Automated Chemiluminescent Hair Cortisol Measurement and Its Association with Acute Myocardial Infarction: A Case-Control Study in Latin American Adults

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Abstract

Background: Chronic and psychosocial stresses are the emerging factors linked to cardiovascular disease. Assessment of cortisol levels in hair can serve as an indicator of an individual's exposure to prolonged stressful events. For its evaluation, mass spectrometry is the reference method. However, because of its limitations for clinical laboratories, an automated chemiluminescent method was developed in our laboratory. The objective of the study is to evaluate the hair cortisol levels measured by an automated method and its association with psychosocial stress and cardiometabolic risk factors in a Latin American population. **Materials and Methods:** Hair samples were obtained from 56 consecutive patients hospitalized with an ST-segment elevation acute myocardial infarction (STEMI) and 56 consecutive controls randomly recruited in routine consultation. Perceived stress and social support were evaluated by the validated questionnaires. Hair cortisol was measured by an automated chemiluminescent method. Glycemia and lipoprotein profile were measured in serum samples. **Results:** Hair cortisol was significantly higher in patients than in controls (175 [40–424] vs. 60.5 [40–155] pg of cortisol/mg of hair [$P < 0.001$]). Hair cortisol was not related to age or body mass index; however, it was related to glycemia ($r = 0.461$, $P < 0.001$) and triglycerides/high-density lipoprotein cholesterol (TGs/HDL-c) index ($r = 0.398$, $P = 0.001$). Perceived stress was related to hair cortisol ($r = 0.425$, $P < 0.001$), age ($r = 0.321$, $P = 0.01$), and social support ($r = -0.208$, $P = 0.028$). TGs/HDL-c index and perceived stress partially explain hair cortisol variation ([$F = 8.69$, $P = 0.004$] and [$F = 24.9$, $P < 0.001$], respectively). **Conclusion:** We observed higher hair cortisol concentrations, measured by an automated method, in STEMI patients than in controls in a Latin American population. In addition, it was related to perceived stress and cardiometabolic parameters.

Keywords: Acute myocardial infarction, automated method, hair cortisol, perceived stress, social support, triglycerides/high-density lipoprotein cholesterol index

Introduction

Despite a significant reduction over the last few years, cardiovascular disease (CVD) continues to be the first leading cause of morbid-mortality worldwide,[1] mainly in low-and middle-income countries.[2,3] There is growing evidence that chronic stress and psychosocial stress are the emerging risk factors linked not only with CVD[4,5] and myocardial infarction (MI),[6] but also with other risk factors such as diabetes mellitus,[7] hypertension,[8] obesity,[9] and smoking[10] among others. In Latin America, psychosocial stress was found to be more associated with MI compared to other world regions.[11]

At least, there are three different ways to study stress: self-report questionnaires, external observation by a professional and biomarkers. Most studies are carried out through self-administered questionnaires and interviews

Received: 28-06-2024; **Accepted:** 21-01-2025; **Published:** 24-02-2025

Access this article online

Quick Response Code:

Website: journals.lww.com/hhmi

DOI: 10.4103/hm.HM-D-24-00099

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How to cite this article: Fernandez Machulsky N, Colla J, Gonzalez D, Fortuna F, Ibar C, Jamardo J, *et al*. Automated chemiluminescent hair cortisol measurement and its association with acute myocardial infarction: A case-control study in Latin American adults. Heart Mind 2025;9:13-20.

Key question

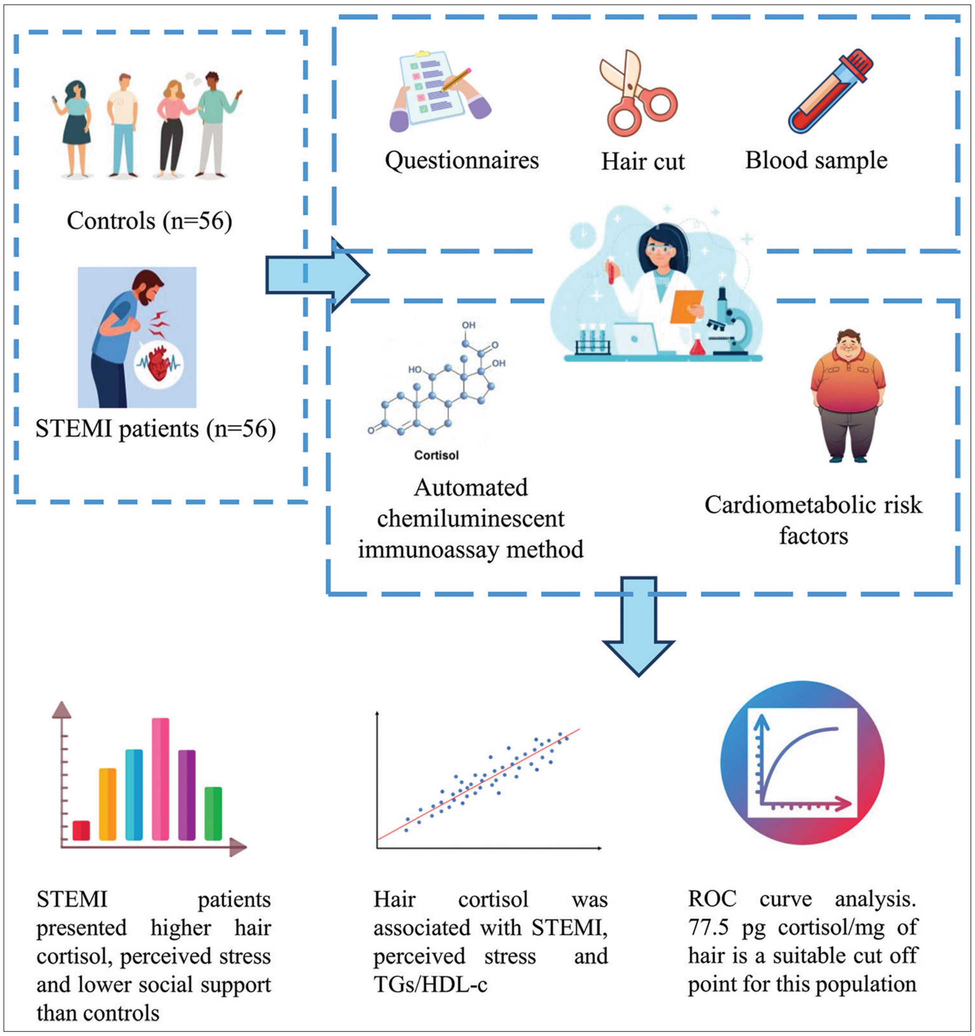
How does psychosocial stress impact cardiovascular disease risk, especially in Latin America population? What role does hair cortisol play in assessing stress and cardiovascular risk?

Key finding

STEMI patients had higher hair cortisol levels, linked to perceived stress and cardiometabolic risk factors. Hair cortisol is a potential biomarker for stress-related cardiovascular risk.

Message for readers

This study emphasizes the significant role of chronic stress in cardiovascular health. Understanding stress biomarkers like hair cortisol can help predict STEMI risk and guide interventions to improve cardiovascular health and quality of life.



Central Illustration: Case-control study of the association of hair cortisol with STEMI and cardiometabolic factors in Latin American patients. STEMI=ST-segment elevation acute myocardial infarction, TGs/HDL-c=Triglycerides/high density lipoprotein cholesterol, ROC=Receiver operating characteristics, pg=Picogram, mg=Milligram

by professionals, through which different stressors and psychosocial factors are studied such as work stress, social isolation, perceived stress, hostility, depression, and social support among others that have been found related to CVD.[12] However, new technologies, such as cell phone applications[13] and biomarkers such as cortisol in alternative matrices, are being increasingly used.

Hypothalamic–pituitary–adrenal (HPA) axis is essential to stress response in humans. This process occurs through a cascade of hormonal reactions involving the hypothalamus, the pituitary gland, and the adrenal cortex, which produce cortisol as the main end product of the axis. One of the key factors connecting CVD with chronic stress is the dysregulation of the HPA axis.[12] Prolonged and repeated cortisol exposure is maladaptive in humans and could lead to long-term physiological alterations in cardiovascular, metabolic, immune, and nervous systems.[14] In relation to CVD, repeated cortisol exposure is related to hyperlipidaemia, insulin resistance, hyperglycemia, hypertension, and abdominal adiposity.[15] Therefore, cortisol assessment for the evaluation of the HPA axis is essential. In particular, the study in alternative biological matrices, such as hair, appears to be useful,[16-20] given the fact that 3 cm of hair would reflect cortisol levels to which the individual was exposed in the past 3 months. Hair cortisol was recently associated with acute coronary syndrome,[21] MI[22,23] and coronary heart disease.[24] It was also related to several cardiometabolic risk factors.[25] Mass spectrometry is the gold standard methodology for its evaluation,[26] but it is expensive and less affordable to clinical laboratories. In order to overcome this limitation, an automated method for hair cortisol measurement was successfully developed in our laboratory,[27] allowing a large number of samples to be processed in a short period of time.

Psychosocial factors potentially relate psychological phenomena to the social environment and to pathophysiological changes[28] have been extensively studied in relation to CVD. Among them, social support and perceived stress have been studied in the CVD populations.[29,30] These factors have been studied in relation to hair cortisol,[31,32] and related to CVD in different populations worldwide[24,33-35] but not in a Latin American country.

Considering this context, our aim was to evaluate the possible association of psychosocial stress (social support and perceived stress) and cardiometabolic risk factors, in a case-control ST-segment elevation acute MI (STEMI) adult population from Latin America, with hair cortisol level measured applying for the first time by an automated chemiluminescent immunoassay.

Materials and Methods

The present case-control study was conducted between April 2017 and December 2018 (period of recruitment and data collection) in the Argerich Hospital, located in Buenos Aires, Argentina. Inclusion criteria: (a) Adults (≥18 years) patients with STEMI admitted to Argerich Hospital and referred for primary angioplasty within 24 h of symptoms onset characterized by prolonged chest pain and ST-segment elevation ≥1 mm in at least two consecutive leads, or a new or presumed new left bundle branch block. (b) Adults (≥18 years) healthy controls attending an annual routine check consultation at the Argerich Hospital with no reported major mental disorders and with no reported CVD. Exclusion criteria: patients and controls with HPA alterations, treatment with glucocorticoids, cancer, stroke or other severe inflammatory disease and with insufficient hair length (<3 cm) on the vertex area of the scalp. One healthy control was enrolled for each STEMI patient, who was not matched for age or sex. The studied population included 56 consecutive patients (37 males, 57 ± 11 years and 19 females, 60 ± 10 years) and 56 consecutive controls (20 males, 46 ± 16 years and 36 females, 47 ± 15 years). Clinical details were recorded for all patients using a pro forma, which included demographic data, smoking status, coronary risk factors, previous clinical history, and treatment. Previous MI was established by evidence of previous hospital admission and a discharge diagnosis of MI.[36]

Biochemical parameters such as fasting glycemia, total cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), creatinine phosphokinase (CPK), and CPK MB fraction (CPK-MB) were measured in serum by COBAS C-501 autoanalyzer. Blood samples were taken with 8 h of fasting, the morning after the admission between 8:00 and 9:00 am. Serum was separated

Table 1: Clinical characteristics of the studied population

	Controls (n = 56)	STEMI patients (n = 56)	P
Age (years)	42 (26–80)	59 (35–88)	< 0.001
Male (percentage)	20 (35.7)	37 (66.1)	0.002
BMI (kg/m^2)	24.8 (18–42)	27.7 (18–39)	0.020
Perceived stress (score)	7 (2)	11 (3)	< 0.001
Social support (score)	16 (3)	14 (3)	0.016
Hair cortisol (pg of cortisol/mg of hair)	60.5 (40–155)	175 (40–424)	< 0.001
Glycemia (mg/dL)	98 (79–130)	131 (40–416)	< 0.001
TG (mg/dL)	82 (37–194)	108 (25–436)	0.055
TC (mg/dL)	184 (31)	202 (38)	0.047
HDL-c (mg/dL)	60 (19)	42 (8)	< 0.001
LDL-c (mg/dL)	109 (26)	133 (40)	0.003
TGs/HDL-cholesterol index	1.55 (0.41–4.85)	2.24 (0.42–13.21)	0.003
Smokers (percentage)	4 (7)	36 (64)	< 0.001
Acetylsalicylic acid (percentage)	2 (3.6)	7 (12.5)	0.237
β-blockers (percentage)	0 (0)	10 (17.8)	-
Statins (percentage)	8 (14.3)	4 (7.1)	0.614

Data are expressed as mean±SD, median (range) or n (%). Differences were evaluated by Student's t-test, Mann–Whitney or Chi-square test, respectively. P < 0.05 was considered statistically significant. STEMI=ST-segment elevation acute myocardial infarction, BMI=Body mass index, HDL-c=High-density lipoprotein cholesterol, LDL-c=Low-density lipoprotein cholesterol, SD=Standard deviation, TGs=Triglycerides, TC=Total cholesterol by centrifugation at 1500 × *g* for 10 min and stored at −70°C until measured.

Coronary angiography and primary angioplasty were performed according to the standard protocols and techniques. All patients were referred to the catheterization laboratory, hemodynamic unit, within 30 min after arriving at the Emergency Department, where they received 100 mg of acetylsalicylic acid, 300 mg of clopidogrel, and intravenous nitroglycerin. The infarct size was determined based on the territory at risk as indicated by the electrocardiographic findings; a large AMI was defined as involving more than four electrocardiographic leads with Grade 3 ischemia.[37] Killip and Kimbal index was evaluated.

After angioplasty, when patients were in a lucid state, we assessed their perceived stress[38] and social support[39] by validated questionnaires. The social support scale presented adequate internal reliability with a Cronbach's alpha of 0.837. Meanwhile, the perceived stress questionnaire presented Cronbach's alpha of 0.504. The total scores for each scale were computed.

Hair samples were obtained with scissors from the posterior vertex as close to the scalp as possible. Three centimeters were collected to evaluate the hair cortisol levels over the past 3 months. Each sample was stored in a paper envelope at the room temperature until processing. Once the samples were obtained, three centimeters were measured from the root segment adjacent to the cutting. For the cortisol extraction, briefly, 50 mg of hair were weighed and placed in a glass tube with 4 mL of methanol for an overnight steroid extraction. After incubation, the supernatant was collected and evaporated at the room temperature for 2 days. The dry remnant was reconstituted by adding the diluent recommended by the manufacturer and cortisol was measured using an automated chemiluminescent method (Immulite 2000 autoanalyzer, Siemens, LA, USA) according to the standardized procedure developed in our laboratory and reported by Gonzalez *et al*.[27] The results were expressed in pg/mg.

We first tested the distribution of variables using normality tests (kurtosis and skewness and Shapiro–Wilk test). Hair cortisol and TG/HDL-c index data were not normally distributed and log transformed values were thus used for inferential analyses. Only for descriptive purposes, data in tables and figures are presented in the original units. Results are expressed as mean ± standard deviation or median (range) according to data distribution. Mean and median differences were evaluated by *t*-test or Mann–Whitney test, respectively. The categorical variables were evaluated with the Chi-square test. Pearson and Spearman correlations were computed between the independent and dependent variables. A regression analysis was performed to evaluate if TG/HDL-c index and perceived stress could explain the variation of hair cortisol concentration. We tested the unstandardized residuals for normality to perform the regression analysis. To evaluate the association between hair cortisol and STEMI, a binary regression analysis was performed. To assess the hair cortisol cutoff point, we performed a receiver operating characteristics (ROCs) curve. The optimal cutoff value was determined by considering the values that maximize sensitivity and specificity. Statistical analysis was performed using IBM SPSS Statistics Version 25.0 (IBM Co., Armonk, NY, USA). $P < 0.05$ was considered statistically significant. The study size was arrived at using Power and Sample Size (PS) Calculation program from Vanderbilt University.

Results

The clinical characteristics of the studied population are presented in Table 1. Notably, hair cortisol and perceived stress scores were higher in STEMI patients than in controls; meanwhile, social support scores were lower. Hair cortisol was not related to age or body mass index (BMI) in controls and patients [Figure 1]; however, it was higher in males than females (187 [40–424] vs. 121 [48–296]) pg cortisol/mg of hair ($P = 0.014$)), only in STEMI patients. By performing a binary logistic regression, we observed that hair cortisol was associated with STEMI (odds ratio: 1.032, 95% confidence interval [CI]: [1.019–1.045], $P < 0.001$).[40,41]

Concerning studied biochemical parameters, hair cortisol was directly associated with fasting glycemia ($r = 0.461$, $P < 0.001$), TGs ($r = 0.338$, $P = 0.005$), and TGs/HDL-c index ($r = 0.398$, $P = 0.001$) and inversely associated with HDL-c ($r = -0.409$, $P < 0.001$) in the whole population. In STEMI patients, it was directly related to fasting glycemia ($r = 0.276$, $P = 0.050$) and TGs/HDL-c index ($r = 0.330$, $P = 0.027$). TGs/HDL-c index explained 11.6% of the variation of hair cortisol levels ($F = 8.69$, $P = 0.004$).[40,41]

Regarding the psychosocial factors studied in the whole population, perceived stress score was directly related to hair cortisol ($r = 0.425$, $P < 0.001$), age (r = 0.321, $P = 0.01$), fasting glycemia ($r = 0.465$, $P < 0.001$), and inversely related to social support ($r = -0.208$, $P = 0.028$) and HDL-c ($r = -0.324$, $P = 0.007$); meanwhile, social support was related inversely with BMI ($r = -0.217$, $P = 0.022$) but not with hair cortisol ($r = -0.176$, $P = 0.065$) or age ($r = -0.158$, $P = 0.098$). Concerning the differences by sex, we found that males had more perceived stress scores than females (11 [3–16] vs. 7 [3–14] score, $P < 0.001$). In relation to these results, when dividing the population by group, we did not find association with hair cortisol, BMI, or age in controls, although social support was inversely related to BMI ($r = -0.272$, $P = 0.045$) in STEMI patients. In a linear regression analysis, we observed that perceived stress explains up to 18.5% of hair cortisol levels variation in our population ($F = 24.9$, $P < 0.001$). The characteristics of the STEMI population are presented in Table 2. Perceived stress was inversely related to the ejection fraction ($r = -0.539$, $P = 0.001$); social support score was lower in patients with a higher degree of Killip and Kimbal index at admission (Class I vs. Class II + III + IV; [12 (9–18) vs. 15 (5–20) score, $P = 0.019$]).

After verifying that hair cortisol is related to STEMI by the binary regression analysis, a ROC curve was tested. As it can be observed in Figure 2, the area under the curve was 0.872 with a 95% CI: 0.808–0.936 ($P < 0.001$). Figure 2 shows that 77.5 pg cortisol/mg of hair is a suitable cutoff point for this population. This value corresponds to a sensitivity of 87.5%, a specificity of 62.5%, a positive predictive value of 70% and a negative predictive value of 83.4%.

Dividing the studied population by the aforementioned cutoff, we observe that patients with hair cortisol over 77.5 pg cortisol/mg had higher perceived stress (10 [3] vs. 8 [3], $P = 0.003$), glycaemia ([128 (72–416) vs. 101 (40–313) mg/dL], $P = 0.003$), TGs ([108 (25–436) vs. 77 (37–201) mg/dL], $P = 0.045$), TGs/HDL-c index (2.20 [0.40–13.2] vs. 1.51 [0.41–4.85], $P = 0.018$) and lower HDL-c ([44 (13) vs. 54 (17) mg/dL], $P = 0.01$).

All patients considered for this study met all the inclusion and exclusion criteria detailed in the materials and methods section. There were no missing data for the present study in the enrolled patients.

Table 2: Clinical characteristics of ST-segment elevation acute myocardial infarction patients

Variable	STEMI patients (n = 56)
Systolic blood pressure (mmHg)	129 (27)
Diastolic blood pressure (mmHg)	75.4 (14.5)
Heart rate (bpm)	79.6 (18.2)
CPK basal (U/L)	999.5 (72–7,725)
CPK peak (U/L)	2,876.1 (477–7,776)
CK-MB basal (U/L)	139 (20–806)
CK-MB peak (U/L)	276.5 (48–806)
Ejection fraction (%)	47 (14–61)
Location of MI	
Inferior	25 (44)
Anterior	25 (44)
Combined	4 (8)
Lateral	2 (4)
Size of MI (established by ECG)	
Large	36 (64)
Small	20 (36)
Killip and Kimbal classification at admission	
Killip Class I	44 (78)
Killip Class II	11 (20)
Killip Class III	0 (0)
Killip Class IV	1 (2)
Killip Class II + III + IV	12 (22)

Data are expressed as mean±SD, median (range) or *n* (%). MI=Myocardial infarction, STEMI=ST-segment elevation acute MI, ECG=Electrocardiogram, CPK=Creatinine phosphokinase, CPK-MB=Creatinine phosphokinase-MB fraction, SD=Standard deviation

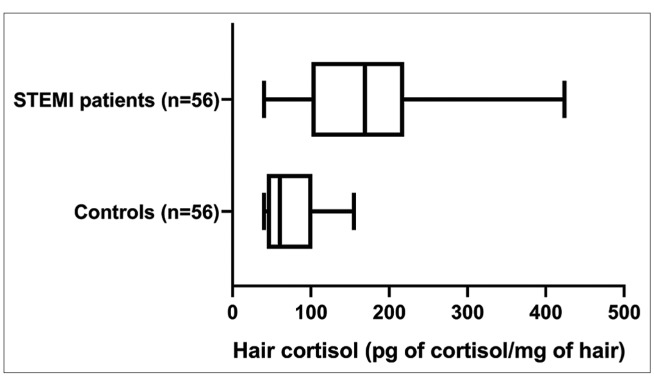


Figure 1: Hair cortisol concentration in the studied populations. Mann–Whitney test $P < 0.001$. STEMI=ST-segment elevation acute myocardial infarction

Discussion

This study examines the association among hair cortisol, measured by an automated chemiluminescent immunoassay method, social support and perceived stress, and different biochemical parameters in a case-control Latin American STEMI population. Our results show that patients with STEMI presented significantly higher hair cortisol than healthy controls. Moreover, hair cortisol was related to STEMI, perceived stress, and cardiometabolic risk factors such as glycemia and TGs/HDL-c index, which in addition to perceived stress partially explained the hair cortisol levels variation in our population.

Hair cortisol was proposed as a biomarker of psychosocial stress,[18] being consistent with a long term HPA-axis activity, considering that hair typically grows approximately 1 cm per month, a 3 cm length of hair would correspond to cortisol levels indicative of exposure to stress over the past 3 months.[20] Being proposed as one of the underlying causes of the deleterious effect of chronic stress on CVD, the dysregulation of the HPA axis[12] could be better assessed with hair cortisol.[42] Even though hair cortisol levels were associated with AMI[22] and acute coronary syndrome,[21] in both cases, nonautomated immunoassays were applied.

Previously, in our laboratory, studying healthy volunteers, we did not observe differences in hair cortisol associated with sex[31] in accordance with other groups.[26,43,44] However, in the large cohort study Whitehall II,[45] higher levels of hair

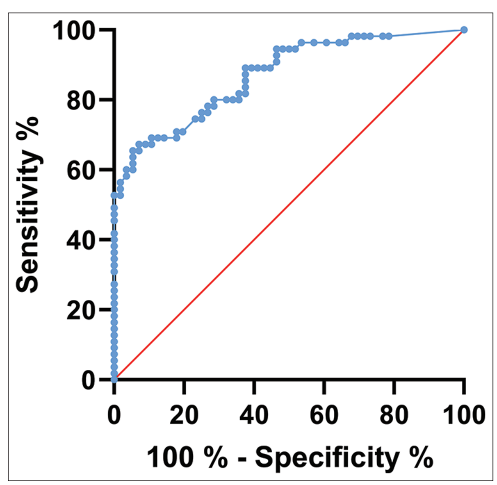


Figure 2: Receiver operating characteristic curve. Hair cortisol as a predictor of STEMI was tested. The area under the curve was 0.872 with a 95% CI: 0.808–0.936 ($P < 0.001$). STEMI=ST-segment elevation acute myocardial infarction, CI=Confidence interval

cortisol were observed in men, using a column switching LC-APCI-MS/MS assay. Our present results would be in accordance with the latter, since men presented higher hair cortisol levels than women. Moreover, the disaggregate study Interheart in Latin America showed a higher association of stress as a risk factor for MI in men than in women.[11]

Furthermore, we do not find associations between hair cortisol and age. In this matter, controversial results have been observed with negative,[31] positive,[46] and no association[42] between hair cortisol and age. Regarding BMI, Stalder *et al*.[47] reported a positive association with hair cortisol. Our study shows similar results considering the whole population; however, no association was observed when dividing population by STEMI. This controversy could be due to the number of patients in our study.

Concerning cardiometabolic risk factors, our results are in agreement with those obtained by other researchers which showed the association of hair cortisol with metabolic syndrome, insulin resistance and diabetes mellitus[48] but controversial results regarding lipoprotein profile[48,49] whose relation varies according to the population studied. In our case, we found that hair cortisol was directly associated with TGs, inversely with HDL-c and not associated with LDL-c. Moreover, TGs/HDL-c index, which is a secondary marker of insulin resistance[50] could partially explain hair cortisol variation in our population. There are scores, like intermountain risk score and the Naples score that combine cardiometabolic risk factors with hematological and anthropometric parameters, which have been shown to be good predictors of STEMI mortality.[51-53] Their association with hair cortisol remains to be studied.

Regarding the associations between perceived stress and hair cortisol, previous studies reported that trauma experienced in childhood, but not perceived stress, was associated with hair cortisol among older adults with coronary artery disease.[24] On the contrary, in healthy workers, an association between perceived stress and hair cortisol was reported.[31] In this opportunity, we found a direct association between this psychosocial factor, age, and hair cortisol in the entire population. Interestingly, we found an inverse association between perceived stress score and ejection fraction. Iob *et al*.[32] showed that people who reported lower positive or greater negative social support had higher levels of cortisol. We did not observe a relationship between social support and hair cortisol in this population. It is important to highlight the inverse association between social support and BMI only in the STEMI population.

Automated measurement of hair cortisol could be considered an interesting tool for the approach to the HPA axis function. We performed a ROC curve to obtain a cutoff point with an adequate sensitivity and specificity. As a first approximation to its use, we observed that patients exceeding the hair cortisol cutoff value had higher perceived stress and cardiometabolic markers more associated with CVD. The cutoff obtained in our study could be used for screening in the future research to demonstrate the potential of stress management programs to reduce CVD risk.

Limitations

There are some limitations in our study, such as the number of patients recruited and the differences in sex and age between groups. In this study, we use the short version of Cohen's Perceived Stress Scale (PSS-4) to evaluate perceived stress, which in our population presented a low Cronbach's alpha. We selected the PSS-4 scale rather than longer versions like the PSS-10 or PSS-14 scale, which may offer better reliability, since the PSS-4 scale is less time-consuming, making it more suitable for rapid clinical data collection. Due to the low reliability, we recommend precaution in the interpretation of results concerning Perceived Stress. In the statistical analysis, we may have underestimated the effect of confounding variables, mainly age and gender, on the results. Nevertheless, this study emphasizes the importance of the measurement of hair cortisol on patients with STEMI, relating it to psychosocial factors and highlighting the impact of dysregulation of the HPA axis in CVD. Besides, this is the first time that this analysis is performed in STEMI patients applying an inexpensive, accessible, automated chemiluminescent immunoassay method.

Conclusion

We observed higher hair cortisol levels, measured by an automated chemiluminescent immunoassay method, in STEMI patients than in controls. In addition, it was related to perceived stress and to various cardiometabolic markers. Hence, we propose this automated method as an approach to study the HPA-axis function in CVD patients.[40-41]

Author contributions

Nahuel Fernandez Machulsky did literature research, experimental studies, data and statistical analysis, manuscript preparation, editing, and review. Julian Colla did literature research, clinical and experimental studies, data acquisition, and analysis. Diego Gonzalez did clinical and experimental studies, data analysis, and manuscript preparation. Federico Fortuna did experimental studies, data analysis, and manuscript preparation. Carolina Ibar did experimental studies, data analysis, and statistical analysis. Juan Jamardo did clinical and experimental studies and data acquisition. Juan Gagliardi did concepts, design, literature research, and manuscript review. Bibiana Fabre did concepts, design, definition of intellectual content, literature research, statistical analysis, manuscript editing, and review. Gabriela Berg did concepts, design, definition of intellectual content, literature research, manuscript editing, review, and guarantor.

Ethical statement

The studies were performed in accordance with the Declaration of Helsinki, and all procedures were carried out with the adequate understanding and written informed consent obtained from all the participants. The protocol was approved by the Ethics Committee of the Argerich Hospital (0740290/2011) and the Faculty of Pharmacy and Biochemistry, University of Buenos Aires (0740290/2011) on June 10, 2014, and November 18, 2011, respectively. Clinical trial registration was waived because of the study's retrospective design.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

This work was supported by a grant from the Universidad de Buenos Aires, Argentina (UBACYT: 20020150100033BA; 2020–2023) and from the Agencia Nacional de Promoción Científica y Tecnológica (ANPCYT) PICT 2016-0920 and PICT 2019-0930.

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