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ORIGINAL RESEARCH

Association Between Haptoglobin Phenotype and Microvascular Obstruction in Patients With STEMI

A Cardiac Magnetic Resonance Study

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ABSTRACT

OBJECTIVES This study aimed to evaluate the correlation between different haptoglobin (Hp) phenotypes and myocardial infarction characteristics as detected by cardiac magnetic resonance (CMR) in consecutive patients after ST-segment elevation myocardial infarction (STEMI).

BACKGROUND Hp is a plasma protein that prevents iron-mediated oxidative tissue damage. CMR has emerged as the gold standard technique to detect left ventricular ejection fraction (LVEF), extent of scar with late gadolinium enhancement (LGE) technique, microvascular obstruction (MVO), and myocardial hemorrhage (MH) in patients with STEMI treated by primary percutaneous coronary intervention (pPCI).

METHODS A total of 145 consecutive STEMI patients (mean age 62.2 ± 10.3 years; 78% men) were prospectively enrolled and underwent Hp phenotyping and CMR assessment within 1 week after STEMI.

RESULTS CMR showed an area at risk (AAR) involving 26.6 ± 19.1% of left ventricular (LV) mass with a late LGE extent of 15.2 ± 13.1% of LV mass. MVO and MH occurred in 38 (26%) and 12 (8%) patients, respectively. Hp phenotypes 1-1, 2-1, 2-2 were observed in 15 (10%), 62 (43%), and 68 (47%), respectively. Multivariable analysis demonstrated that body mass index, Hp2-2, diabetes, and peak troponin I were independent predictors of MVO with Hp2-2 associated with the highest odds ratio (OR) (OR: 5.5 [95% confidence interval [CI]: 2.1 to 14.3; $p < 0.001$]). Hp2-2 significantly predicted both the presence (area under the curve [AUC]: 0.63 [95% CI: 0.53 to 0.72; $p = 0.008$]) and extent of MVO (AUC: 0.63 [95% CI: 0.54 to 0.72; $p = 0.007$]).

CONCLUSIONS Hp phenotype is an independent predictor of MVO. Therefore, Hp phenotyping could be used for risk stratification and may be useful in assessing new therapies to reduce myocardial reperfusion injury in patients with STEMI. (J Am Coll Cardiol Img 2019;12:1007–17) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AAR = area at risk

AUC = area under the curve

CMR = cardiac magnetic resonance

Hp = haptoglobin

LGE = late gadolinium enhancement

LV = left ventricle

LVEF = left ventricular ejection fraction

MH = myocardial hemorrhage

MI = myocardial infarction

MSI = myocardial salvage index

MVO = microvascular obstruction

pPCI = primary percutaneous coronary intervention

RV = right ventricle

TTE = transthoracic echocardiography

STEMI = ST-segment elevation myocardial infarction

The goal of primary percutaneous coronary intervention (pPCI) in patients with ST-segment elevation myocardial infarction (STEMI) is to reduce infarct size (1). Accordingly, major efforts have been made to reduce the door-to-balloon time with the concept that "time is muscle." However, reperfusion therapy with PCI may cause additional injury that is not due to the ischemic period (2). Haptoglobin (Hp) is a plasma protein that binds extracorpuscular hemoglobin (Hb) and prevents iron-mediated oxidative tissue damage (3). In humans, the Hp gene exists in 2 major co-dominant alleles Hp 1 and Hp 2 that give rise to 3 distinct protein phenotypes: small tetrameric Hp1-1, linear homodimeric Hp2-1, and large cyclic multimeric Hp2-2 (4,5). Hp2-2 was reported to be less efficient than Hp1-1 in binding Hb and preventing oxidation by stabilizing heme iron within Hb, thereby displaying lower antioxidant activity (6,7). Recently, cardiac magnetic resonance (CMR) has emerged as the gold standard technique to detect wall motion, extent of myocardial salvage index (MSI), microvascular obstruction (MVO), and myocardial hemorrhage (MH) (8). These variables have been shown to predict functional recovery and the risk of cardiovascular events regardless of the recanalization result of the culprit epicardial coronary artery (8–10). The aim of this study was to evaluate the correlation between different Hp phenotypes and MI characteristics as detected by CMR in consecutive patients with STEMI after pPCI.

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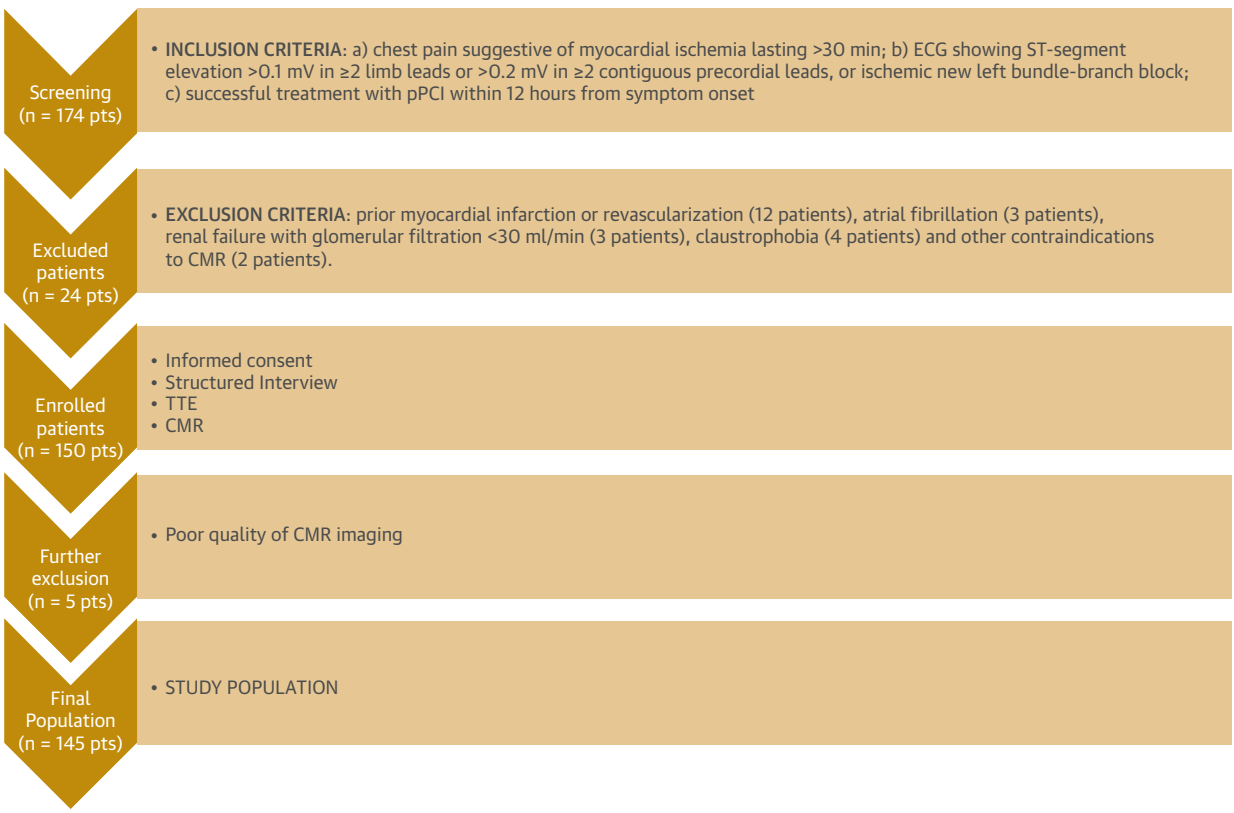
METHODS

STUDY POPULATION. Between January 2015 and May 2017, consecutive patients with acute STEMI were prospectively screened for study eligibility by site personnel to identify those who met all selection criteria (**Figure 1**). Inclusion criteria were chest pain suggestive of myocardial ischemia lasting >30 min; electrocardiogram (ECG) showing ST-segment elevation >0.1 mV in ≥2 limb leads or >0.2 mV in ≥2 contiguous precordial leads, or presumed new left

FIGURE 1 Study Flow Protocol



CMR = cardiac magnetic resonance; pPCI = primary percutaneous coronary intervention; TTE = transthoracic echocardiography.

bundle-branch block; and successful treatment with pPCI within 12 h from the onset of symptoms. Exclusion criteria were previous myocardial infarction (MI) or revascularization, time to pPCI >12 h, atrial fibrillation, renal failure with glomerular filtration <30 ml/min, claustrophobia, and other contraindications to CMR. After exclusion, 150 patients were enrolled. Five patients were excluded owing to poor image quality of CMR. The final population was composed of 145 patients (mean age 62.2 ± 10.3 years; 78.6% men). The study complied with the Declaration of Helsinki. The ethics committee approved the research protocol (R114/14-CCM 125), and informed consent was obtained from each subject.

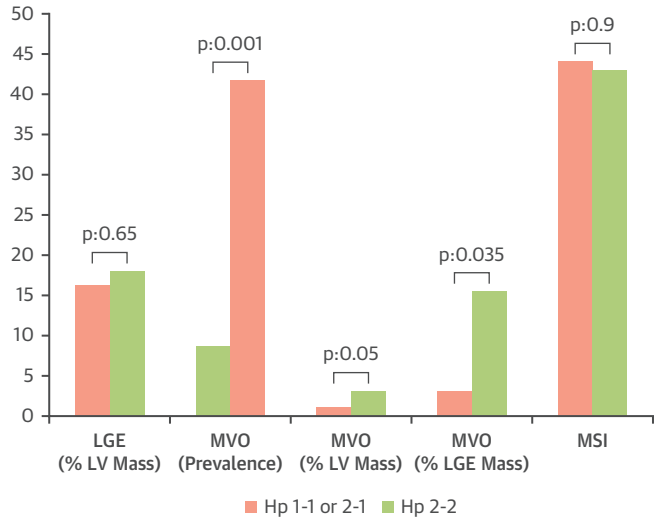
COLLECTION OF CLINICAL VARIABLES. Clinical history was recorded from each patient by 1 trained physician. The following variables were collected: demographic characteristics (age, sex, and body mass index [BMI]) and cardiovascular risk factors including hypertension; current or previous smoking; hyperlipidemia; diabetes mellitus; family history of CAD in first-degree relatives; medical therapy; vital parameters including blood pressure and heart rate, site of MI, peak troponin I, Killip class; and time to pPCI, defined as the interval time between the onset of continuous chest pain and the recanalization of the infarct-related artery by pPCI. Finally, a GRACE (Global Registry of Acute Coronary Events) 2.0 risk score was calculated for each patient.

Haptoglobin phenotyping. Hp phenotype was assessed as follows: briefly, human plasma was diluted in sample loading buffer (1:100) (20 g/l sodium dodecyl sulfate, 100 ml/l glycerol, 25 mmol/l Tris [pH 6.8], 0.05 g/l bromophenol blue, 50 mmol/l dithiothreitol), and loaded on a 18% polyacrylamide gel with Hp standards 1-1 and 2-2 (Sigma-Aldrich, Milan, Italy). Immunoblotting was performed with a 1:10,000 dilution of polyclonal rabbit anti-human Hp (Sigma-Aldrich) and a goat anti-rabbit immunoglobulin-G horseradish peroxidase conjugated (Bio-Rad Laboratories, Milan, Italy), diluted 1:10,000 in tris-buffered saline and Polysorbate 20 (TBST) as secondary antibody.

Invasive coronary angiography analysis. An experienced interventional cardiologist analyzed all coronary angiograms. The following parameters were collected: additional medications before pPCI, infarct-related artery and Thrombolysis In Myocardial Infarction (TIMI) flow grade before and after pPCI.

Transthoracic echocardiography protocol. Transthoracic echocardiography (TTE) was performed within 3 days after pPCI with patients in the left lateral

FIGURE 2 CMR Findings in Late Revascularization (pPCI >3 h)



CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; MSI = myocardial salvage index; MVO = microvascular obstruction; pPCI = primary percutaneous coronary intervention.

TABLE 1 Baseline Characteristics of the Study Population

	All Patients (N = 145)	Hp 1-1 or 2-1 (n = 77)	Hp 2-2 (n = 68)	p Value
Demographic characteristics				
Age, yrs	62.2 ± 10.3	63 ± 10.7	61 ± 9.8	0.331
Male	114 (78.6)	58 (75)	56 (82)	0.30
Body mass index, kg/m^2	26.1 ± 3.6	25.7 ± 3.1	26.6 ± 3.9	0.167
Cardiovascular risk factors				
Hypertension	69 (47.6)	33 (42.9)	36 (52.9)	0.225
Current or previous smoking	82 (56.6)	46 (59.7)	36 (52.9)	0.410
Hyperlipidemia	51 (35.2)	25 (32.5)	26 (38.2)	0.468
Diabetes	23 (15.9)	12 (15.6)	11 (16.2)	0.922
Family history of CAD	30 (20.7)	11 (14.3)	19 (27.9)	**0.043**
Medication before hospital admission				
Beta-blockers	31 (21.4)	16 (20.8)	15 (22.1)	0.851
ACE-I/ARB	50 (34.5)	22 (28.6)	28 (41.2)	0.111
Diuretic agent	7 (4.8)	6 (7.8)	1 (1.5)	0.08
Calcium-channel blockers	11 (7.6)	7 (9.1)	4 (5.9)	0.466
Antithrombotic agents	41 (28.3)	16 (20.8)	25 (36.8)	**0.033**
Anticoagulant agents	4 (2.8)	3 (3.9)	1 (1.5)	0.374
Nitrates	3 (2.1)	2 (2.6)	1 (1.5)	0.634
Statins	28 (19.3)	9 (11.7)	19 (27.9)	**0.013**
Amiodarone	0 (80.0)	0 (0)	0 (0)	-
Propafenone	1 (0.7)	0 (0)	1 (1.5)	0.286
Flecainide	0 (0)	0 (0)	0 (0)	-
Sotalol	2 (1.4)	2 (2.6)	0 (0)	0.181
Killip class				0.075
I	135 (93.1)	69 (89.6)	66 (97.0)	
II	1 (0.7)	1 (1.3)	0 (0.0)	
III	1 (0.7)	0 (0.0)	1 (1.5)	
IV	8 (5.5)	7 (9.1)	1 (1.5)	
Site of myocardial infarction				
Anterior myocardial infarction	61 (42.1)	30 (39)	31 (45.6)	0.420
Nonanterior myocardial infarction	84 (57.9)	46 (61)	37 (54.4)	-

Continued on the next page

TABLE 1 Continued

	All Patients (N = 145)	Hp 1-1 or 2-1 (n = 77)	Hp 2-2 (n = 68)	p Value
Myocardial enzymes				
Peak Troponin I, ng/dl	29.1 (14.5–65.8)	25.8 (11.2–57.8)	33.1 (19.1–80.9)	0.134
Time to pPCI, h	2.5 (1.5–5.0)	2.0 (1.5–4.0)	3.0 (1.4–5.1)	0.308
TIMI flow-grade pre-PCI				0.672
0	93 (64.1)	93 (64.1)	44 (64.7)	
1	38 (26.2)	38 (26.2)	13 (19.1)	
2	9 (6.2)	9 (6.2)	7 (10.3)	
3	5 (3.4)	5 (3.4)	4 (5.9)	
TIMI flow-grade post-PCI				0.040
0	2 (1.4)	1 (1.3)	1 (1.5)	
1	4 (2.8)	1 (1.3)	3 (4.4)	
2	11 (7.6)	3 (3.9)	8 (11.8)	
3	128 (88.3)	72 (93.5)	56 (82.4)	
GRACE-risk score (% risk)	3.4 ± 5.6	4.2 ± 7.4	2.4 ± 1.7	0.06

Values are mean ± SD, n (%), or median (confidence interval). **Bold** values indicate significant differences among groups.

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; GRACE = global registry of acute coronary events; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MACE = major adverse cardiac events; pPCI = primary percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 2 TTE and CMR Baseline Characteristics

	All Patients (N = 145)	Hp 1-1 or 2-1 (n = 77)	Hp 2-2 (n = 68)	p Value
TTE baseline characteristics				
LVEDV, ml/m^2	56.2 ± 18.3	55.3 ± 16.7	57.3 ± 19.9	0.521
LVESV, ml/m^2	27.6 ± 13.8	26.9 ± 10.6	28.4 ± 16.7	0.545
LVEF, %	51.9 ± 9.5	51.3 ± 9.3	52.5 ± 9.8	0.432
TAPSE, mm	22.1 ± 3.9	21.8 ± 3.9	22.3 ± 3.9	0.449
PASP, mm Hg	30.1 ± 8.3	30.4 ± 9.1	29.7 ± 7.1	0.693
CMR baseline characteristics				
LVEDV, ml/m^2	82.5 ± 11.9	78.6 ± 17.1	84.6 ± 7.9	0.289
LVESV, ml/m^2	38.2 ± 12.9	35.3 ± 14.5	39.9 ± 12.2	0.468
LVEF, %	49.5 ± 10.5	50.2 ± 9.8	48.8 ± 11.2	0.429
LV mass, g	118.1 ± 33.6	114.8 ± 32.7	121.8 ± 34.8	0.208
RVEDV, ml/m^2	68.6 ± 14.8	67.6 ± 15.3	69.8 ± 14.1	0.361
RVESV, ml/m^2	28.1 ± 10.5	27.4 ± 10.4	28.9 ± 10.7	0.398
RVEF, %	60.1 ± 8.3	60.3 ± 8.7	59.9 ± 7.9	0.824
AAR, g	28.5 (15.3–40.0)	26.4 (10.3–40.7)	29.1 (17.5–39.9)	0.439
AAR, % LV mass	23.2 (14.0–32.6)	23.1 (12.5–33.4)	24.2 (14.2–32.6)	0.633
MH, prevalence	12 (8)	3 (4)	9 (13)	**0.04**
LGE mass, g	15.3 (6.9–22.8)	14.0 (5.3–22.6)	15.9 (8.6–22.9)	0.271
LGE, % LV mass	12.6 (5.6–20.7)	13.2 (4.9–20.7)	12.4 (7.7–20.8)	0.602
MVO, prevalence	38 (26)	11 (14.3)	27 (39.7)	**0.001**
MVO mass, g	1.8 ± 4.8	0.9 ± 2.9	2.8 ± 6.0	**0.015**
MVO mass, % LV mass	1.6 ± 3.8	0.8 ± 2.7	2.5 ± 4.5	**0.006**
MVO mass, % LGE mass	7.3 ± 19.5	2.7 ± 8.6	12.7 ± 26.1	**0.002**
MSI	0.43 ± 0.32	0.44 ± 0.35	0.42 ± 0.30	0.734

Values are mean ± SD, median (confidence interval), or n (%). **Bold** values indicate significant differences among groups.

AAR = area at risk; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MACE = major adverse cardiac events; MH = myocardial hemorrhage; MSI = myocardial salvage index; MVO = microvascular obstruction; PASP = pulmonary artery systolic pressure; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

decubitus position, using a commercially available system (IE33 system, Philips Medical System, Andover, Massachusetts) in the parasternal (long-axis and short-axis) and apical (2-, 3- and 4-chamber) views. An expert reader blinded to patient clinical history performed echocardiography measurements according to the American Society of Echocardiography guidelines (11). For each patient, left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV), wall motion analysis according to 17-segment model proposed by the American Heart Association (AHA) (12), left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery systolic pressure (PASP) were measured.

CMR protocol and analysis. All patients were studied with a 1.5-T scanner (Discovery MR450, GE Healthcare, Milwaukee, Wisconsin) within 1 week after pPCI. All CMR data were transferred to a dedicated workstation (CMR 4.2, Calgary, Canada) and were evaluated twice by an expert reader (M.G.) with more than 5 years of experience in CMR performance and analysis. Another expert reader (G.P.) with more than 5 years of experience in CMR performance and analysis repeated the data evaluation to measure intraobserver and interobserver variability. The scan protocol was performed according to the guidelines of the Society of Cardiovascular Magnetic Resonance (13).

The following indexes were calculated from the short axis cine images: LVEDV, LVESV, LVEF, LV mass, right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV), and right ventricular ejection fraction (RVEF). Breath-hold black-blood T2-weighted short inversion-time inversion-recovery fast spin-echo (T2-weighted imaging) was performed with the same prescription of cine CMR images. T2-weighted image quality using a 4-grade score was performed: 1 = poor, 2 = moderate, 3 = good, and 4 = excellent. Exams with a score 1 were excluded. Myocardium with a signal intensity >2 SD above the mean signal intensity of remote noninfarcted myocardium was considered the area at risk (AAR) and it was measured as absolute mass and as a percentage of entire LV mass (14). Moreover, the black-blood T2-weighted images were used to define MH as a hypoenhanced region within the AAR. When present, MH was included in the hyperintense myocardium for AAR quantification. Afterward, 0.1 mmol/kg of Gadolinium-BOPTA (Multihance, Bracco, Milan, Italy) was administered at a flow rate of 3 ml/s followed by 20 ml of saline flush. Ten minutes

after injection of contrast material, breath-hold contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo sequences were acquired with the same prescriptions for cine-images to detect late gadolinium enhancement (LGE) (15). The inversion time was individually adjusted to null normal myocardium. On post-contrast imaging, the following steps were followed to detect LGE and MVO as showed in **Figure 2**: Step 1: LV endocardial and epicardial border were manually detected; Step 2: LGE was automatically marked by dedicated software with threshold approach considered to be present if signal intensity of the hyperenhanced myocardium was >5 SD above the mean signal intensity of remote myocardium (16); Step 3: the area of LGE automatically detected was manually overviewed and eventually corrected; Step 4: MVO was defined as the hypoenhanced region within the LGE area and was quantified by careful manual delineation of this hypoenhanced region. Both LGE and MVO were finally measured as absolute mass and as percentage of entire LV mass.

STATISTICAL ANALYSIS. Statistical analysis was performed with SPSS version 23 (SPSS Inc., Chicago, Illinois) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± SD or median (25th to 75th percentile) as appropriate and discrete variables as absolute numbers and percentages. Intraobserver and interobserver variability for the evaluation of CMR variables were defined by the intraclass coefficient correlation.

Because of the relatively small size of the cohort and the resulting inadequate power to assess the effects of the 3 individual phenotypes, we prespecified that the combined Hp1-1 and Hp2-1 group (or non-Hp2-2) would be compared with the high-risk Hp2-2 phenotype for all analyses. Student's independent *t*-tests or Mann-Whitney tests were used as appropriate to compare continuous variables among patients with different Hp phenotypes. Comparisons among groups of discrete variables were performed by chi-square or Fisher exact test if the expected cell count was <5. Binary logistic regression was used to assess the association between baseline covariates and the Hp phenotype (results presented as odds ratio [OR] and 95% confidence interval [CI]). Variables with $p < 0.10$ at univariable analysis were then included as covariates in multivariable analysis. A receiver-operating characteristic (ROC) was performed to evaluate the accuracy of Hp phenotype to predict reperfusion myocardial injury. All tests were 2-tailed, and a value of $p < 0.05$ was considered to be statistically significant.

TABLE 3 Univariable and Multivariable Predictors of Presence of MVO

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	p Value	HR (95% CI)	p Value
Demographic characteristics				
Age, yrs	1.00 (0.97–1.04)	0.959	-	-
Male	0.97 (0.39–2.41)	0.954	-	-
Body mass index, kg/m^2	0.84 (0.74–0.95)	**0.007**	0.78 (0.67–0.92)	**0.002**
Hp phenotypes genotypes				
Hp 2-2 vs. Hp 1-1 or 2-1	3.95 (1.77–8.81)	**0.001**	5.58 (2.14–14.56)	**<0.001**
Cardiovascular risk factors				
Hypertension	0.64 (0.30–1.36)	0.245	-	-
Current or previous smoking	1.69 (0.78–3.64)	0.183	-	-
Hyperlipidemia	1.10 (0.51–2.38)	0.802	-	-
Diabetes	2.58 (1.02–6.52)	**0.045**	3.24 (1.02–10.33)	**0.047**
Family history of CAD	1.27 (0.52–3.09)	0.596	-	-
Medication before hospital admission				
Beta-blockers	1.20 (0.50–2.90)	0.687	-	-
ACE-I/ARB	0.98 (0.45–2.15)	0.967	-	-
Diuretic agents	0.46 (0.05–3.91)	0.473	-	-
Calcium-channel blockers	0.26 (0.03–2.12)	0.209	-	-
Antithrombotic agents	1.05 (0.46–2.37)	0.915	-	-
Anticoagulant agents	-	-	-	-
Nitrates	1.42 (0.13–16.11)	0.778	-	-
Statins	1.16 (0.46–2.91)	0.752	-	-
Amiodarone	-	-	-	-
Propafenone	-	-	-	-
Flecainide	-	-	-	-
Sotalol	2.87 (0.18–46.97)	0.461	-	-
Killip class	1.36 (0.85–2.18)	0.199	-	-
Site of myocardial infarction				
Anterior wall	2.07 (0.98–4.38)	**0.057**	1.89 (0.77–4.64)	0.166
Myocardial enzymes				
Peak troponin I, ng/ml (increase of 10 ng/ml)	1.090 (1.034–1.149)	**0.001**	1.08 (1.01–1.15)	**0.019**
Time to pPCI, min	1.00 (0.95–1.05)	0.954	-	-
TIMI flow-grade pre-PCI	0.67 (0.38–1.19)	0.171	-	-
TIMI flow-grade post-PCI	0.49 (0.26–0.95)	**0.035**	0.46 (0.21–1.04)	0.063
GRACE risk score (% risk)	1.00 (0.99–1.02)	0.410	-	-

Bold values indicate significant differences among groups.

AAR = area at risk; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CMR = cardiac magnetic resonance; GRACE = global registry of acute coronary events; LGE = late gadolinium enhancement; LVEDV = left ventricle end-diastolic volume; LVEF = left ventricle ejection fraction; LVESV = left ventricle end-systolic volume; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; MH = myocardial hemorrhage; MVO = microvascular obstruction; PASP = pulmonary artery systolic pressure; RVEDV = right ventricle end-diastolic volume; RVEF = right ventricle ejection fraction; STEMI = ST-segment elevation myocardial infarction; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

RESULTS

The baseline characteristics are listed in **Table 1**. The mean Killip class was 1.2 ± 0.7, and the overall GRACE-risk score was 3.4 ± 5.6%. The mean LVEF at TTE and CMR were 51.9 ± 9.5% and 49.5 ± 10.5% (**Table 2**), respectively. In addition, CMR showed an

TABLE 4 Univariable and Multivariable Predictors of MVO ≥2.6% of Left Ventricle Myocardial Mass

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	p Value	HR (95% CI)	p Value
Demographic characteristics				
Age, yrs	1.02 (0.98–1.06)	0.399	-	-
Male	0.38 (0.11–1.36)	0.137	-	-
Body mass index, kg/m^2	0.90 (0.79–1.03)	0.111	-	-
Hp phenotypes genotypes				
Hp 2-2 vs. Hp 1-1 or 2-1	7.36 (2.61–20.75)	**0.001**	11.70 (3.13–43.67)	**<0.001**
Cardiovascular risk factors				
Hypertension	0.66 (0.28–1.53)	0.329	-	-
Current or previous smoking	2.75 (1.09–6.97)	**0.033**	5.34 (1.61–17.78)	**0.006**
Hyperlipidemia	1.03 (0.44–2.44)	0.947	-	-
Diabetes	2.10 (0.77–5.75)	0.147	-	-
Family history of CAD	1.36 (0.52–3.59)	0.532	-	-
Medication before hospital admission				
Beta-blockers	1.29 (0.49–3.39)	0.604	-	-
ACE-I/ARB	1.07 (0.45–2.53)	0.879	-	-
Diuretic agents	0.69 (0.08–5.93)	0.731	-	-
Calcium-channel blockers	0.40 (0.05–3.23)	0.387	-	-
Antithrombotic agents	1.88 (0.79–4.45)	0.154	-	-
Anticoagulant agents	-	-	-	-
Nitrates	2.13 (0.19–24.36)	0.543	-	-
Statins	1.94 (0.75–5.02)	0.172	-	-
Amiodarone	-	-	-	-
Propafenone	-	-	-	-
Flecainide	-	-	-	-
Sotalol	4.30 (0.26–70.88)	0.308	-	-
Killip class	1.24 (0.74–2.06)	0.412	-	-
Site of myocardial infarction				
Anterior wall	2.13 (0.93–4.92)	**0.076**	2.20 (0.76–6.31)	0.144
Myocardial enzymes				
Peak Troponin I, ng/ml (increase of 10 ng/ml)	1.11 (1.05–1.17)	**0.001**	1.13 (1.05–1.22)	**0.001**
Time to pPCI, min	1.02 (0.97–1.07)	0.405	-	-
TIMI flow-grade pre-PCI	0.65 (0.34–1.26)	0.201	-	-
TIMI flow-grade post-PCI	0.38 (0.19–0.75)	**0.005**	0.30 (0.14–0.67)	**0.003**
GRACE risk score (% risk)	1.01 (0.99–1.03)	0.283	-	-

AAR = area at risk; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CMR = cardiac magnetic resonance; GRACE = global registry of acute coronary events; LGE = late gadolinium enhancement; LVEDV = left ventricle end-diastolic volume; LVEF = left ventricle ejection fraction; LVESV = left ventricle end-systolic volume; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; MH = myocardial hemorrhage; MVO = microvascular obstruction; PASP = pulmonary artery systolic pressure; RVEDV = right ventricle end-diastolic volume; RVEF = right ventricle ejection fraction; STEMI = ST-elevation myocardial infarction; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

AAR involving 26.6 ± 19.1% of LV mass, with an LGE extent of 15.2 ± 13.1% of LV mass (Table 2). MVO and MH occurred in 38 (26%) and 12 (8%) of patients (Table 2), respectively.

CMR intraobserver and interobserver intraclass correlation agreement for LVEF, MSI, MVO, and MH detection were 0.86, 0.91, 0.88, 0.82 and 0.83, 0.84, 0.80, 0.75, respectively.

In our study population, 15 (10%) patients had Hp phenotype 1-1, 62 (43%) Hp2-1, and 68 (47%) Hp2-2, consistent with the prevalence reported in the published data. Baseline associations comparing the different Hp phenotypes in study participants clustering Hp1-1 with Hp2-1 are presented in Tables 1 and 2.

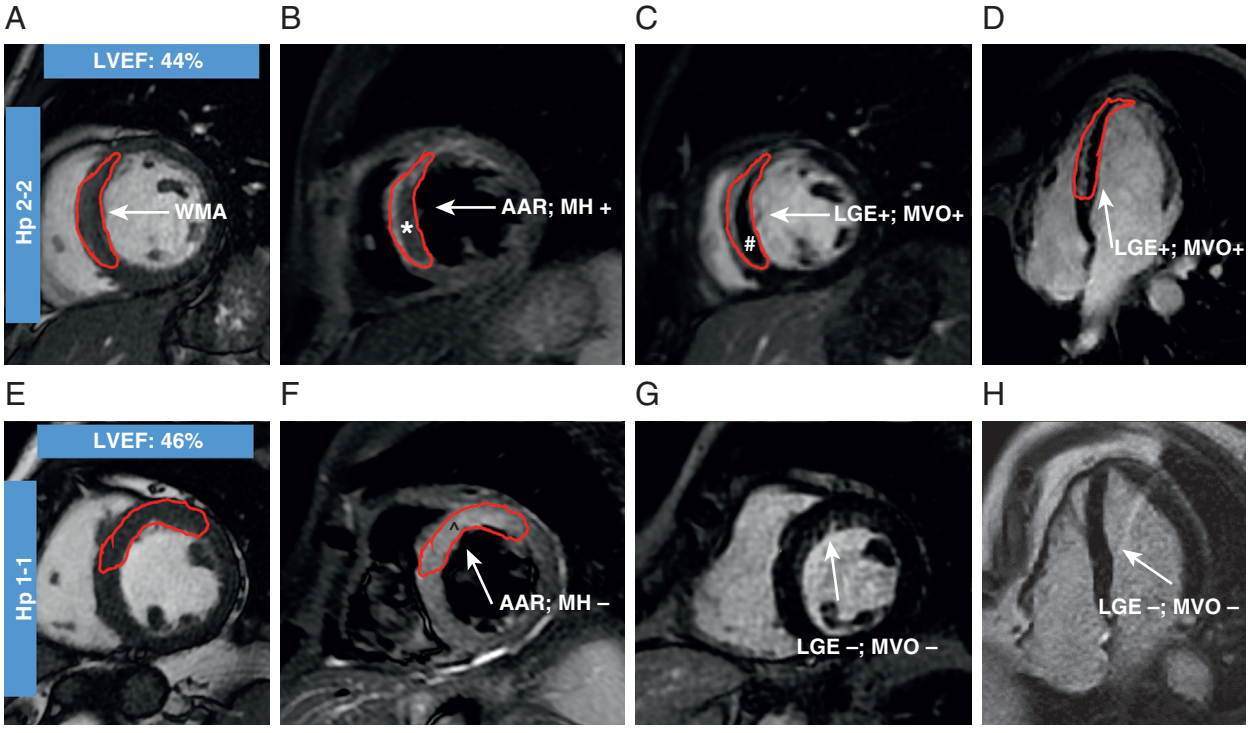
In terms of TTE baseline characteristics, no significant differences were found among groups (Table 2), whereas CMR showed a higher prevalence of MH (13% vs. 4%; p = 0.04) and MVO (39.7% vs. 14.3%; p = 0.001) in patients with Hp2-2 when compared with those without this Hp phenotype (Table 2). Also, patients with Hp2-2 showed higher amounts of MVO expressed as absolute mass (p = 0.015) or relative value normalized to LV mass (p = 0.006) or LGE mass (p = 0.002) compared with patients without this phenotype (Table 2), compared with Hp2-1 and Hp2-2 that showed an MVO prevalence of 17% (10 of 62 patients) and 40 (27 of 68 patients), respectively. Accordingly, univariable analysis showed that BMI, Hp2-2, diabetes, anterior myocardial infarction, peak troponin I, and TIMI flow-grade post-PCI were all predictors of MVO (Table 3). Including all variables that clustered patients with MVO with a value of p < 0.10 and correcting for baseline demographic characteristics, multivariable analysis demonstrated that BMI, Hp2-2, diabetes, and peak troponin I were independent predictors of MVO (Table 3). Hp2-2 phenotype was associated with the highest OR to predict MVO (OR: 5.58 [95% CI: 2.14 to 14.56]; p < 0.001) (Table 3). Moreover, MVO was still an independent predictor of an MVO extent ≥2.6% of LV mass (OR: 11.70 [95% CI: 3.13 to 43.67]; p < 0.001) (Table 4) that has been shown to be associated with poor prognosis (8). In the subset of patients with late revascularization (>3 h from onset of symptoms), the cluster of Hp1-1 and Hp2-1 phenotype was associated with a lower prevalence (8.6% vs. 41.7%) and amount of MVO (1 ± 3.6% vs. 3.1 ± 5.4% of LV mass and 3.1 ± 10.7% vs. 15.5 ± 32.5% of LGE mass) compared with the Hp2-2 group (Figure 2). The ROC showed that Hp2-2 significantly predicted the presence of MVO (AUC: 0.63 [95% CI: 0.53 to 0.72]; p = 0.008) and MVO ≥2.6% LV mass (AUC: 0.63 [95% CI: 0.54 to 0.72]; p = 0.007), a validated prognostic threshold (8).

Figures 3 and 4 show representative cases of STEMI in patients with Hp1-1 or Hp2-2 phenotype, respectively. Despite similar baseline characteristics in terms of LVEF, patients with Hp2-2 always showed MVO that was not present in patients with Hp1-1.

DISCUSSION

The main findings of our study are that myocardial injury expressed by the presence and extent of

FIGURE 3 **Cardiac Magnetic Resonance of 2 Patients With Hp2-2 and Hp1-1 Phenotypes After Anterior STEMI and Successful pPCI**

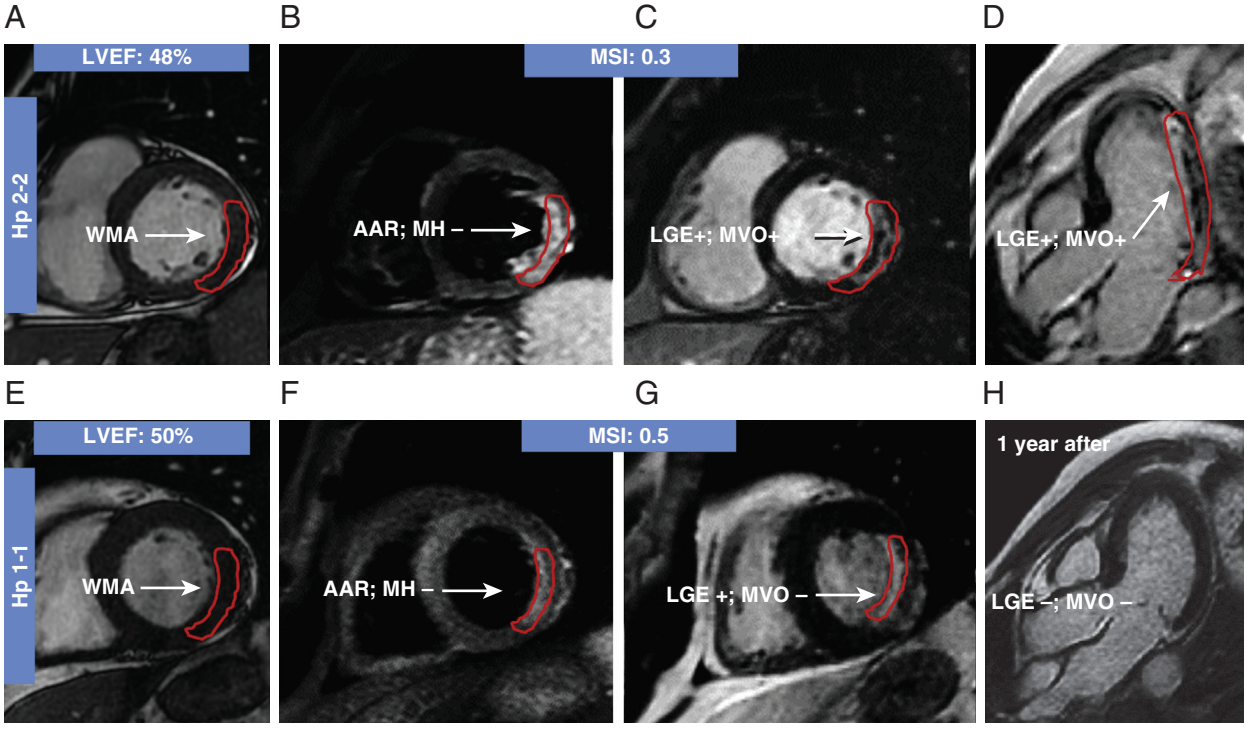


The **top row** shows a patient with Hp2-2, the **bottom row** shows a patient with Hp1-1. The presentation was similar in the 2 cases, but CMR showed different features. **(A and E)** Steady-state free precession cine sequences of LV short-axis to detect WMA. **(B and F)** Black-blood T2-weighted short inversion-time inversion-recovery fast spin-echo sequences to detect AAR and MH. **(C, D, G, H)** Contrast enhanced segmented T1-weighted inversion-recovery gradient-echo sequences in LV short and long axis to detect LGE and MVO. Despite similar baseline characteristics and LVEF for Hp2-2 and Hp 1-1 (44% vs. 46%, respectively), the Hp2-2 patient showed both MH **(*)** and MVO **(#)** that were not present in Hp1-1 patient. AAR = area at risk; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MH = myocardial hemorrhage; MVO = microvascular obstruction; MSI = myocardial salvage index; pPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; WMA = wall motion abnormalities.

MVO after pPCI in consecutive patients with STEMI is Hp phenotype dependent, Hp2-2 being the strongest predictor of MVO. To the best of our knowledge, this is the first demonstration of a correlation between myocardial reperfusion injury as detected by CMR and Hp phenotypes in human subjects.

Several studies were published regarding the prognostic value of CMR in post-STEMI patients showing that both MVO (1,17-19) and MH (20) have emerged as key variables to risk stratify patients after STEMI. TIMI risk score is able to predict MVO and prognosis (21), but it underestimates the prevalence of MVO compared with CMR (22). CMR is an excellent tool to detect MVO with high sensitivity and specificity and with an excellent correlation with adverse remodeling and death (23,24). Therefore, identification of additional early and easy measurable determinants of reperfusion injury beyond door-to-balloon time is crucial to better risk stratify these patients. Hp is α2-glycoprotein that is present in humans with 3 predominant phenotypes– Hp1-1, Hp2-1, and Hp2-2–that showed 2 potential cardioprotective mechanisms that may be of clinical relevance, such as antioxidant properties and neo-angiogenesis induction (4). Moussa et al. (25) found an association between Hp2-2 phenotypes and significant coronary stenosis. Chapelle et al. (26) found an increase in severity but not in frequency of acute MI in Hp2-2 versus other phenotypes. The Strong Heart study found a borderline statistical significance link between Hp2-2 phenotype and cardiovascular events in patients with diabetes (27). In addition, Haas et al. (28) showed that the presence of Hp2-2 and low plasma levels (below 1.4 g/l) of Hp were associated with a higher

FIGURE 4 Cardiac Magnetic Resonance of 2 Patients With Hp2-2 and Hp1-1 Phenotypes After Lateral STEMI and Successful pPCI



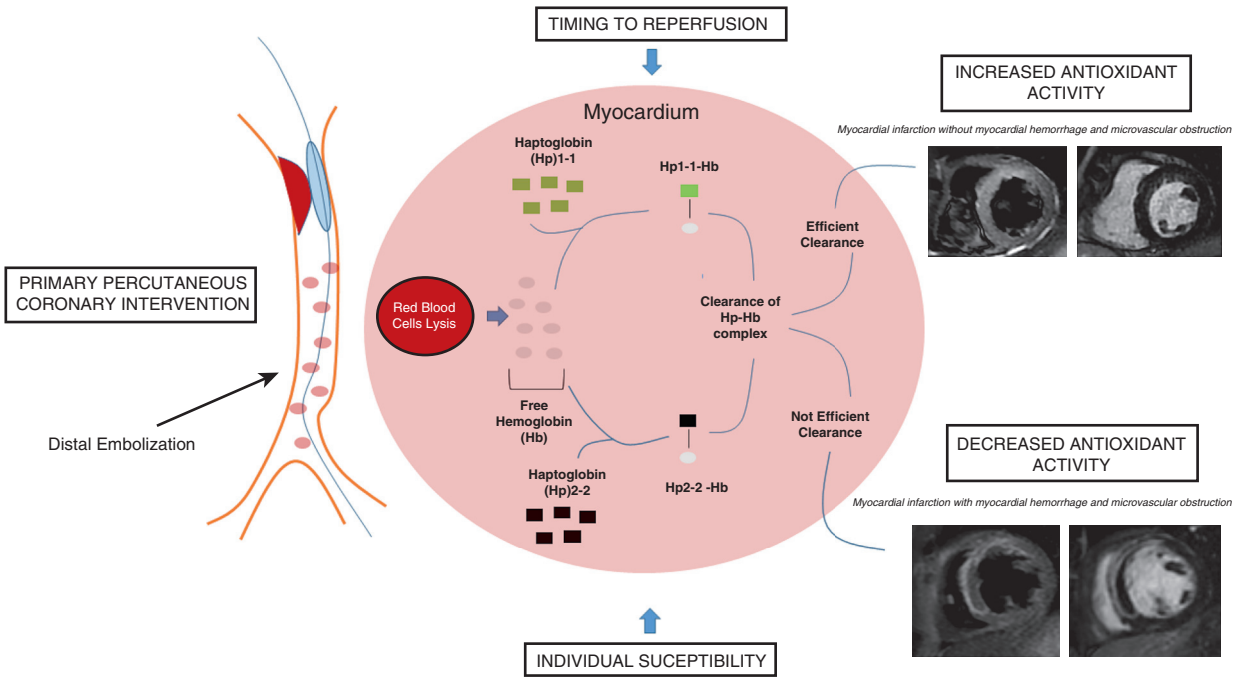
The **top row** shows a patient with Hp2-2, the **bottom row** shows a patient with Hp1-1. The presentation was similar in the 2 cases, but CMR showed different features. **(A and E)** Steady-state free precession cine-sequences of LV short-axis to detect WMA. **(B and F)** Black-blood T2-weighted short inversion-time inversion-recovery fast spin-echo sequences to detect AAR and MH. **(C, D, G)** Contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo sequences in LV short and long axis to detect LGE and MVO. Despite similar baseline characteristics and LVEF for Hp 1-1 and Hp 2-2 (48% vs. 50%, respectively), the Hp2-2 patient showed MVO **(arrows)** that were not observed in the Hp1-1 patient. **(H)** CMR 1 year after STEMI showed no LGE in lateral wall in Hp11 patient. Abbreviations as in Figure 3.

risk of heart failure and poor functional outcomes following STEMI. Some experimental evidences support this hypothesis that antioxidant and anti-inflammatory functions of the Hp 1 and Hp 2 allelic proteins can determine infarct size (29).

Our study is the first to demonstrate the association between Hp and reperfusion injury in consecutive patients with STEMI after pPCI as expressed by MVO detected by CMR, regardless of diabetes status. Indeed, we found that the Hp 1 allele is associated with a lower prevalence and extent of MVO. Of note, it does not appear to have impact on LGE extent and MSI. Several studies showed that MVO is a more robust predictor of adverse remodeling and poor outcome compared with LGE extent and MSI (8). The evidence that different Hp forms are related to reperfusion injury as detected by MVO and MH could be explained by function of Hp as the scavenger of free hemoglobin. In a genetically modified animal model, Arslan et al. (30) observed a higher mortality in Hp−/− mice despite similar infarct size among groups. Death was commonly caused by cardiac rupture in Hp−/− animals, and histological analysis revealed more frequent and more severe intramural hemorrhage and increased leukocyte infiltration in Hp−/− mice. Moreover, analyses of nonruptured hearts revealed increased oxidative stress and enhanced vascular endothelial growth factor.

The influence of Hp phenotype on reperfusion injury after STEMI could have several clinical implications. First, a potential use could be to screen high-risk patients with Hp2-2. As a result, in this subset of patients with known Hp2-2, the primary prevention strategy based on vitamin E supplementation could provide significant cardiovascular protection in case of STEMI. In this regard, Blum et al. (31) showed that patients with Hp2-2 and diabetes

FIGURE 5 Summary of Potential Correlation Between Haptoglobin Phenotypes and Reperfusion Injury



The picture shows the potential mechanisms involving haptoglobin that are responsible for the myocardial reperfusion injury in revascularized patients with ST-segment elevation myocardial infarction.

derived significant cardiovascular protection from vitamin E supplementation. Indeed, diabetes and Hp2-2 play a synergic role in the downregulation of CD163 that is pivotal in Hb clearance (32). This suggests that antioxidant therapy may provide benefit only to a selected population with markedly increased oxidative stress such as patients with diabetes and/or Hp2-2 phenotype. Second, in patients with STEMI, a quick identification of Hp phenotype could define a subset of patients in which potential therapeutic strategy, such as direct Hp1-1 infusion or targeted therapy against Hp2-2, could be developed. Thus, personalized medicine based on Hp genotyping could enable customized approaches to alleviate myocardial damage. However, replication of these data and dedicated prospective studies in a larger sample size are required to confirm the findings from the current study. **Figure 5** shows a summary describing correlation between Hp phenotypes and reperfusion injury.

STUDY LIMITATIONS. First, the proportion of patients with specific Hp phenotype in our population was too small to allow conclusions in all 3 groups separately. Consequently, tests of interaction were underpowered, especially when adjusted for covariates. Therefore, bias from residual confounding factors could still be present. Second, we did not perform systematic follow-up with CMR in these patients. Indeed, evaluation of LV remodeling at discharge and follow-up could be very useful to test the clinical impact of our data. Third, we only studied the Hp phenotype. Therefore, no conclusion can be made regarding the impact of Hp plasma levels that were found to correlate with the occurrence of heart failure after MI (28). Fourth, AAR and MH were detected by dark-blood T2-weighted images that may have been affected by imaging artifacts. On the contrary, both T1 and T2 mapping may overcome this limitation. However, black-blood T2-weighted images are still the most widely used techniques in clinical practice because they are more easily applicable compared with a model including mapping sequences. Of note, we included only patients with CMR exams showing adequate CMR image quality. Fifth, the absence of correlation between time to reperfusion and MVO could be

explained by the potential influence of prodromal angina. Sixth, we have excluded patients with previous histories of MI. The reason is that when myocardial necrosis occurred in an area already damaged by a previous infarction, the 2 areas of LGE cannot be distinguished, and therefore a potential confounding factor could be present.

Finally, the characterization of Hp is time consuming. Indeed, in our study, we carried out the Hp phenotyping by immunoblotting, which requires a whole day of analysis. To this end, we are developing a rapid and robust Hp phenotyping that may be useful in the setting of patients with acute damage.

CONCLUSIONS

Hp phenotyping may be used as a tool for risk stratification and may be useful in assessing new therapies that attempt to reduce myocardial reperfusion injury after pPCI in patients with STEMI. Indeed, it would be beneficial to have a rapid diagnostic assay that could identify the Hp phenotypes, allowing for potential therapeutic intervention. Thus, Hp phenotyping may provide a personalized approach to alleviating myocardial damage.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The goal of pPCI in patients with STEMI is to restore blood flow to ischemic myocardium and to reduce infarct size. However, reperfusion therapy with pPCI may cause additional injury that is not due to the ischemic period. Haptoglobin is a plasma protein that binds extracorpuscular hemoglobin and prevents iron-mediated oxidative tissue damage. In humans, 3 distinct protein phenotypes exist: Hp1-1, Hp1-2, and large cyclic multimeric Hp2-2. Hp 2-2 was reported to be less efficient than Hp 1-1 in binding Hb and preventing oxidation by stabilizing heme iron within Hb, thereby displaying lower antioxidant activity. Recently, CMR has emerged as the gold standard technique to detect the MVO and MH. These variables have been shown to predict functional recovery and the risk of cardiovascular events regardless of the recanalization result of the culprit epicardial coronary artery. The main findings of our study are that myocardial injury expressed by the presence and extent of MVO after pPCI in consecutive patients with STEMI is Hp phenotype dependent, Hp2-2 being the strongest predictor of MVO.

TRANSLATIONAL OUTLOOK: The influence of Hp phenotype on reperfusion injury after STEMI has several clinical implications. Indeed, Hp phenotyping may be used as a tool for risk stratification and may be useful in assessing new therapies that attempt to reduce myocardial reperfusion injury after pPCI in patients with STEMI. Thus, Hp genotyping may provide a personalized approach to alleviating myocardial damage.

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