Myocardial perfusion SPECT as a potential mediator on circulating chromogranin A in patients with old myocardial infarction

Xanthi Xourgia[1] MD, PhD
Spyridon Tsiouris[1] MD, PhD
Theofilos Kolettis[2] MD, PhD
Ioannis Goudevenos[2] MD, PhD
Angelos Arseniou[2] MD, PhD
Andreas D. Fotopoulos[1] MD, PhD

1. Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece
2. First Department of Cardiology, University Hospital of Ioannina, Ioannina, Greece

Keywords: Chromogranin A
- Myocardial infarction
- Myocardial perfusion SPECT

Corresponding author:
Xanthi Xourgia, MD, PhD
University Hospital of Ioannina
Nuclear Medicine Dept.
Stavros Niarchos Avenue
Ioannina 455 00, GREECE
Tel.: +30 26510 99379
xanthi.xourgia@gmail.com

Received:
24 April 2021
Accepted revised:
11 June 2021

Abstract

Objective: Chromogranin A (CgA) is a soluble polypeptide stored within and released from secretory granules of endocrine and other cell types (including cardiomyocytes); CgA appears to be a marker of the overall neuroendocrine activity. Increased levels of serum CgA have been found not only in patients with neuroendocrine neoplasms but also with other malignancies, hypertension, myocardial infarction, heart, or renal failure. **Subjects and Methods:** A population of 307 patients (202 males, 105 females) was enrolled. The study group consisted of 118 individuals (38.4%) with myocardial infarction more than one year old (MI group); the remaining 189 (61.6%) had no known heart disease (control group). All patients underwent myocardial perfusion scintigraphy (MPS) after blood withdrawal for serum CgA measurement. To test whether a possible effect of old infarction on serum CgA is mediated by MPS findings, we employed analysis of co-variance for three distinct categories of left ventricular (LV) perfusion deficits as dichotomous predictors: (1) any-type deficits (abnormal MPS); (2) reversible deficits (ischemia); and (3) fixed deficits (scar). **Results:** In all three MPS conditions, the effect of age, gender, and LV ejection fraction (EFLV) on serum CgA was statistically significant: women exhibited higher CgA levels than men (P=0.008-0.023), whereas increasing age and decreasing EFLV were associated with increasing CgA (all P<0.001). Conversely, no statistically significant differences in mean CgA levels were found between MI patients and normal controls with either abnormal MPS, scar, or ischemia, or their degree and extent. **Conclusions:** Although serum CgA is significantly associated with age, gender, and EFLV in patients with an old MI, no association was found between CgA levels and either old MI history or MPS findings. The verified involvement of circulating CgA in the acute/subacute phase of infarction appears to be blunted in infarctions older than a year.

Hell J Nucl Med 2021; 24(2): 114-121 *Epub ahead of print: 6 August 2021* *Published online: 27 August 2021*

Introduction

Chromogranin A (CgA), the major member of the granin family, is a soluble hydrophilic polypeptide of 439 aminoacids, with a molecular weight of 48 kDa. It was discovered in the 1960s in chromaffin granules in the core of the adrenal medulla [1, 2]. Nowadays, CgA is the most extensively studied of all granins and our understanding of its structure and function has considerably increased. Chromogranin A is present all over the neuroendocrine system, in endocrine secretory cells, in central and peripheral neurons, and also in the diffuse endocrine system (DES) [3-5]. The pituitary gland and the parathyroid glands are CgA-rich, though CgA is also present in endocrine cells in the thyroid gland, the pancreas, and the placenta [6]. Chromogranin-A is coexpressed with hormones and neurotransmitters and it is stored within secretion granules among catecholamines or other hormones [7]. There is evidence of an intracellular and extracellular CgA function as a prohormone with autocrine, paracrine, and endocrine activities [8].

The first measurement of human serum CgA by radioimmunoassay was performed four decades ago in patients with pheochromocytoma; CgA levels were found elevated in 80-90% of the cases [9]. Radioimmunoassay is a reliable method of serum CgA measurement that has proven useful for the diagnosis and prognosis of neuroendocrine neoplasms (NEN) but it is also considered a diagnostic and prognostic marker for several diseases including tumors (e.g. prostate cancer), or failure of various organs (kidney, liver, and heart) [10,11].

Increased serum CgA is also observed in patients with acute or subacute myocardial infarction (MI); it correlates with cardiac dysfunction and is considered predictive of increased mortality in patients with chronic heart failure, possibly because it reflects on neuroendocrine activation [12,13]. In this study, we investigated serum CgA in patients with an

old MI, examining for a possible association between this biomarker and the findings of myocardial perfusion scintigraphy (MPS).

Subjects and Methods

Study population

The enrolled population consisted of 307 individuals (202 males [65.8%] and 105 females [34.2%]) that were submitted to myocardial perfusion imaging by single-photon emission computed tomography (SPECT) in the nuclear medicine department of a tertiary hospital over 39 months. All referred patients fulfilled the official indications to undergo the examination for the diagnosis of coronary artery disease (CAD) and left ventricular (LV) ischemia and were classified into two groups: those with a previous type I infarction with or without electrocardiographic ST-segment elevation (STEMI and non-STEMI [NSTEMI], respectively, according to the fourth universal definition of MI [14]), dating at least one year earlier (MI group, n=118); and those with no known previous history of cardiovascular disease (control group, n=189). Patients with diagnoses or clinical conditions known to interfere with serum CgA (e.g. malignancy, liver or renal failure, inflammatory bowel disease, proton pump inhibitor medication) were excluded from the study [10,11]. A complete transthoracic echocardiography study was performed in every patient shortly before MPS, with the calculation of the ejection fraction (EF) of the LV (EFLV) by the biplane Simpson's method and reporting of regional wall motion abnormalities.

The study protocol and MPS SPECT procedure were explained in detail to the enrolled patients and they granted their informed consent to participate. The study followed the ethical principles of the Declaration of Helsinki and was approved by the Ethical Committee of the hospital.

Myocardial perfusion scintigraphy

The patients were submitted to MPS SPECT according to the imaging guidelines of the European Association of Nuclear Medicine and Molecular Imaging (EANMMI) and the American Society of Nuclear Cardiology (ASNC) [15,16]. Stress and rest images were acquired on the same day (one-day protocol). Any medications containing nitrates, beta-blockers, calcium channel antagonists, and methyl-xanthines were discontinued for 24 hours. Patients were fasting for at least 4 hours before the exam and abstained from caffeine and other methyl-xanthine-containing beverages for 24 hours.

All studies were performed with the technetium-99m (^{99m}Tc)-labeled radiopharmaceutical tetrofosmin (^{99m}Tc-TF) (Myoview, GE Healthcare AS, Oslo, Norway) that was radiolabelled in-house according to the manufacturer's instructions. The stress test protocol was selected according to the patient's characteristics (age, exercise tolerance, administered medications, etc.). Maximal or symptom-limited treadmill exercise (Bruce protocol) was performed in suitable patients. In those individuals that maximal treadmill exercise was not feasible or was contraindicated, pharmacological stress was carried out instead, mostly by intravenous (IV) administration of the vasodilative agent dipyridamole (0.56 mg/kg body weight, alone or in combination with a single-stage Bruce treadmill walk), or by the IV inotropic dobutamine in a small proportion of patients. The time interval between stress and rest imaging was 2 hours on average.

Two experienced board-certified nuclear medicine physicians performed in-consensus assessment of each MPS scan, blinded to clinical or other information (except echocardiography) and sought for an agreement, resolving possible discrepancies by discussion. Image reading involved the visual assessment of the presence and extent of LV perfusion abnormalities. The results were categorized as normal (including MPS with borderline or equivocal findings) and abnormal. Further categorization of abnormal findings included fully reversible deficits (indicating ischemia), irreversible (or fixed) deficits, and partially reversible (or mixed) deficits. An irreversible deficit on MPS could represent a myocardial scar or an artifact (photon attenuation by the breast or the diaphragm, left bundle branch block [LBBB], apical thinning, etc). The reporting physicians characterized every fixed deficit as a scar or an artifact, taking also into consideration the motion findings of the corresponding wall in the preceding recent echocardiography; the MPS studies that exhibited only findings deemed as artifacts were classified as normal. Depending on the number of segments with abnormal perfusion, the extent of every MPS abnormality (ischemia, fixed deficit, etc.) was characterized as small (1-2 segments, or <10% of the LV myocardium), medium (3-4 segments, or 10-20%), or large (≥5 segments, or >20%), respectively [17,18].

In addition to visual reading, semiquantitative analysis was also performed in all scans. Regarding their degree, myocardial perfusion deficits were graded on a 5-point scale of tracer uptake, ranging from 0 (normal uptake) to 4 (absence of uptake) and the 17-segment LV model was used to calculate the summed stress score (SSS) and the summed rest score (SRS). The summed difference score (SDS) was calculated by subtraction of SRS from SSS, representing the degree of reversible deficits, while SRS was used as an indicator of the irreversible (fixed) ones. An SDS>3 was considered abnormal, with a further categorization of the perfusion abnormality degree as mild (SDS=3-4), moderate (SDS=5-6), or significant (SDS>6)[18,19].

Serum CgA measurement

On the day of the exam, before SPECT, all patients had a blood sample drawn by a peripheral antecubital vein for serum CgA measurement. This was centrifuged at 3000 rpm for 10 min and the serum was separated and refrigerated at -20°C until analyzed. Chromogranin A was measured using a solid-phase, two-site radioimmunometric assay according to the manufacturer's instructions (CgA-RIA CT, CIS Bio International, Saclay, France), with a sensitivity of 1.5 ng/mL. All measurements were performed in duplicate and their average was used for the analysis. The radioactivity was counted in a scin-

tillator gamma-counter (Wizard2, Perkin Elmer Inc., Shelton, CT, USA). Serum CgA levels <98 ng/mL were considered as normal.

Statistical analysis

The 2-sample Student's t-test for continuous variables and the chi-square (χ^2) test for categorical variables were used to examine for differences between the MI and the control group. Multivariate logistic regression was performed to assess the association between CgA (as the dependent variable) and several predictors: age, gender, smoking, hypertension, diabetes, hypercholesterolemia, EFLV, medications, and MI.

To test whether the effect of infarction on serum CgA could be mediated by the findings of MPS, we employed analysis of covariance (ANCOVA) –after adjusting for differences in age, gender, and EFLV– for the following three distinct categories of LV perfusion deficits as dichotomous predictors: (1) presence of deficits of any type (abnormal MPS); (2) presence of reversible deficits (ischemia); and (3) presence of fixed deficits (scar). The analyses were performed with CgA as the dependent variable that was log-transformed to 100*ln(CgA) to approximate the normal distribution. The gender and MI were also introduced as dichotomous predictors, whilst the covariates age and EFLV were standardized to 1 standard deviation (SD) (Z-age, Z-EFLV).

Continuous quantitative variables are expressed as mean ± SD, or percentages for categorical variables. All data analyses were performed using the software SPSS v.23 (IBM, Armonk, NY, USA). For the analysis of covariance, the MIXED procedure in SPSS was used, whereas custom SPSS syntax was used to estimate model-implied effects (along with their standard errors and levels of significance) not directly provided by the software output. Levels of P-values lower than 0.05 were considered significant.

Results

Patient characteristics

The 307 enrolled patients (aged 65.5±10.0 years) were classified in the MI group (n=118, or 38.4%) and the control group (n=189, or 61.6%). Their respective demographic, clinical and imaging data are displayed in Table1. In the former group, the elapsed time since infarction was 6.4±6.3 years (range, 1-23). Specifically, it was 1-2 years in 43 (36.4%), 2-5 in 23 (19.5%), 5-10 in 22 (18.7%), and over 10 years in 30 (25.4%). The majority of patients with prior MI had been managed with coronary revascularization (percutaneous coronary intervention [PCI] and/or coronary artery bypass grafting [CABG], n=95, or 80.5%), while 23 (19.5%) had received optimal medical therapy alone. Pharmacologic vasodilation by dipyridamole was the cardiac stress protocol performed in the majority of cases (n=224, or 72.9%), either alone, or in combination with mild treadmill exercise. The Bruce treadmill exercise protocol was performed in 80 patients (26.1%) and only 3 (1.0%) received the dobutamine stress test.

MPS imaging findings

Expectedly, the rate of normal MPS scans was significantly higher in the control group than in the MI group (77.8 vs. 31.4%, P<0.001). From the semiquantitative LV perfusion analysis, the vast majority (93.1%) of individuals in the control group had no or only minor abnormal findings on rest SPECT (SRS<4), while this percentage was 52.6% in the MI group. No patients in the control group had a significantly abnormal rest scan (SRS>14), with only one exhibiting a mildly abnormal scan (SRS=9); on the other hand, 37 patients (28.8%) in the MI group had moderate or significant perfusion findings on rest imaging. As regards the degree of ische-

Table 1. *Patient characteristics.*

Parameter	MI group (n=118)	Control group (n=189)	P-value
Gender (Male/Female)	105/13	97/92	<0.001
Age (years)	66.0±9.8	65.2±9.8	0.45
Active smoker	30 (25.4%)	39 (20.6%)	0.33
Hypertension	106 (89.8%)	136 (71.9%)	<0.001
Hypercholesterolemia	105 (89.0%)	108 (57.1%)	<0.001
Diabetes	37 (31.3%)	43 (22.7%)	0.09
EFLV (%)	53.7±10.3	66.2±5.6	<0.001
Serum CgA (ng/ml)	172.4±176.1	103.8±120.3	<0.001
Normal MPS	37 (31.4%)	147 (77.8%)	<0.001

mia, the proportion of patients with mild (SDS<3), moderate (SDS=3-4), or significant (SDS>6) abnormality in the MI group was significantly higher than that in the control group (34.7%, 14.4%, and 19.5% vs. 14.3%, 4.7%, and 3.2%, respectively; P<0.001).

Association of serum CgA with demographic, clinical, and imaging parameters

Multivariate logistic regression analysis revealed that age, gender, and EFLV had significant association with serum CgA (P= 0.025, P= 0.001 and P<0.001, respectively). On the contrary, smoking, hypertension, diabetes, medications, and hypercholesterolemia were not found to have any effect, hence they were not included as predictors in the covariance models.

The parameter estimates for each of the three log-transformed models are provided in Tables 2-4. In all three models, the effect of gender was unconditional and statistically significant, with females exhibiting higher mean CgA levels than males (P=0.008 to 0.023); the effects of age and EFLV were also unconditional and statistically significant, with 1 SD increase in age associated with increased CgA and 1 SD increase in EFLV associated with decreased CgA (all P<0.001).

Due to its interaction with all three potential MPS mediators (abnormal MPS, ischemia, or scar), no statistically significant differences in the mean CgA levels were found between MI patients and normal controls in either of the three MPS categories. Specifically, among patients with infarction, those with normal MPS scans tended to exhibit higher CgA levels compared to those with abnormal MPS but the difference did not reach significance levels (P=0.086; Table 2 & Figure 1). Likewise, neither MI patients with ischemia vs. those without, nor MI patients with scar vs. those without scar exhibited significant differences in serum CgA (Tables 3, 4 & Figures 2, 3). Non-significant differences were found also in the control group (Tables 2-4 & Figures 1-3). Since none of the analysis of covariance models proved any of the three studied MPS factors to be a significant mediator of the effect of old MI on circulating CgA, further covariance analysis on the same effect for other MPS-related factors (namely the extent and degree of perfusion deficits) was waived.

Table 2. *Analysis of covariance for the effect of abnormal MPS (any-type perfusion deficits) on serum CgA in patients with an old infarction.*

						95% Confidence Interval	
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	465.14	13.09	300	35.529	**<0.001**	439.37	490,90
[gender=male]	-25.01	10.97	300	-2.279	**0.023**	-46.60	-3.42
[gender=female]	0[a]	0	.	.	.	.	.
[MI=no]	-18.30	16.26	300	-1.126	0.261	-50.30	13.69
[MI=yes]	0[a]	0	.	.	.	.	.
[MPS=normal]	32.09	18.65	300	1.720	0.086	-4.62	68.80
[MPS=abnormal]	0[a]	0	.	.	.	.	.
Z–age	17.18	4.55	300	3.774	**<0.001**	8.22	26.14
Z–EFLV	-27.39	5.74	300	-4.771	**<0.001**	-38.69	-16.09
[MI= no] * [MPS=normal]	-24.59	23.55	300	-1.044	0.297	-70.94	21.76
[MI= no] * [MPS=abnormal]	0	0	.	.	.	.	.
[MI=yes] * [MPS=normal]	0	0	.	.	.	.	.
[MI=yes] * [MPS=abnormal]	0	0	.	.	.	.	.

[a] *refers to the reference group. The effect of MI is conditional specifically on its interacting predictor set to 0 (MPS=abnormal).*

Table 3. *Analysis of covariance for the effect of ischemia on serum CgA in patients with an old infarction.*

						95% Confidence Interval	
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	470.32	13.26	300	35.479	**<0.001**	444.23	496.41
[gender=male]	-25.88	11.01	300	-2.352	**0.019**	-47.54	-4.22
[gender=female]	0[a]	0	.	.	.	.	.
[MI=no]	-23.29	16.40	300	-1.420	0.157	-55.56	8.99
[MI=yes]	0[a]	0	.	.	.	.	.
[ischemia=no]	8.37	15.29	300	0.547	0.585	-21.72	38.45
[ischemia=yes]	0[a]	0	.	.	.	.	.
Z–age	17.67	4.56	300	3.873	**<0.001**	8.69	26.65
Z–EFLV	-25.76	5.69	300	-4.528	**<0.001**	-36.94	-14.56
[MI= no] * [ischemia=no]	-1.53	21.32	300	-0.072	0.943	-43.48	40.42
[MI= no] * [ischemia=yes]	0	0	.	.	.	.	.
[MI=yes] * [ischemia=no]	0	0	.	.	.	.	.
[MI=yes] * [ischemia=yes]	0	0	.	.	.	.	.

[a] refers to the reference group. The effect of MI is conditional specifically on its interacting predictor set to 0 (ischemia=yes).

Table 4. *Analysis of covariance for the effect of scar on serum CgA in patients with an old infarction.*

						95% Confidence Interval	
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	478.14	14.91	300	32.073	**<0.001**	448.81	507.48
[gender=male]	-27.70	10.32	300	-2.683	**0.008**	-48.02	-7.38
[gender=female]	0[a]	0	.	.	.	.	.
[MI=no]	-19.04	12.78	300	-1.490	0.137	-44.19	6.11
[MI=yes]	0[a]	0	.	.	.	.	.
[scar=no]	-6.14	15.47	300	-0.397	0.692	-36.58	24.29
[scar=yes]	0[a]	0	.	.	.	.	.
Z–age	17.50	4.54	300	3.859	**<0.001**	8.58	26.43
Z–EFLV	-24.74	6.21	300	-3.985	**<0.001**	-36.96	-12.52
[MI= no] * [scar=no]	0	0	.	.	.	.	.
[MI=yes] * [scar=no]	0	0	.	.	.	.	.
[MI=yes] * [scar=yes]	0	0	.	.	.	.	.

[a] refers to the reference group. The effect of MI is conditional specifically on its interacting predictor set to 0 (scar=yes).

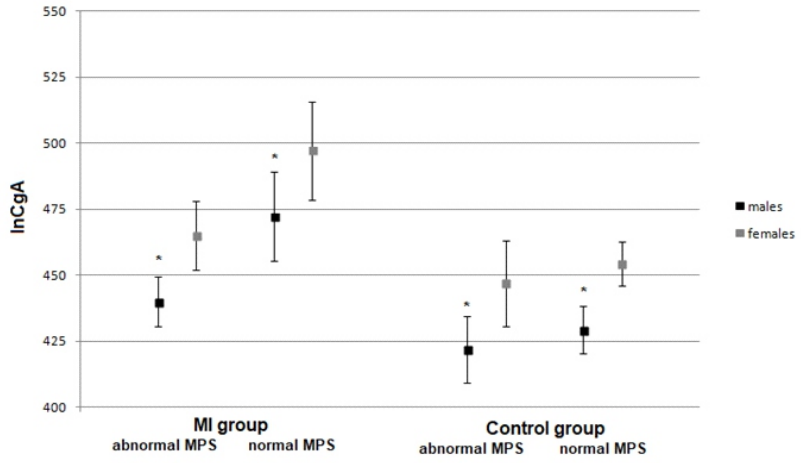

Figure 1. Log-transformed serum CgA in patients with normal or abnormal MPS in the two study groups. Ln(CgA) levels are provided as mean ± SD (*P<0.05 for males vs. females).

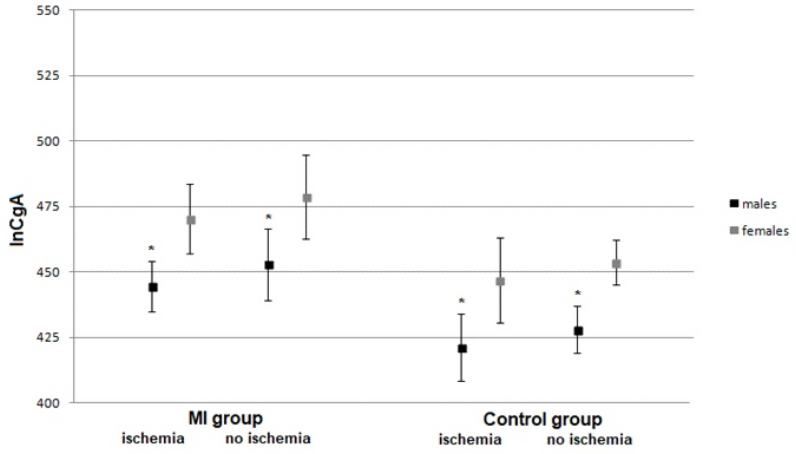

Figure 2. Log-transformed serum CgA in patients with or without presence of reversible perfusion deficit (ischemia) in the two study groups. Ln(CgA) levels are provided as mean ± SD (*P<0.05 for males vs. females).

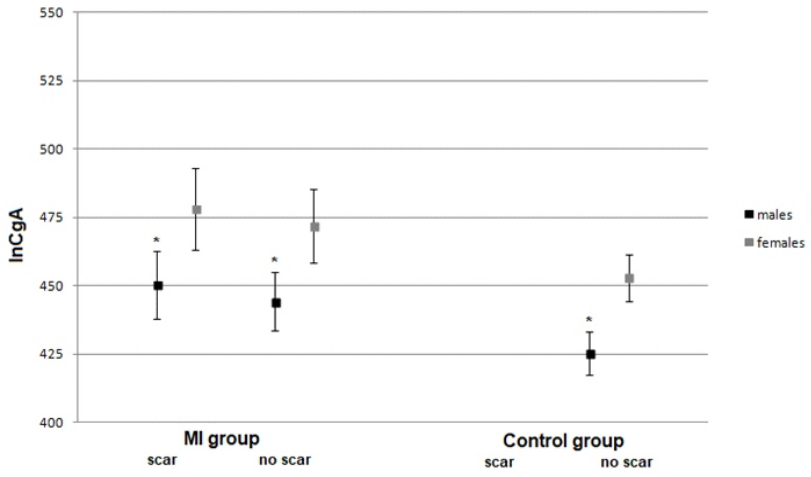

Figure 3. Log-transformed serum CgA in patients with or without presence of fixed perfusion deficit (scar) in the two study groups. No patient in the control group had scan findings consistent with a scar. Ln(CgA) levels are provided as mean ± SD (*P<0.05 for males vs. females).

Discussion

Serum CgA is an established tumor marker for the diagnosis, prognosis, and evaluation of response to treatment in NEN [10]. However, elevated CgA levels have been reported also in patients with neoplasia of mixed cell types, such as prostate or breast cancer [11]. It is considered a diagnostic and prognostic marker in several clinical conditions, including tumors and other non-neoplastic diseases [20]. In normal subjects, there are contradictory findings for the association of serum CgA with factors such as age, gender, fasting, or diurnal variation [21]. In our study, we observed a significant association of CgA with both age and gender in patients with an old MI and in the control group as well: older individuals and women were more likely to exhibit increased CgA.

Earlier studies reported that essential hypertension is associated with elevated serum CgA [8,11]. The role of CgA as a biomarker in cardiovascular disease has been addressed previously. Increased levels of CgA have been detected in the circulation of patients with hypertrophic cardiomyopathy, infarction, acute coronary syndromes, and heart failure, with important prognostic implications in several cases [12,13,22-26]. Serum CgA in patients who suffered an infarction was first reported in 2003, where increased levels were found to correlate with long-term mortality [13]. It has also been found that CgA –among other indicators– is a strong, independent prognostic factor for adverse outcomes such as heart failure or death, in patients with MI [24]. In this study, although multivariate analysis did not reveal a significant association between either systemic hypertension or infarction and serum CgA, we did observe that patients with an old MI exhibited significantly higher mean CgA levels compared to those without. However, the confidence intervals of CgA values in these two groups were similar and overlapping, while no significant effect of infarction on serum CgA was found in any of our statistical models. These findings suggest that, at least in patients with an old MI, any possible effects of hypertension or infarction on circulating CgA are hindered and minimized to non-significant levels by the unambiguously stronger influence of other factors such as age, gender, and EFLV.

The pathophysiologic mechanisms that drive CgA elevation after MI are not clearly defined. In the acute phase, a complex neurohormonal and immune activation occurs, whose duration and degree seem to correlate with the extent of myocardial injury [24]. Additionally, CgA levels in the acute and subacute phase of infarction may also be affected by sympathetic activation due to various coexisting actuators (e.g., pain, hemodynamic instability, anxiety, etc.). We avoided such interferences by implementing the study at a time point sufficiently remote from the acute and subacute phase, to ensure patient stability and avoid factors that could interfere with serum CgA and potentially confound our results. Nevertheless, we cannot disregard the fact that a range of other MI-associated factors was not included in the analysis. To name a few, the time elapsed since the infarction, its type (STEMI or NSTEMI), time, and method of revascularization (PCI or CABG) could potentially impact circulating CgA levels and need to be accounted for in future study designs, to clarify their potential interfering.

Since CAD is one of the most common causes of disability and death in Europe, MPS –among other diagnostic tests– is widely used based on the guidelines for appropriate use criteria, not only for diagnosing CAD but also for risk stratification in patients with already diagnosed CAD [27,28]. Expectedly, there was a significant difference in the type of MPS findings between the MI group and the control group. From the semiquantitative analysis, the majority of MI patients had abnormal MPS and only about one-third had a normal scan. In the control group, the great majority had a normal scan and less than one-fourth exhibited MPS abnormalities, mostly involving mild findings. Although our observed proportion of normal or near-normal MPS in patients with MI might seem relatively large, it could be explained by early and efficient reperfusion intervention that can minimize the myocardial ischemic injury [29]. Of note, a normal MPS study in patients with previous MI is not that uncommon and has been shown to correlate with a favorable long-term prognosis [30].

This study has certain limitations. We chose to rely primarily on the reporting physicians' appraisal to characterize fixed deficits as scars or artifacts, after taking into consideration the wall motion information obtained by echocardiography. A more suitable approach for distinguishing scars from attenuation artifacts might involve gated-SPECT, prone position imaging, or computed tomography (CT)-based attenuation correction [31-36]; however, several of these techniques were either unavailable or difficult to implement in the entirety of our cohort. Even so, our approach could be deemed acceptable, because most of the MPS artifacts can be recognized by experienced readers and this can further improve with the addition of echocardiographic information [37]. Another limitation pertains to the inclusion of patients with heart failure in the MI group. Various studies have considered heart failure as a factor likely to affect serum CgA, hence the possibility of these patients impacting the measured CgA levels in the MI group cannot be ruled out [23,26,38]. A similar possible interference of hypertension with serum CgA was alleviated by including hypertensive patients in both study groups. The postulation that the dissimilar prescription rates of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers between the two groups might have accounted for their observed differences in serum CgA was not substantiated by the regression analysis; moreover, other studies have demonstrated that antihypertensive regimens involving ACE inhibition, β-adrenergic blockade, diuretics, or dietary sodium restriction have no significant effect on serum CgA concentration [39,40]. Lastly, although minimal, we cannot entirely rule out the likelihood of undiagnosed malignancies or other underlying clinical conditions interfering with our measured CgA levels. This situation could have been accounted for if a long-term follow-up was available for all patients, but still, such cases are likely scarce.

In conclusion, although it is already known that increased

serum CgA is observed in patients during the acute and subacute phase of MI, this study involving patients with an infarction dating a year or older did not replicate this outcome, nor did it demonstrate any statistically significant association between circulating CgA and myocardial perfusion abnormalities (ischemia and/or scar) depicted by myocardial perfusion SPECT. The neuroendocrine activation observed during the early phases of MI appears to be blunted in the chronic phase, where it is overshadowed by the unequivocally stronger influence of other factors such as age, gender, and EFLV on serum CgA. Future research on the field could focus specifically on the role of other MI-related factors such as time elapsed since the insult, infarction type, method, and time of revascularization, which could potentially exert an impact on serum CgA that extends beyond the early phases of infarction.

Bibliography

1. Banks P, Helle K. The release of protein from the stimulated adrenal medulla. *Biochem J* 1965;97: 40C-41C.
2. Helle KB. Some chemical and physical properties of the soluble protein fraction of bovine adrenal chromaffin granules. *Mol Pharmacol* 1966; 2: 298-310.
3. O'Connor DT, Frigon RP. Chromogranin A, the major catecholamine storage vesicle soluble protein. Multiple size forms, subcellular storage, and regional distribution in chromaffin and nervous tissue elucidated by radioimmunoassay. *J BiolChem* 1984; 259: 3237-47.
4. O'Connor DT. Chromogranin: widespread immunoreactivity in polypeptide hormone producing tissues and in serum. *Regul Pept* 1983; 6: 263-80.
5. Helle KB, Corti A, Metz-Boutigue MH, Tota B. The endocrine role for chromogranin A: a prohormone for peptides with regulatory properties. *Cell Mol Life Sci* 2007; 64: 2863-86.
6. Deftos LJ. Chromogranin A: Its Role in Endocrine Function and as an Endocrine and Neuroendocrine Tumor Marker. *Endocr Rev* 1991; 12: 181-7.
7. Ferrari L, Seregni E, Bajetta E et al. The Biological Characteristics of Chromogranin A and Its Role as a Circulating Marker in Neuroendocrine Tumours. *Anticancer Res* 1999; 19: 3415-27.
8. Taupenot L, Harper KL, O'Connor DT. The chromogranin-secretogranin family. *N Engl J Med* 2003; 348: 1134-49.
9. O'Connor DT, Bernstein KN. Radioimmunoassay of chromogranin A in plasma as a measure of exocytotic sympathoadrenal activity in normal subjects and patients with pheochromocytoma. *N Engl J Med* 1984; 311: 764-70.
10. Louthan O. Chromogranin a in physiology and oncology. *Folia Biol* 2011; 57: 173-81.
11. O'Connor DT, Mahata SK, Taupenot L et al. Chromogranin A in human disease. *Adv Exp Med Biol* 2000; 482: 377-88.
12. Ceconi C, Ferrari R, Bachetti T et al. Chromogranin A in heart failure; a novel neurohumoral factor and a predictor for mortality. *Eur Heart J* 2002; 23: 967-74.
13. Omland T, Dickstein K, Syversen U. Association between plasma chromogranin A concentration and long-term mortality after myocardial infarction. *Am J Med* 2003; 114: 25-30.
14. Thygesen K, Alpert JS, Jaffe AS et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018; 72: 2231-64.
15. Henzlova MJ, Duvall WL, Einstein AJ et al. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol* 2016; 23: 606-39.
16. Verberne HJ, Acampa W, Anagnostopoulos C et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. *Eur J Nucl Med Mol Imaging* 2015; 42: 1929-40.
17. American Society of Nuclear Cardiology. Imaging guidelines for nuclear cardiology procedures, part 2. *J Nucl Cardiol* 1999; 6: G47-G84.
18. Tilkemeier PL, Bourque J, Doukky R et al. ASNC imaging guidelines for nuclear cardiology procedures: Standardized reporting of nuclear cardiology procedures. *J Nucl Cardiol* 2017; 24: 2064-128.
19. Czaja M, Wygoda Z, Duszańska A et al. Interpreting myocardial perfusion scintigraphy using single-photon emission computed tomography. Part 1. *Kardiochir Torakochirurgia Pol* 2017; 14: 192-9.
20. Tota B, Quintieri AM, Di Felice V, Cerra MC. New biological aspects of chromogranin A-derived peptides: focus on vasostatins. *Comp Biochem Physiol A* 2007; 147: 11-8.
21. Goetze JP, Alehagen U, Flyvbjerg A, Rehfeld JF. Chromogranin A as a biomarker in cardiovascular disease. *Biomark Med* 2014; 8:133-40.
22. Mahata SK, Corti A. Chromogranin A and its fragments in cardiovascular, immunometabolic, and cancer regulation. *Ann NY Acad Sci* 2019; 1455: 34-58.
23. Pieroni M, Corti A, Tota B et al. Myocardial production of chromogranin A in human heart: a new regulatory peptide of cardiac function. *Eur Heart J* 2007; 28: 1117-27.
24. Estensen ME, Hognestad A, Syversen U et al. Prognostic value of plasma chromogranin A levels in patients with complicated myocardial infarction. *Am Heart J* 2006; 152: 927. e1-e6.
25. Jansson AM, Røsjø H, Omland T et al. Prognostic value of circulating chromogranin Alevels in acute coronary syndromes. *Eur Heart J* 2009; 30: 25-32.
26. Røsjø H, Masson S, Latini R et al. GISSI-HF Investigators. Prognostic value of chromogranin A in chronic heart failure: data from the GISSI-Heart Failure trial. *Eur J Heart Fail* 2010; 12: 549-56.
27. Dorbala S, Ananthasubramaniam K, Armstrong IS et al. Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging Guidelines: Instrumentation, Acquisition, Processing, and Interpretation. *J NuclCardiol* 2018; 25: 1784-846.
28. Hendel RC, Berman DS, Di Carli MF et al. Appropriate Use Criteria for Cardiac Radionuclide Imaging: *J Am Coll Cardiol* 2009; 53: 2201-29.
29. Ibáñez, B., Heusch G, Ovize M et al. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am CollCardiol* 2015; 65: 1454-71.
30. Ottenhof MJ, Wai MC, Boiten HJ et al. 12-Year outcome after normal myocardial perfusion SPECT in patients with known coronary artery disease. *J Nucl Cardiol* 2013; 20: 748-54.
31. Fleischmann S, Koepfli P, Namdar M et al. Gated ^{99m}Tc- tetrofosmin SPECT for discriminating infarct from artifact in fixed myocardial per-fusion defects. *J Nucl Med* 2004; 45: 754-59.
32. DePuey EG, Rozanski A. Using gated technetium-99m-sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. *J Nucl Med* 1995; 36: 952-55.
33. Chen J, Caputlu-Wilson SF, Shi H et al. Automated quality control of emission-transmission misalignment for attenuation correction in myocardial perfusion imaging with SPECT-CT systems. *J Nucl Cardiol* 2006; 13: 43-9.
34. Hayes SW, De Lorenzo A, Hachamovitch R et al. Prognostic implications of combined prone and supine acquisitions in patients with equivocal or abnormal supine myocardial perfusion SPECT. *J Nucl Med* 2003; 44: 1633-40.
35. Nishina H, Slomka PJ, Abidov A et al. Combined Supine and Prone Quantitative Myocardial Perfusion SPECT: Method Development and Clinical Validation in Patients with No Known Coronary Artery Disease. *Soc Nuclear Med* 2006; 47: 51-8.
36. Stathaki M, Koukouraki S, Papadaki E et al. The Benefits of Prone SPECT Myocardial Perfusion Imaging in Reducing Both Artifact Defects and Patient Radiation Exposure. *Arq Bras Cardiol* 2015; 105: 345-52.
37. DePuey G. How to detect and avoid myocardial perfusion SPECT artifacts. *J Nucl Med* 1994; 35: 699-702.
38. Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008; 358: 2148-59.
39. Takiyyuddin MA, Parmer RJ, Kailasam MT et al. Chromogranin A in human hypertension. Influence of heredity. *Hypertension* 1995; 26: 213-20.
40. Wu RA, Kailasam MT, Cervenka JH et al. Does lipophilicity of angiotensin converting enzyme inhibitors selectively influence autonomic neural function in human hypertension? *J Hypertens* 1994; 12: 1243-47.