mortality.[24–35] The present finding of an independent association between whole blood viscosity and decreased myocardial

MEEi coupled with results of previous studies showing the role of impaired myocardial energetics in the development of CV disease[1–3,10] may be viewed as evidence that reduced myocardial MEEi may represent one of the physio-pathologic mechanisms contributing to the increased risk of CV disease observed in individuals with elevated blood viscosity.[28,33]

Strengths of the current study include the large sample size equally comprising men and women, a careful clinical characterization with anthropometric and metabolic features gathered according to a standardized protocol that allowed us to adjust for multiple confounders, the measurement of biochemical and haematological parameters in fresh, rather than stored, blood samples thus preventing possible problem of degradation and cell lysis, the exclusion of individuals with disorders potentially affecting haemoglobin concentration or treated with corticosteroids, antiplatelet and anticoagulant drugs.

Nevertheless, some limitations should be considered. Firstly, MEEi was evaluated by indirect measures rather than by coronary sinus catheterization[11] or noninvasive positron emission tomography,[12] two techniques unsuitable in large epidemiological studies based on routine examinations. Secondly, we did not perform direct assay of blood viscosity by capillary viscometry. Nonetheless, assessments of whole blood viscosity were based on a prediction equation that has been validated in previous studies.[13,62,63] Furthermore, our large sample size counterbalances the lower accuracy of blood viscosity measures, and the consistency of the observed associations using routine haematological parameters may have useful implications for the clinical practice. Moreover, the cross-sectional nature of the present study precludes us from drawing any firm conclusion on the role of increased whole blood viscosity in inducing depressed MEEi, and therefore, it is not possible to discern cause-effect relationship using this design. Additionally, this study is not a randomized controlled trial, but rather an observational investigation, and thus, the results may be subject to residual unknown confounding factors. Finally, the results are based only on Caucasian outpatients with one or more risks for cardio-metabolic disease attending a referral university hospital, and thus, it is not possible to generalize the findings to the general population and other ethnic groups.

5 | CONCLUSION

The current study suggests that whole blood viscosity is associated with reduced myocardial MEEi in a large cohort of nondiabetic Caucasian individuals independently of other cardio-metabolic risk factors, including hypertension and insulin resistance. This finding supports the idea that a decrease in cardiac energetics, measured by myocardial MEEi, may be one of the key mechanisms leading to increased CV risk in individuals with elevated blood viscosity. However, other studies are required to confirm the presence of a cause-effect relationship of these results in the general population.

AUTHOR CONTRIBUTIONS

A.R. conceived the study, analysed the data and critically reviewed and edited the manuscript. C.M.A.C. critically reviewed and edited the manuscript. C.M. and L.V. analysed the data and critically reviewed the manuscript. T.V.F., M.R., M.M., E.S., M.P., A.S. and F.A. collected the data and critically reviewed the manuscript. G.S. designed the study, analysed data, wrote the first draft and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DISCLOSURE

The authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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