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Ischemic Versus Non-Ischemic (Neurogenic) Myocardial Contractility Impairment in Acute Coronary Syndromes: Prevalence and Impact on Left Ventricular Systolic Function Recovery

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Background: Neurogenic mechanism is believed to contribute to left ventricular (LV) systolic dysfunction in acute coronary syndromes (ACS); its extreme form is known as takotsubo cardiomyopathy. However, the magnitude of neurogenic contribution to LV dysfunction in all-comer first-time ACS remains unknown.

Material/Methods: In 120 consecutive patients with first-time ACS (age 66.3±12.3years, 40 women) coronary angiograms were individually matched to the echocardiographic left ventricular (LV) segments (17-segment model). Baseline contractility impairment was classified as ischemic (I): confined to the stenotic artery(ies) supply area(s), neurogenic (N): in absence of attributable coronary stenosis, or partially ischemic/partially neurogenic (I&N). Echocardiography was repeated at 6 months to determine LV systolic function recovery.

Results: Neurogenic component (NC) contribution to myocardial contractility impairment was present in 24.2% of ACS patients, with pure N in 6.7% and I&N in 17.5%. Diabetes/pre-diabetes was present in 38.5% *vs.* 33.5% *vs.* 0% (I *vs.* I&N *vs.* N; p=0.02). Major stressor preceding symptom onset was reported in 3.3% in I, 9.5% in I&N, and 25.0% in N (p=0.03). The number of LV segments with contractility impairment was 2±4 in I, 17±11 in I&N, and 3±16 in N (p<0.05). NC presence was independently associated with better recovery of global LV systolic function (OR 2.99, 95% CI: 1.16–7.76; p=0.024).

Conclusions: Novel findings from this study are: (1) NC may contribute to myocardial contractility impairment in 1 in every 4 first-time ACS patients, (2) NC contribution to contractility impairment in ACS is blunted in diabetes or pre-diabetes, and (3) LV systolic function recovery is better in patients with NC.

MeSH Keywords: Acute Coronary Syndrome • Myocardial Contraction • Myocardial Stunning • Sympathetic Nervous System • Takotsubo Cardiomyopathy • Ventricular Dysfunction, Left

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Background

Neurogenic contraction impairment is believed to play a role in myocardial dysfunction in acute coronary syndrome (ACS), but this contribution has not been quantified. The term stunning was first introduced to indicate a solely ischemic phenomenon [1]. However, identification of stress-related takotsubo cardiomyopathy has brought attention to neurogenic stunning [2–5]. The purely neurogenic stunning, manifested as short-term regional wall-motion abnormalities (RWMA) occurring beyond the supply area of a single coronary artery (and usually in absence of any significant coronary stenosis), is a hallmark of stress-related cardiomyopathy syndrome spectrum [2–6]. Although sympathetic overstimulation and ischemia affect myocardial contractility through different mechanisms (Figure 1), they may both contribute to clinically relevant myocardial contractility reduction in ACS. Since myocardial ischemia is a potent stressor leading to sympathetic overstimulation, ACS (in predisposed individuals in particular) might be associated with the neurogenic myocardial stunning and contraction-band necrosis that may coexist with the "direct" ischemic stunning and relaxed-state necrosis (Figure 1). Neurogenic myocardial stunning and necrosis occur, in a clinically relevant manner, independently of coronary artery disease [4–8], but (surprisingly) their role in ACS has not been systematically evaluated. Our incidental clinical observations, consistent with those of Carasso et al. [9], suggested that RWMA in ACS may not be confined to the vascular supply area(s) of the occluded or significantly stenosed artery(ies).

This study aimed to: (1) evaluate the prevalence of remote non-ischemic (neurogenic) RWMA in an all-comer cohort of first-time ACS patients, and (2) to investigate the predisposing factors and outcomes.

Material and Methods

We studied a cohort of consecutive first-time ACS patients admitted to our institution over 18 months with a diagnosis of ACS, who underwent urgent coronary angiography (and, if indicated, percutaneous coronary intervention, PCI) plus detailed transthoracic echocardiography (TTE) within 24 h of hospitalization and who had a detailed follow-up TTE at 6 months. Subjects with a history of ACS or heart failure and those referred to cardiac surgery were excluded.

ACS was diagnosed according to the current international guidelines. Myocardial infarction (MI) was diagnosed according to the 3rd Universal Definition of Myocardial Infarction [10] including the clinical picture, electrocardiogram (ST segment elevation), and ischemic injury markers: 5th generation high-sensitivity cardiac Troponin T (hs-cTNT) and creatine kinase isoenzyme MB activity (CK-MB). Patients with secondary myocardial injury (e.g., thyrotoxicosis, type 2 MI [11]) were excluded. All study subjects underwent urgent coronary angiography.

Echocardiography was performed by cardiologists skilled in echocardiographic assessment, and recordings were saved for further analysis. Using a 17-segment model [12], visual wall-motion scoring, based on myocardial movement and thickening, was performed by an agreement of 2 experienced echocardiographers. Regional wall-motion was ranked as follows: 1 – normal or hypercontraction, 2 – mild hypokinesis, 3 – severe hypokinesis or akinesis, and 4 – dyskinesis. We also calculated the number of affected segments (ranked >1, ranging from 0 to 17) and the wall motion score (WMS), representing the average of ranks in all segments [12]. Global left ventricular ejection fraction (LVEF) was calculated using the Simpson's bi-plane method. In 11 patients baseline (n=7) and/or follow-up (n=5) echocardiograms were judged as incomplete or of non-satisfactory quality, and 120 subjects (Table 1) met the study criteria. RWMA segments were matched with corresponding coronary

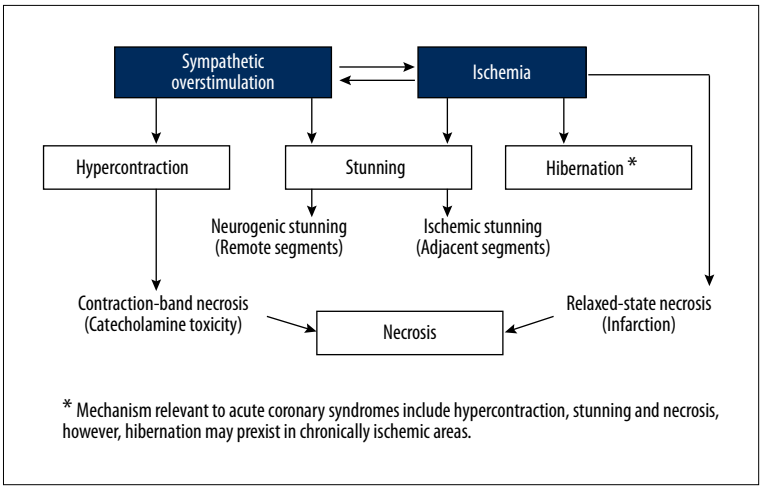

Figure 1. Effects of sympathetic overstimulation and ischemia on myocardial contractility, shows the theoretical concept underpinning the study. Slightly overlapping mechanisms of both pathways lead to necrosis and stunning. However, while ischemic stunning encompasses segments within and adjacent to ischemic insult, stunning in remote segments is considered neurogenic.

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Table 1. Patient characteristics by referral diagnosis.

	Unit	All (N=120)	NSTE-ACS (N=82)	STE-ACS (N=38)	p Value
Clinical features					
Female	%	33.3	34.1	31.6	NS
Age	Years	66.8±18.4	68.4±15.8	63.5±21.7	NS
Hypertension	%	75.8	80.5	65.8	NS
Hyperlipidemia	%	60.8	69.5	42.1	0.004
DM	%	23.3	24.4	21.1	NS
DM or prediabetes	%	35.0	35.4	34.2	NS
Smoking	%	29.2	23.2	42.1	0.04
COPD	%	7.5	8.5	5.3	NS
PAD	%	5.0	4.9	5.3	NS
Stroke	%	4.2	3.7	5.3	NS
AF or AFl	%	12.5	17.1	2.6	0.04
Resting chest pain on admission	%	65.8	53.7	92.1	<0.001
Recent major psychological stressor	%	5.8	6.1	5.3	NS
TTE, CAG and lab. data					
LV hypertrophy	%	44.5	44.4	44.7	NS
RWMA on admission	%	75.0	68.3	89.5	0.02
Segments with RWMA	–	3±6.0	3±6.0	4±9.0	0.047
Admission troponin T	ng/ml	0.11±0.37	0.09±0.20	0.21±0.64	0.006
Admission CK-MB	U/l	20.0±30.0	18.5±13.5	34.0±53.0	<0.001
Peak troponin T	ng/ml	0.40±2.00	0.13±0.75	2.41±6.33	<0.001
Peak CK-MB	U/l	32.5±86.0	22.0±30.0	124.0±199.0	<0.001
Peak NT-proBNP	$\times 10^3$ pg/ml	1.32±5.34	1.35±5.35	1.29±3.07	NS
Without significant atherosclerosis	%	7.5	6.1	2.6	NS
Borderline stenosis	%	2.5	3.7	0	NS
Critical stenosis in coronary angiography	%	90.0	89.0	92.1	NS
Vessels with critical obstruction	–	2.0±1.0	1.5±1.0	2.0±1.0	NS
PCI	%	86.7	84.1	92.1	NS

STE-ACS – ST segment-elevation acute coronary syndrome; NSTE-ACS – non-STE-ACS; TTE – transthoracic echocardiography; CAG – coronary angiography; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; PAD – peripheral arterial disease; AF – atrial fibrillation; AFl – atrial flutter; LV – left ventricular; RWMA – regional wall-motion abnormalities; PCI – percutaneous coronary intervention.

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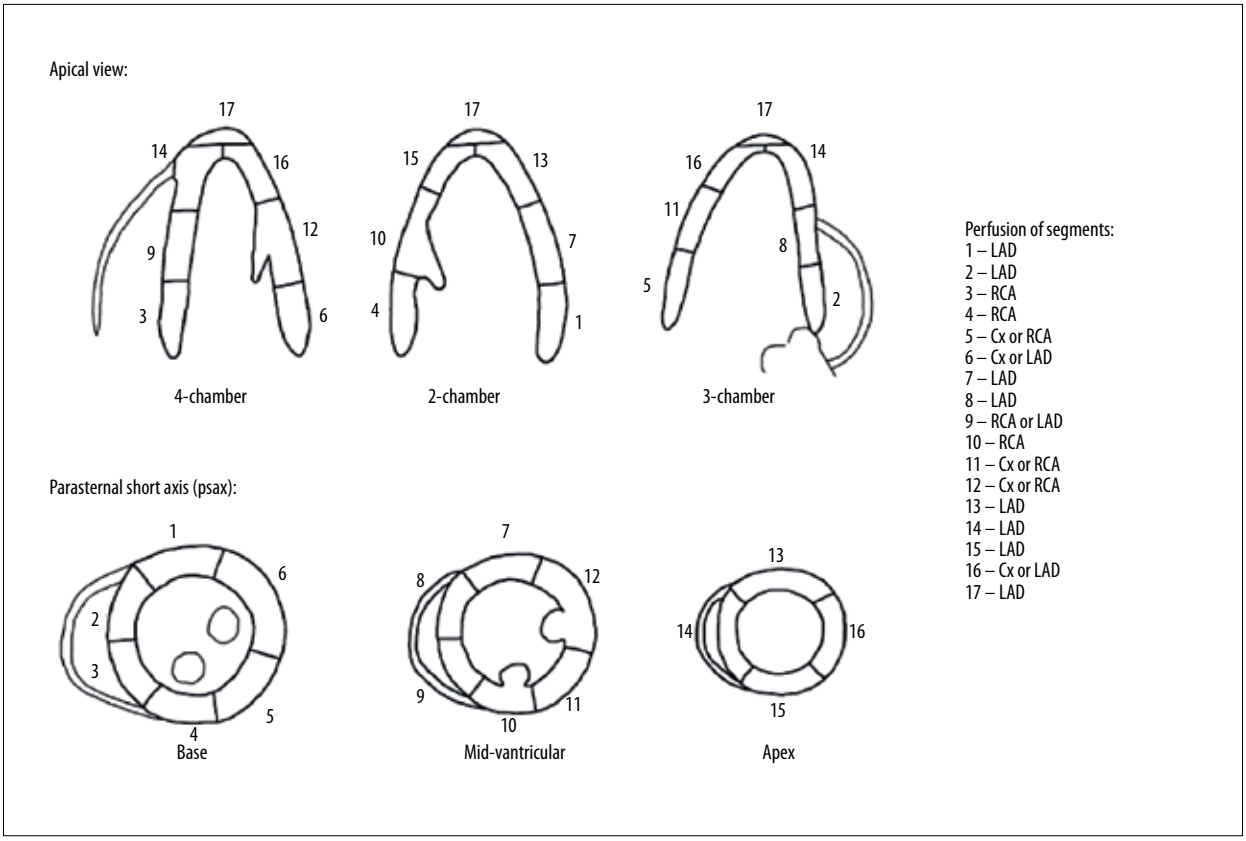

Figure 2. The 17-segment model and its correspondence to perfusion by coronary arteries (according to References [8], [12], and [13], modified), depicts the fundamental methodological approach.

arteries according to American Society of Echocardiography and European Society of Cardiovascular Imaging recommendations [12] and were consistent with the perfusion territories segmentation [13], according to the model shown in Figure 2. Each patient's individual coronary anatomy on angiogram was reviewed and matched to corresponding segments on echocardiogram by agreement by 2 experienced echocardiographers [14] and an invasive cardiologist [15]. When matching coronary lesions (the ACS culprit lesion plus, if present, other lesions ≥70% diameter stenosis) with RWMA segments, anatomical variants were considered [12]. In case of RWMA presence in segment(s) adjacent to the ischemic region, the adjacent segment stunning was regarded as ischemic [13]. Contractility impairment in absence of the attributable ischemic cause was considered neurogenic. Six-month control echocardiograms were compared, on a segmental basis, with the index recordings; regional and global systolic function was evaluated and compared against the baseline. For a full clinical and demographic characteristic of the study subgroups, see Table 1. Clinical data were captured into the study database from each individual's medical history. The presence of a recent (within 7 days) major psychological stressor self-reported by the patient was recorded. Major psychological stressor was defined as a severe, acute, untypical and unexpected, life-changing event [16,17]. The study complied with the local bioethics requirements, in concordance with the Declaration of Helsinki.

Statistical analysis

Shapiro-Wilk's test was used to evaluate continuous data distribution and Levene's test was applied to check for homogeneity of variances. Because almost all variables did not meet the criteria required for parametric testing, the between-group differences were assessed with Mann-Whitney's U test or Kruskal-Wallis rank ANOVA, as appropriate. Values are presented as medians ± interquartile range. Chi-square testing of proportions was applied, as appropriate. Logistic regression analysis was done uni- and multivariately using the backward elimination method. Type I error margin was set at α=0.05. Analysis was performed using the STATISTICA ver. 12 data analysis software system (StatSoft, Inc., 2014).

Results

ST segment elevation ACS (STE-ACS) was present in 38 (31.7%) study patients, whereas 82 (68.3%) suffered from non-ST segment elevation ACS (NSTE-ACS; Table 1). The NSTE-ACS group

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Table 2. Key clinical, echocardiographic and angiographic data by final diagnosis inclusive of the neurogenic component (parameters evaluated as per Table 1 – only significant differences shown).

	Unit	I (N=91)	I&N (N=21)	N (N=8)	p Value
Clinical features					
Hypertension	%	80.2	76.2	25.0	0.002
DM or prediabetes	%	38.5	33.3	0	0.02
Recent major psychological stressor	%	3.3	9.5	25.0	0.03
TTE and CAG data					
RWMA on admission	%	68.1	100	87.5	0.007
Segments with RWMA	–	2±4.0	17±11.0	3±16.5	<0.05
Without significant atherosclerosis	%	1.1	0	100	<0.001
Critical stenosis in coronary angiography	%	97.8	90.5	0	<0.001
Vessels with critical obstruction	–	2±1.0	1±0.0	0±0.0	<0.001
PCI	%	94.5	85.7	0	<0.001

I – ischemic contractility impairment; I&N – partially ischemic & partially neurogenic contractility impairment; N – pure neurogenic contractility impairment; DM – diabetes mellitus; TTE – transthoracic echocardiography; CAG – coronary angiography; RWMA – regional wall-motion abnormalities; PCI – percutaneous coronary intervention.

was 59.8% patients with NSTEMI and 40.2% with unstable angina (UA). Purely neurogenic, N, contractility impairment (i.e., in the absence of ischemic evidence) occurred in 8 (6.7%) patients, whereas in 21 (17.5%) study subjects, both ischemic and neurogenic, I&N, and myocardial contractility impairment were identified, as shown in Table 2. In the remaining 91 subjects (75.8%) no evidence of neurogenic contractility impairment was found (the purely ischemic group, I). Neurogenic component (NC), contributing to myocardial contractility impairment in either pure N or I&N, occurred in 24.2% of the overall study cohort; its prevalence was similar in STE-ACS *vs.* NSTE-ACS (28.9% *vs.* 21.9% p=0.41).

A major stressor preceding symptom onset was reported in 3.3% of patients in I, 9.5% in I&N, and 25.0% in N (p=0.03). Diabetes or pre-diabetes was present in 38.5% *vs.* 33.5% *vs.* 0% (I *vs.* I&N *vs.* N; p=0.02). The number of LV segments with contractility impairment was higher in I&N (17±11) than in I and N (2±4, p<0.001 and 3±16, p=0.044, respectively; Table 2).

The wall-motion score (WMS), indicating the magnitude of contractility impairment, was higher in I&N than in I and N, both at baseline (respectively 2.000±0.764 *vs.* 1.176±0.294; p<0.001 and 1.265±0.971; p<0.05) and at 6 months (1.529±0.882 *vs.* 1.118±0.353; p=0.006 and 1.000±0.147; p=0.02). However, this group (I&N) also showed greater improvement than the I group, expressed as WMS reduction at 6 months (–0.353±0.706 *vs.* 0.000±0.176; p<0.001; Figure 3). LVEF at baseline was lower in I&N than in I (37±13.6 *vs.* 52.8±11; p<0.001), but at 6 months there were no significant between-group differences (Figure 3). Nevertheless, baseline-to-follow-up LVEF change was of significantly lower value in the I than in I&N and N groups (2.2±7.8 *vs.* 11.6±11.2; p=0.002 and 12.7±9.7; p<0.05, respectively).

NC presence was not related to age, sex, or peak myocardial necrosis markers (hs-cTNT or CK-MB; p value 0.16, 0.29, 0.44 and 0.77, respectively). NC was, however, only half as frequent in patients with history of hypertension and hyperlipidemia (19.8 *vs.* 37.9%, p=0.047 and 17.8% *vs.* 34.0%, p=0.043 correspondingly). Patients with NC presented with lower global LVEF on admission (45±17.5 *vs.* 55±14, p<0.001), whereas LVEF after 6 months was not statistically different between groups (52±15 *vs.* 60±12, p=0.26). The magnitude of LVEF improvement was significantly greater if NC was present (12±15.5 *vs.* 0.5±8, p<0.001).

Baseline-to-follow-up increase in LVEF was observed in 67 individuals (56.3%), more often if NC was present (75.9% *vs.* 50.0%, relative risk RR=1.52, p=0.026). In multiple logistic regression analysis, factors univariately associated with LVEF increase at 6 months follow-up included presence of major psychological stressor in anamnesis (p=0.004) and presence of NC (p=0.012); younger age was borderline insignificant (p=0.08). In multivariate analysis, after adjusting for age, sex, and peak necrotic markers (hs-cTnT and CK-MB), the presence of NC was associated with LVEF increase (OR=2.99, 95%CI: 1.16–7.76, p=0.024).

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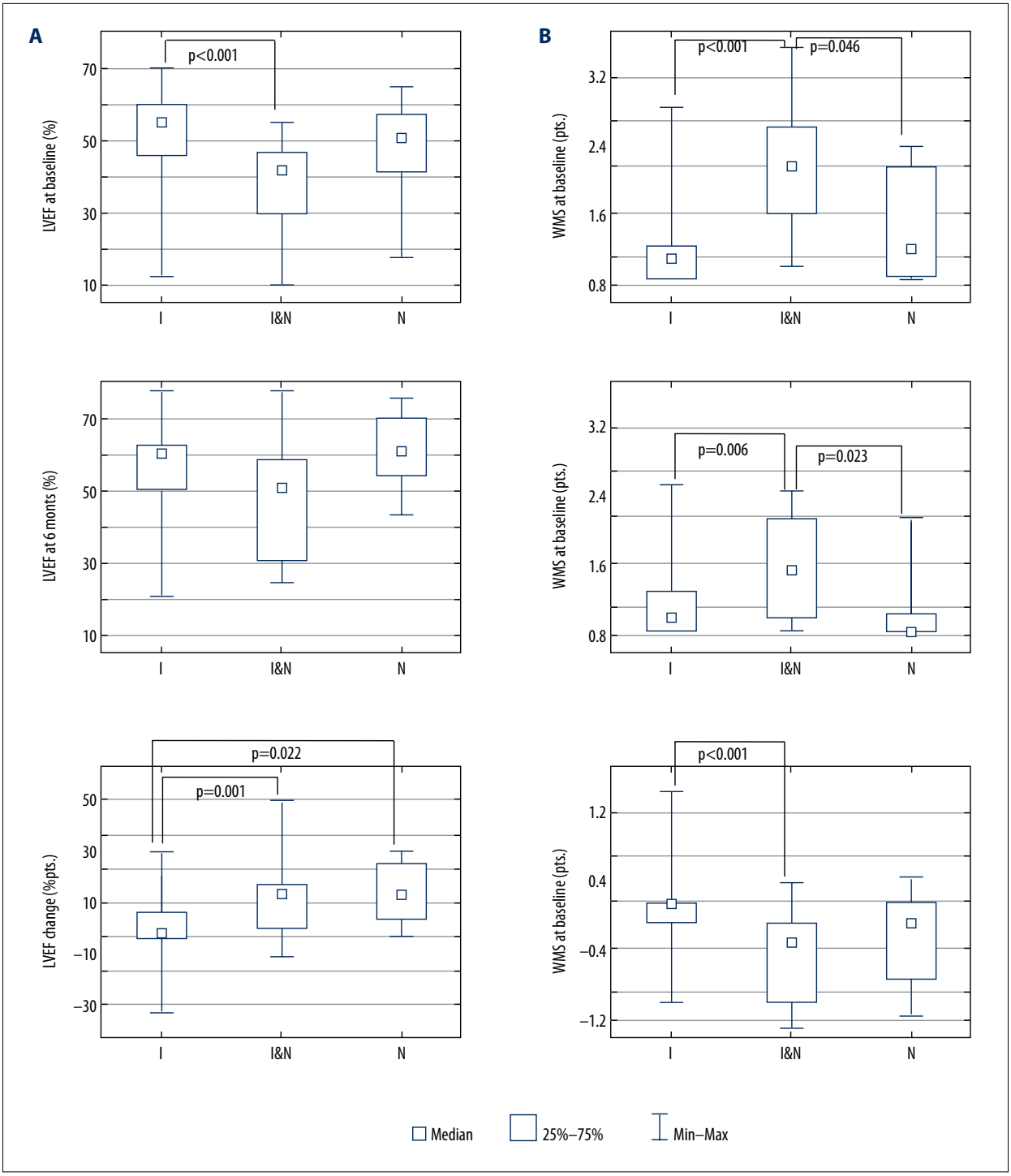

Figure 3. Contractility indices by final diagnosis. (**A**) Left ventricular ejection fraction (LVEF). (**B**) Wall motion score (WMS – higher value indicates greater contractility impairment). All significant differences are indicated in the graphs (Kruskal-Wallis non-parametric ANOVA and post hoc multiple comparison test). I – ischemic contractility impairment group, I&N – partially ischemic & partially neurogenic contractility impairment group, N – neurogenic contractility impairment group, pts. – points. This represents some of the most important findings from the study.

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Discussion

The principal novel findings from this work are: (1) one in every four first-time ACS patients exhibit RWMA remote to the ischemic region(s), indicating a neurogenic rather than ischemic mechanism; (2) NC contribution to contractility impairment in ACS is blunted in diabetes or pre-diabetes; and (3) LV systolic function recovery is better in patients with NC.

The recognition of NC in this study in nearly 24.2% of first-time ACS patients (and without any previous history of CAD or heart failure), suggests that NC is not only theoretically (Figure 1), but also clinically important. Indeed, our results indicate that NC presence is associated with better prognosis on LV systolic function recovery at 6 months after ACS both in univariate and multivariate analyses (Figure 3).

Although the role of stress receives growing attention in cardiovascular medicine, the understanding of stress as a risk factor and disease contributor in the clinical setting has been limited [18]. This work provides important input into the emerging field of psychosomatic cardiology [19]. So far, the interest in the role of NC in acute contractility impairment has been practically limited to takotsubo syndrome, reported to occur in 0.7% to 5% of ACS patients [20–22]. These estimates, however, focus mainly on the classic form of apical ballooning takotsubo syndrome accounting for about 80% of recognized and reported cases, whereas in neurogenic and experimental stress cardiomyopathies, the classic pattern accounts for only 40–50% of cases [4,6,20,22]. Hibernation [23] did not affect assessment of neurogenic stunning in remote segments in our study, since RWMA in areas with critical stenoses were attributed to ischemia. Also, we only included new-comer ACS patients, without any previous history of coronary disease or heart failure, to minimize the risk of attributing any old RWMA to current neurogenic or ischemic damage related to ACS.

In parallel to takotsubo syndrome, which has been attracting the attention of cardiologists [2,3,6,20,24], as it may have significant clinical consequences [25], the importance of neurologically-mediated LV contractility impairment has been highlighted by research in neurology, which identified the substantial role of neurogenic stress cardiomyopathy in acute neurologic states [4,5,7], including exacerbations of psychiatric disorders [26]. Short-term RWMA extending beyond the supply area of a single coronary artery are typically found in takotsubo syndrome and other conditions from stress-related cardiomyopathy syndrome spectrum [4,6,8,24,27,28]. These conditions are caused by various stressors, either psychological or physical, or insults to stress regulatory pathways in the central nervous system, and share similar clinical presentation, as well as laboratory and pathologic findings, and usually require the same treatment [4,8,22,24,28]. They also seem to have a common, well-established pathogenesis of sympathetic catecholamine overload at the nerve terminals in the heart, although some alternative theories exist [4,6]. Our present findings are thus consistent with recent developments in elucidation of the "brain-heart crosstalk" and its clinical implications [3,4,6,7,20–22,24,28].

Infarct size has been documented as the key determinant of LV function recovery after ACS [15,29]. Our present findings indicate that the NC also plays an important role. On the one hand, NC aggravates the magnitude of LV contractility reduction in the acute phase, but on the other hand, the LV function recovery is better in subjects with NC involvement at baseline (Figure 3). Circumstantial evidence shows that cytokines may also play a role in ischemic myocardial stunning [9,27,30]. The relative contributions of the NC and cytokines, and their role in acute contractility impairment [27,31], infarct size, and LV function recovery, require further evaluation [4].

Our findings suggest that the neurogenic contribution to myocardial contractility impairment in all-comer ACS is blunted in diabetes (Table 2). The role of diabetes in myocardial function recovery after ACS is a subject of intensive research [32–34]. The prevalence of diabetes is lower in takotsubo patients [35], consistent with the role of intact cardiac autonomic innervation and individual susceptibility in precipitating neurogenic and/or psychological stress-induced contractility impairment [4,6,36,37].

Limitations

This work, although relatively large by standards in the field [8,13], is only able to estimate rather than precisely evaluate the prevalence of NC contribution because certain phenomena (such as purely neurogenic contractility impairment) are rare. Therefore, exact determination of the proportion of patients with purely neurogenic and partly neurogenic contractility impairment requires a larger-study sample. Importantly, we have evaluated an all-comer ACS sample; this, on the one hand, is a strength of this work; but on the other hand, particularities may exist for STE- and NSTE-ACS patients [15,38]. Secondly, even though we used the commonly accepted model to correlate coronary anatomy (taking into consideration anatomic variants) with RWMA [12], the match cannot be considered fully accurate, due to the limitations inherent to the methods [13]. Thirdly, the present work has focused on systolic function, but it is known that ischemia affects (in a subtler manner) the diastolic function as well [14,38,39]. Finally, in this study, ischemic damage could be attributed only to lesions visualized on coronary angiography, so an undocumented coronary spasm or a spontaneously resolved intracoronary thrombus could not be considered, although there has been a report struggling to differentiate these conditions [40].

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Conclusions

ACS patients exhibit RWMA remote to the ischemic region(s), consistent with a neurogenic rather than ischemic mechanism. The neurogenic contribution to contractility impairment in ACS is blunted in diabetes or pre-diabetes. LV systolic function recovery is better in patients with NC. Our findings provide novel evidence to support the concept of a broad spectrum of neurocardiogenic injury [41]. Further work is needed to explore the role of individual susceptibility to the clinical manifestations of the brain-heart crosstalk and its relevance to long-term prognosis.

Conflict of interest

None.

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