Atherosclerotic Renal Artery Stenosis Prevalence and Correlations in Acute Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Interventions: Data From Nonrandomized Single-Center Study (REN-ACS)—A Single Center, Prospective, Observational Study

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Background—We are the first to evaluate the prevalence of renal artery stenosis (RAS) in consecutive patients with acute myocardial infarction (AMI) referred for primary percutaneous coronary intervention from a single tertiary center. As a novelty, we assessed hydration and metabolic status and measured arterial stiffness. We elaborated a predicting model for RAS in AMI.

Methods and Results—One hundred and eighty-one patients with AMI underwent concomitantly primary percutaneous coronary intervention and renal angiography. We obtained data on demographics, medical history, cardiovascular risk factors, echocardiography, Killip class, and blood tests. In the first 24 hours post–primary percutaneous coronary intervention, we assessed bioimpedance through Body Composition Monitoring® and arterial stiffness through pulsed-wave velocity, SphygmoCor®. Significant RAS (>50% lumen narrowing, RAS+) was present in 16.6% patients. In the RAS+ group we recorded significantly higher stiffness, CRUSADE score and dehydration, and more women with higher prevalence of multivascular coronary artery disease and heart failure. In our multivariate models, variables independently associated with RAS+ were previous percutaneous coronary intervention, low estimated glomerular filtration rate, multivascular coronary artery disease, and total/extracellular body water. These models had good specificity and low sensitivity.

Conclusions—We observed that RAS+ AMI patients have a particular hydration, metabolic, and endothelial profile that could generate more future major adverse cardiac events. Hence, renal angiography in AMI should be considered in specific subsets of patients.

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Key Words: angiography • arteries • hypertension • myocardial infarction • renal

R ecently, renal artery stenosis (RAS) incidence increased, reflecting widespread atherosclerosis in a population with extensive comorbidity burden.[1] Simultaneous atherosclerotic determinations in at least 2 major territories are common and managed as multisite artery disease.[2] This complexity of artery determinations generates a variety of clinical scenarios (major adverse cardiac events [MACE], stroke, peripheral artery disease [PAD], end-stage renal disease), raising difficulties in approaching diagnostic and treatment algorithms.[3] Thus, when a significant atherosclerotic lesion is discovered following a vascular event, it is justified to identify other sites where this disease could silently manifest. Screening algorithms for a second site need to be developed and assessed, since there is a greater risk of complications and recurrent symptoms for the first lesion.[4]

RAS has a higher prevalence in patients with concomitant PAD or coronary artery disease (CAD).[5] Data obtained using cardiac catheterization and simultaneous renal angiography (RA) showed that RAS is present in 15% to 20% of CAD patients.[6–9] All previous studies reported data on RAS prevalence in nonemergency CAD. There are no data reporting

RAS prevalence in patients presenting with acute myocardial infarction (AMI). These patients may have a particular inflammatory, metabolic, and endothelial profile, which could be associated with a higher RAS incidence.

Such patients may have extensive vascular damage. There are few studies describing multisite atheromatosis and large artery stiffness parameters. Arterial stiffness is an important cardiovascular risk factor and an independent predictor of cardiovascular morbidity and mortality[10] in patients with hypertension,[11] diabetes mellitus,[12] and chronic kidney disease (CKD).[13] Pulsed-wave velocity (PWV), as a measure for arterial stiffness, is an independent predictor of primary coronary events,[14] and also a strong predictive factor for MACE post-AMI,[15] but no studies have been published evaluating the discriminatory power of PWV in RAS versus non-RAS AMI patients.

Fluid balance is often modified in RAS patients.[16] Recent data suggest that dehydration could be a trigger for AMI[17] and a predictor of death post-AMI.[18] There are no studies evaluating hydration status in AMI patients with RAS, both entities being characterized by a complexity of neurohumoral responses.

We aimed (1) to evaluate RAS prevalence in consecutive AMI patients from a single tertiary center; (2) to evaluate for the first time the hydric and metabolic status in RAS (versus non-RAS) AMI patients; (3) to assess vascular stiffness; (4) to elaborate a multivariate model that could predict RAS; and (5) to propose an accurate screening standard for RAS in AMI. In a follow-up study, we plan to examine the impact of RAS and stiffness on AMI short-term and long-term outcome (Clinicaltrials.gov protocol NCT02388139).

Methods

Study Design and Population

Between October 2014 and March 2015, all consecutive patients with AMI included in Romanian National Program of Primary Percutaneous Revascularization were enrolled in our prospective, nonrandomized single-center study (REN-ACS). ClinicalTrials.gov registration number is NCT02388139. The "Gr. T. Popa" Iasi University Ethics Committee approved the protocol. All patients provided written informed consent. No sex-based or racial/ethnic-based differences were present.

All patients were admitted for emergency percutaneous coronary intervention (PCI) and treated following European standard protocols.[19] In the same procedure we performed diagnostic RA. On the basis of clinical examination and interview defined previously[20] (adapted after the European CARDS registration data standards), we obtained data on the following: medical history (relevant to CAD and RAS—previous PCI, CKD, chronic heart failure, and PAD), cardio-

vascular risk factors (smoking, dyslipidemia, diabetes mellitus, hypertension), and Killip class. Cardiac echography was performed prior to angiography. In the first 24 hours post-PCI we assessed bioimpedance-derived parameters and arterial stiffness.

Coronary and Renal Arteries Angiographic Assessment

We performed coronary angiography via right femoral artery and treated coronary lesions (thrombus aspiration, coronary stenting) as usual.[19] Therapeutic decisions were not influenced by study requirements. After coronarography, RA was performed by selective injection of 10 mL contrast medium through a 6F diagnostic catheter in renal arteries. Coronarographic lesions were assessed and reported during the procedure.

After the PCI procedure, all patients received standard intravenous and oral hydration fluids (500 to 1000 mL saline iv and 1000 mL water, respectively).

RA images were analyzed offline in the first 24 hours by 2 independent operators, using angiographic software tools. Using the catheter as a scaling device, percent diameter stenosis and renal diameters were computed (Philips Allura XPER FD10 Digital; Philips, the Netherlands).[21]

All segments of the coronary arteries were characterized and recorded in the database following standard segmentation and lesion classification. All intraprocedural complications (death, coronary perforation, stroke, hemorrhages, malignant arrhythmia, and mechanical ventilation) were recorded.

The threshold for RAS was set at >50% stenosis (and defined as RAS+) based on the American Heart Association Guidelines for the reporting of renal artery revascularization in clinical trials.[22]

Biological Analysis

Serum glucose, hemoglobin, leukocytes, platelets, total cholesterol, high density lipoprotein and low density lipoprotein fractions, uric acid, C-reactive protein, troponin I, creatine kinase–MB fraction, serum urea, and creatinine (estimated glomerular filtration rate, [eGFR], by CKD-Epi formula) were recorded at admission, before PCI.

Body Composition Analysis

For this analysis we used the Body Composition Monitor (BCM®, Fresenius Medical Care, Germany) portable device. With the patient in supine position, we placed electrodes on 1 hand and 1 foot. Results were recorded in 2 minutes on a dedicated card, and transferred through Fluid Management Tool® software (Fresenius Medical Care Singapore Pte Ltd, Singapore). A single physician performed all measurements.

Extracellular water (ECW), intracellular water (ICW), total body water (TBW), lean body mass, and fat tissue mass were recorded in the 24 hours following PCI.

Bioimpedance spectroscopy[23] evaluates total, extra- and intracellular fluid status and fat/nonfat tissue mass, with excellent intra- and interobserver reproducibility.[24] Bioimpedance–derived parameters had a prognostic significance[25] not only in hemodialysis, but also in early stages of CKD,[26] including correlations between fluid imbalance and severity of CAD.[27]

Arterial Stiffness Measurements

The SphygmoCor® (AtCor, Australia) device was used to acquire carotid-femoral (cf-PWV) and carotid-radial PWV wave velocities and aortic augmentation index in the 24 hours following PCI. The contralateral artery was used differently from the angiographic puncture site. Methods, techniques, and acquisition software have been described previously.[28] cf-PWV is the "gold standard" for arterial stiffness and brings the greatest epidemiological evidence for its predictive value for MACE.[29]

Statistical Analysis

Continuous variables are expressed as mean±SD and nominal data as number with percent frequency. Normality of the distribution of the variables was tested with the Shapiro–Wilk test. Between-group comparisons were performed for nominal data with the χ^2 test, and by independent t test or Mann–Whitney test for the rest of variables, as appropriate.

Univariate logistic regression was used to assess the association between all variables and RAS+. Stepwise multivariate logistic regression analysis including all univariate associates of RAS+ ($P<0.05$) was used to evaluate different predictive models for RAS+. Due to multicollinearity, variables derived from the BCM measurements (TBW, ECW, ICW) that were associated with RAS+ in the univariate regression analysis were introduced separately in the multivariate logistic regression analysis. We determined the Bayesian information criterion and the Akaike information criterion for each final model; there is no statistical test that compares different Bayesian or Akaike information
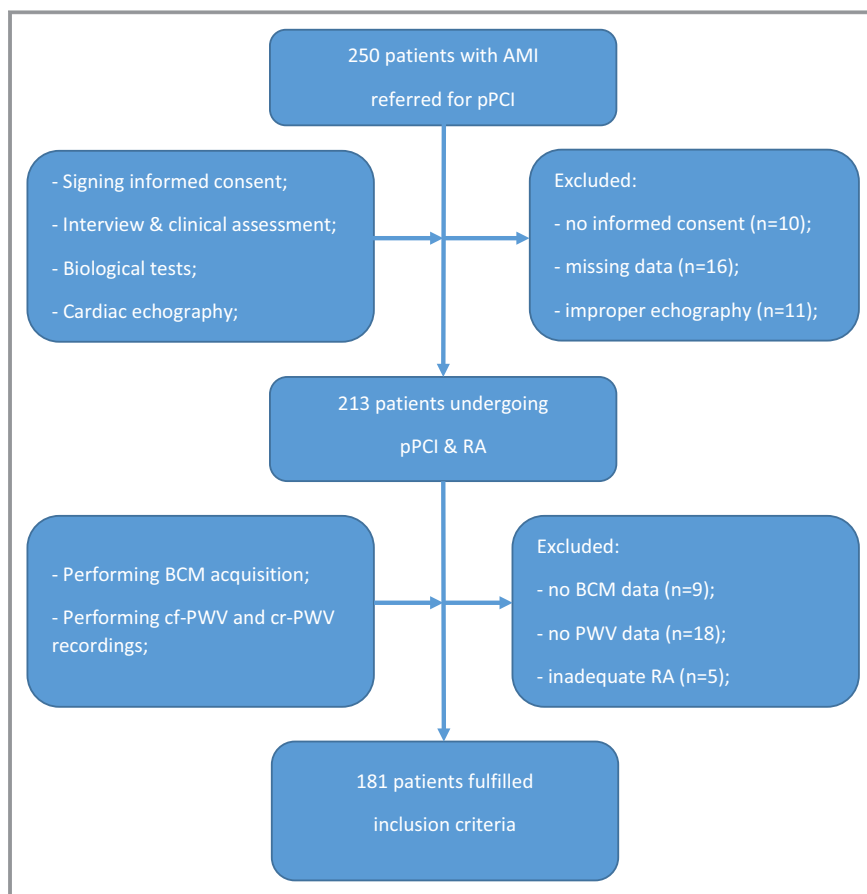
Figure 1. Flowchart of patient recruitment. Missing data: 3 patients without full demographics, 4 patients without complete medical history, 9 patients without laboratory data. AMI indicates acute myocardial infarction; BCM, body composition monitor; cf- and cr- PWV, carotid-femoral and carotid-radial pulsed-wave velocity; pPCI, primary percutaneous coronary intervention; RA, renal angiography.

Table 1. Characteristics of the Study Population According to the Occurrence of RAS

Characteristic	All Patients (n=181)	RAS− (n=151)	RAS+ (n=30)	P Value
Male, n (%)	135 (74.6)	117 (77.5)	18 (60.0)	0.045[†]
Age, y*	61.55±11.82	60.72±12.21	65.73±8.65	0.048[†]
Weight, kg*	83.79±15.56	85.55±14.69	79.97±19.20	0.141
Abdominal perimeter, cm*	97.27±13.95	97.87±13.82	94.27±14.56	0.183
Body mass index, kg/m²*	29.00±4.67	29.07±4.39	28.66±5.95	0.339
Previously known CAD, n (%)	55 (30.4)	39 (25.8)	16 (53.3)	0.003[†]
Previously known CKD, n (%)	13 (7.2)	9 (6.0)	4 (13.3)	0.153
Previous PCI, n (%)	6 (3.3)	2 (1.3)	4 (13.3)	0.007[†]
Previously known CHF, n (%)	36 (19.9)	26 (17.2)	10 (33.3)	0.043[†]
CABG, n (%)	1 (0.6)	0 (0.0)	1 (3.3)	0.166
Stroke, n (%)	11 (6.1)	9 (6.0)	2 (6.7)	1
Previously known PAD, n (%)	11 (6.1)	9 (6.0)	2 (6.7)	1
Smoking, n (%)	113 (62.4)	97 (64.2)	16 (53.3)	0.26
Previously known diabetes, n (%)	37 (20.4)	27 (17.9)	10 (33.3)	0.055
Previously known hypertension, n (%)	96 (53.0)	77 (51.0)	19 (63.3)	0.216
Previous diuretic therapy, n (%)	43 (23.8)	33 (21.9)	10 (33.3)	0.177
Hb (g/L)*	14.19±1.75	14.26±1.76	13.79±1.66	0.144
White blood cells, n×10³	12.16±3.77	12.23±3.85	11.79±3.38	0.597
Platelets, n×10³	239.18±59.41	240.80±56.89	231.02±71.29	0.377
Glucose, mg/dL*	128.18±58.18	127.83±59.71	129.97±50.65	0.356
Cholesterol total*	192.65±47.78	194.06±48.87	185.53±44.24	0.496
LDL*	112.35±40.06	112.54±41.02	111.4±35.47	0.924
HDL*	53.76±22.09	54.6±23.49	49.53±12.31	0.513
eGFR, mL/min*	79.48±20.04	81.62±18.89	68.71±22.43	0.001[†]
BUN:creatinine ratio	19.2	19.1	19.5	0.79
CK-MB at admission*	83.16±96.31	86.81±97.64	64.76±89.89	0.131
CK-MB peak*	234.83±222.89	236.78±207.27	225.00±293.34	0.442
Fibrinogen, mg*	503.7±156.11	491.17±154.07	566.78±153.45	0.011[†]
CRUSADE score*	25.9±11.66	24.68±10.98	32.03±13.2	0.004
Killip class, n (%)				0.304
Class 1	164 (90.6)	139 (92.1)	25 (83.3)	
Class 2	10 (5.5)	7 (4.6)	3 (10)	
Class 3	5 (2.8)	4 (2.6)	1 (3.3)	
Class 4	2 (1.1)	1 (0.7)	1 (3.3)	
LVEF echo, n (%)				0.796
>50%	38 (21)	33 (21.9)	5 (16.7)	
41 to 50%	56 (30.9)	46 (30.5)	10 (33.3)	
31 to 40%	54 (29.8)	46 (30.5)	8 (26.7)	
<30%	33 (18.2)	26 (17.2)	7 (23.3)	
Coronarography, n (%)				0.005[†]
1	79 (43.6)	73 (48.3)	6 (20.0)	
≥2	102 (56.4)	78 (51.7)	24 (80.0)	

Continued

Table 1. Continued

Characteristic	All Patients (n=181)	RAS− (n=151)	RAS+ (n=30)	P Value
AIx*	22.78±12.71	22.39±12.83	24.71±12.15	0.371
cf-PWV*	9.39±2.54	9.17±2.41	10.47±2.92	0.026[†]
cr-PWV*	7.00±1.15	6.98±1.19	7.12±0.92	0.321
AFO, L*	−1.69±2.51	−1.75±2.59	−1.45±2.11	0.707
RFO, %*	−10.62±15.13	−10.74±15.46	−10.01±13.56	0.91
TBW, L*	30.77±7.77	40.51±7.86	36.02±6.12	0.003[†]
ECW, L*	17.11±2.90	17.35±2.86	15.91±2.87	0.007[†]
ICW, L*	22.66±5.74	23.16±5.91	20.11±4.01	0.003[†]
LTM, kg*	46.17±15.22	47.44±15.73	39.78±10.42	0.005[†]
FTM, kg*	28,74±12.39	28.46±12.34	30.14±12.71	0.596

AFO indicates absolute fluid overload; AIx, augmentation index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; cf- and cr-PWV, carotid-femoral and carotid-radial pulsed-wave velocity; CHF, chronic heart failure; CKD, chronic kidney disease; CK-MB, creatine kinase MB fraction; ECW, extracellular water; eGFR, estimated glomerular filtration rate; FTM, fat tissue mass; Hb, hemoglobin; HDL, high density lipoprotein; ICW, intracellular water; LDL, low density lipoprotein; LTM, lean tissue mass; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RAS, renal artery stenosis; RFO, relative fluid overload; TBW, total body water.
*Mean±SD.
[†]P values are statistically significant.

criterion estimations, and a lower value indicates a better fitted model.

All statistical analyses were performed with SPSS 19.0 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

One hundred eighty-one of the 250 consecutive patients who underwent primary PCI (pPCI) fulfilled the inclusion criteria (Figure 1), of which 81 (45%) had renal atherosclerotic lesions (both significant and not significant lesions), 59 (32.6%) had unilateral RAS, and 22 (12.2%) had bilateral RAS. RAS+ (as defined by >50% stenosis) was present in 16.6% of the population. Clinical, demographic, and biological characteristics are presented in Table 1. There were 135 (64.5%) men, 55 (30.4%) of the patients had pre-existing CAD, 13 (7.2%) had CKD, and 36 (20%) had chronic heart failure. Coronarography revealed that 102 patients (56.4%) had multivascular coronary artery disease. Twenty percent of the population had left ventricular ejection fraction >50%, and 18.2% had left ventricular ejection fraction <30%. The mean cf-PWV was 9.4±2.5 m/s. Fluid status measurements showed mean values for relative fluid overload—10.62±15.13% (Table 1).

RAS+ Versus RAS− AMI Patients

We further stratified the study population according to the presence of RAS+ (Table 1). The presence of most cardio-vascular risk factors (smoking, CKD, dyslipidemia, hypertension), as well as PAD and stroke were not different between the 2 groups. However, there were more women with RAS+ and a higher prevalence of CAD and chronic heart failure. These patients were older, suffering more from previous PCI and from multivascular coronary artery disease. Killip class and left ventricular ejection fraction were not significantly different between the 2 groups. Fibrinogen and CRUSADE score were higher, while eGFR was significantly lower in the RAS+ subgroup. RAS+ patients had significantly higher

Table 2. Univariate Associates of RAS

Parameters	Odds Ratio	95% CI
Gender	2.294	1.006 to 5.231
Age	1.039	1.003 to 1.078
PCI	11.462	1.996 to 65.808
CAD	2.404	1.008 to 5.731
eGFR	0.971	0.952 to 0.989
Fibrinogen	1.003	1.000 to 1.005
Number of affected vessels	3.374	1.448 to 9.678
cf-PWV	1.202	1.039 to 1.391
TBW	0.915	0.861 to 0.973
ECW	0.822	0.703 to 0.961
ICW	0.882	0.805 to 0.966

CAD indicates coronary artery disease; cf-PWV, carotid-femoral pulsed-wave velocity; ECW, extracellular water; eGFR, estimated glomerular filtration rate; ICW, intracellular water; PCI, percutaneous coronary intervention; RAS, renal artery stenosis; TBW, total body water.

Table 3. Multivariate Associates of RAS (With TBW)

Parameters	Odds Ratio	95% CI
PCI	8.590	1.319 to 55.928
eGFR	0.978	0.958 to 0.999
Number of affected vessels	3.113	1.127 to 8.593
TBW	0.933	0.875 to 0.995

eGFR indicates estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RAS, renal artery stenosis; TBW, total body water.

cf-PWV but no differences in carotid-radial-PWV. The same subgroup had lower TBW, ECW, intracellular water, and lean tissue mass, but similar AFO and relative fluid overload as compared to the RAS− patients. There was also no difference between the 2 groups in regard to blood urea nitrogen: creatinine ratio (as another estimation of dehydration) and in the use of diuretics.

Determinants of RAS in Patients With AMI

All independent determinants of RAS+, with odds ratios and 95% CIs are shown in Table 2.

In multivariate models, variables that remained independently associated with RAS+ were previous PCI, eGFR, multivascular coronary artery disease, and TBW or ECW (Tables 3 and 4). The model that included TBW had lower Akaike information criterion (143.2 versus 143.7) and Bayesian information criterion (148.6 versus 149.2) scores, but higher area under receiver operating characteristic (AUROC) (0.786, 95% CI 0.705 to 0.867 versus 0.774, 95% CI 0.692 to 0.857) than the model with ECW (Figure 2). Both models had identical accuracy (84.5%), specificity (98.7%), sensitivity (13.3%), and positive (66.7%) and negative (83.4%) predictive values.

Discussion

This cross-sectional, real-life observational study evaluated clinical and paraclinical characteristics of AMI patients with respect to angiographically diagnosed RAS.

Table 4. Multivariate Associates of RAS (With ECW)

Parameters	Odds Ratio	95% CI
PCI	8.097	1.178 to 55.646
eGFR	0.974	0.954 to 0.995
Number of affected vessels	3.143	1.143 to 8.646
ECW	0.845	0.716 to 0.997

ECW indicates extracellular water; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RAS, renal artery stenosis.
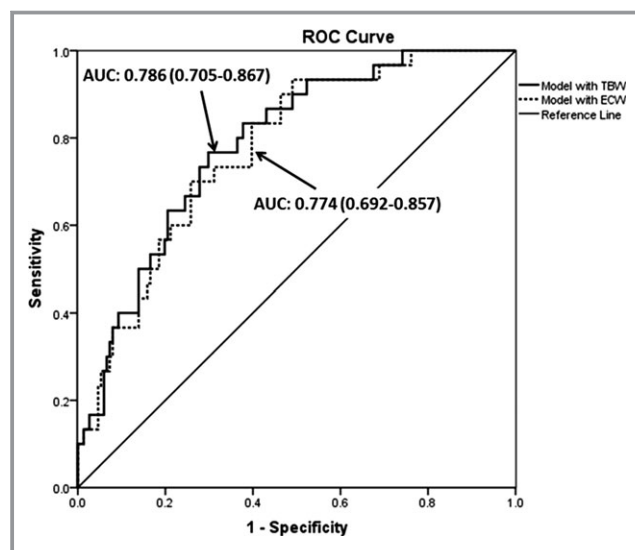
Figure 2. Performance of the models for predicting RAS. The difference between the 2 AUCs is 0.012, not significant (*P*=0.37, DeLong method). The numbers inside the brackets indicate the 95% CIs of the AUCs. AUC indicates area under curve of ROC; ECW, extracellular water; RAS, renal artery stenosis; ROC, receiver operating characteristics; TBW, total body water.

We investigated (1) RAS prevalence in this cohort, and (2) the relationship between RAS, arterial stiffness, and hydration status.

There are few trials[5] that analyzed the incidence of RAS in CAD, whereas no study evaluated an AMI cohort. All previous studies excluded this category of patients. We performed systematic RA in consecutive AMI patients, regardless of other risk factors suggesting RAS (severe hypertension, PAD, or abdominal bruits). Data showed concordant values of RAS prevalence in AMI (16.6%) to those reported in well-recognized risk groups (suspected renovascular hypertension[5,30]—14.1%, hypertension and diabetes mellitus[31]—17.1%, chronic CAD[5,32,33]—9.1% to 10.8%) but lower values than in patients with chronic heart failure[34]—54.1%, aortic abdominal aneurysm[35]—38%, end-stage renal disease[36]—40.8%. Differences between reports are driven by inclusion of patients with different stages of atheromatous disease and inflammation.

The relationship between extent of CAD and RAS has been previously evaluated in elective patients[37]: the number of diseased coronary arteries roughly multiplies by 5 the prevalence of RAS.[5] In our study, the degree of CAD was a strong predictor for RAS in multivariate analysis, reflecting progressive stages of multisite disease.

This is the first reported trial that assessed arterial stiffness (PWV) and hydration status (BCM) in AMI patients. Previous studies have observed a predictive role for cf-PWV in primary[14] and recurrent coronary events.[38] Our data suggests that arterial rigidity is associated with increased prevalence of RAS in AMI. Stiffness and RAS could be a result of extensive

atheromatosis, or marker for an aggressive risk factor profile (severe hypertension, CKD, inflammation). In both scenarios, elevated rigidity after AMI would predict high risk of secondary MACE.[39] Further research is needed to refine predictive power of the interaction between stiffness and RAS+ phenotype.

One of the strongest predictors for RAS+ in our study was eGFR decline. AMI RAS+ patients had significantly lower eGFR, which is linked to more extensive and severe CAD[40] and correlated with higher MACE after an AMI.[41] A decline in eGFR could be due to RAS (chronic ischemic nephropathy) and/or coexistence of multiple risk factors. Moreover, CRUSADE score was significantly higher in the RAS+ subgroup, leading to future greater MACE risk.[42]

We are the first suggesting the importance of bioimpedance with respect to RAS coexistence in AMI. Previous studies (in AMI) derived hydration status from blood and urine osmolality, not taking into account RAS as modulator.[17,43–45] Using a more objective[46] and reproducible[47] measurement we revealed that (1) all patients with AMI were relatively dehydrated, dehydration being possibly an unrecognized risk factor for AMI[17,44]; (2) RAS+ patients were significantly more dehydrated than the RAS– population. This information appears counterintuitive, considering that RAS activates the renin–angiotensin–aldosterone system, thus promoting water retention. However, severe dehydration in AMI could be a distinct and multiorigin risk factor that cannot be compensated by the renin system hyperactivity. Since BCM parameters are easily acquired at the patient's bedside by nonspecialized medical personnel, this investigation could be performed routinely in AMI and should be included in a screening protocol. More studies using bioimpedance are necessary to understand the role of hydration status in AMI.

Previous data has raised the concern of elaborating a predictive model for RAS, in chronic CAD.[6,48] Considering that RA is a simple and harmless technique for RAS diagnosis, we recommend it as screening (at the same time as pPCI), when dealing with particular subsets of AMI patients (previous PCI, multivascular coronary artery disease, lower eGFR, and dehydrated). Our multivariate model has good specificity and low sensitivity. The advantages of a screening protocol could be the following: better prediction of further MACE risk,[33] reducing cardiovascular risk, optimal adjustment of antiplatelet, anticoagulant, and angiotensin-converting enzyme inhibitors treatment,[49] better control of hypertension,[50] and limitation of progression to end-stage renal disease.[36]

Limitations

Our study was done in a single center and referral bias could be a limiting factor. Data were derived from 181 patients, but a larger group might have given us more precise information. It is not clear whether hydration should be evaluated before or after pPCI. Although our study suggests a screening protocol, more data are required to improve characteristics of the RAS+AMI subgroup. RAS significance cut-off was set at >50%, but trans-stenotic gradient was not performed to determine RAS hemodynamic relevance. If we had set the cut-off value at a different limit, relevance of variables included in analysis could have been different.

Conclusions

We recorded RA, PWV, and bioimpedance-derived parameters in consecutive AMI patients referred for pPCI. We observed several correlations between RAS+ and clinical/paraclinical variables. A prediction model was elaborated in order to perform RA concomitantly with pPCI. RAS+ AMI patients have a particular hydration, metabolic, and endothelial profile that could generate further MACE. Hence, RA in AMI should be considered in specific subsets of patients.

Disclosures

Adrian Covic is a member of the Advisory Boards Fresenius NephroCare. All other authors have no conflicts of interest to declare.

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