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Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome

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Aims To study coronary microvascular dysfunction as possible pathogenetic mechanism in Apical Ballooning Syndrome (ABS).

Methods and results Fifteen ABS patients (all women, 68 ± 14 years) underwent myocardial contrast echocardiography at baseline during adenosine infusion (140 μg/kg/min) and at 1-month follow-up and compared with a group of anterior ST-elevation myocardial infarction (STEMI) patients with similar clinical characteristics. Myocardial perfusion was assessed by contrast score index (CSI) and endocardial length of contrast defect (contrast defect length, CDL), whereas myocardial dysfunction by wall motion score index (WMSI), endocardial length of contractile dysfunction (wall motion defect length, WMDL), and LV ejection fraction (LVEF). At baseline, no difference in myocardial perfusion and dysfunction were present between the two groups. During adenosine challenge, while no changes were observed in STEMI group, in ABS patients CSI, CDL, WMSI, and WMDL significantly decreased compared with baseline ($P < 0.001$ vs. baseline for all parameters) and LVEF significantly increased ($P = 0.01$ vs. baseline). At 1-month follow-up, myocardial perfusion and dysfunction completely recovered in ABS patients ($P < 0.001$ vs. baseline for all parameters), whereas no significant changes were observed in STEMI group.

Conclusion Our data strongly suggest that in ABS, irrespectively of its underlying aetiology, acute and reversible coronary microvascular vasoconstriction could represent a common pathophysiological mechanism.

Keywords Apical Ballooning Syndrome • Adenosine • Coronary microvascular dysfunction • Myocardial contrast echocardiography

Introduction

Apical Ballooning Syndrome (ABS), also known as Tako-Tsubo or stress cardiomyopathy, is an emerging clinical syndrome presenting with acute chest pain or dyspnoea, associated with new ST-T segment abnormalities, regional transient myocardial dysfunction, typically localized at left ventricular (LV) apex and usually extended beyond a single vessel territory, serum cardiac enzyme release, and absence of significant coronary lesions at coronary angiography.[1] Among patients presenting with clinically suspected acute coronary syndrome (ACS), its prevalence is reported to range between 1.2 and 2.0% and it occurs almost exclusively in postmenopausal women, being often associated with emotional or physical stress.[2,3]

Although initially clinically indistinguishable from an ACS, some characteristics of ABS, such as the involvement of a myocardial area that extends beyond a single coronary vessel territory and that completely and rapidly recovers in few days or weeks, together with the slight elevation in serum cardiac enzyme levels, make of ABS a unique model of transient and completely reversible myocardial dysfunction, in the absence of significant epicardial coronary artery disease.

Even if several etiopathogenetic mechanisms have been proposed, such as multivessel epicardial spasm,[4,5] catecholamine-induced

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myocardial stunning,[6,7] spontaneous coronary thrombus lysis,[8] and acute microvascular spasm,[9–11] the causes of ABS are still debated. We hypothesized that, irrespectively of the underlying etiopathogenetic mechanism, ABS could be characterized by a common pathophysiological pattern involving acute and transient coronary microvascular dysfunction. To test this hypothesis, we studied consecutive patients presenting with clinical characteristics of ABS using myocardial contrast echocardiography (MCE) at baseline, during adenosine infusion, and at 1-month follow-up when compared with a group anterior ST-elevation myocardial infarction (STEMI) patients with similar clinical characteristics.

Methods

Study population

We designed an observational study to assess, in patients with ABS, the presence of microvascular dysfunction at rest, along with possible changes during adenosine infusion and at follow-up. We subsequently compared presence, extent, pharmacological and temporal changes of microvascular dysfunction observed in ABS patients with that observed in a group of STEMI patients with microvascular damage (no-reflow), in order to select a control group with similar perfusion defect and myocardial dysfunction at presentation.

Specifically, from November 2007 to June 2009, we enrolled 15 consecutive patients presenting with ABS and 15 anterior STEMI patients with similar clinical characteristics admitted to the coronary care unit of our Institution. Apical ballooning syndrome patients were enrolled accordingly to the commonly accepted Mayo Clinic criteria[1]: (i) clinical presentation with acute chest pain, dyspnoea, or syncope; (ii) new ST-T segment abnormalities in at least two contiguous ECG leads; (iii) cardiac troponin T (cTnT) concentration three times higher than the upper normal level (normal value <0.03 ng/mL); (iv) ventriculographic and echocardiographic evidence of apical a-dyskinesia, and (v) absence of coronary stenosis $>50\%$ at coronary angiography. Exclusion criteria included previous history of myocardial infarction, idiopathic cardiomyopathy or coexistence of acute subaracnoid haemorrhage or pheochromocytoma. ST-elevation myocardial infarction group was represented by 15 patients presenting with (i) typical chest pain; (ii) ST-segment elevation >0.2 mV in at least two contiguous anterior ECG leads; (iii) cTnT concentration three times higher than the upper normal level, (iv) angiographic evidence of acute thrombotic occlusion of left anterior descendent artery, and (v) evidence of microvascular damage (no-reflow) at MCE at $3 + 2$ days after the acute event.

Coronary angiography and left ventriculography was performed in all ABS patients, within 6 h from symptoms onset in those presenting with ST-segment elevation, or within 48 h in those presenting with ST-segment changes but without elevation. Cocaine abuse was excluded in all our patients by specific dosage of urinary catabolites. In the acute phase, ABS and STEMI patients, as they had a similar clinical presentation, were treated with acetilsalicylic acid, clopidogrel (600 mg oral bolus followed by 75 mg daily), heparin (initial weight adjusted intravenous bolus then further boluses administered). Unless contraindicated, abciximab (0.25 mg/kg bolus plus infusion of 0.125 g/kg/min for 12 h) was intravenously administered in STEMI patients undergoing primary percutaneous coronary intervention (PCI). Coronary artery disease was defined as 50% stenosis in the luminal diameter of the major epicardial coronary artery. ST-elevation myocardial infarction patients were successfully submitted to primary PCI, within 6 h from symptoms onset. Briefly, after crossing the target lesion with the guidewire, direct stent implantation was attempted, if judged possible by the operator, whereas in the remaining cases, manual thrombus aspiration, and/or predilation with an undersized balloon was used before stent implantation, as previously described.[12] Cardiac isoenzymes, including creatine kinase-MB (CK-MB) sub-fraction and cTnT, were serially measured in all patients.

Myocardial contrast echocardiography

Both groups of patients were studied using MCE within 3 ± 2 days after symptoms onset. For functional analysis, LV was divided into the standard 16-segment segmentation. Myocardial contrast echocardiography study was performed using real-time contrast pulse sequencing operating on a Sequoia ultrasound system (Siemens, Acuson S129). As previously described,[12] contrast pulse sequencing is able to provide an image with excellent signal-to-noise ratio and with particular high sensitivity and penetration using a very low mechanical index. A second-generation ultrasound contrast agent Sonovue® (Bracco, Milan, Italy) was administered intravenously at 1 mL/min infusion rate. No side effects were observed in all patients studied during and after administration of Sonovue®. Myocardial contractility and perfusion were studied at baseline and at peak of 90 s intravenous infusion of adenosine (140 μg/kg/min). Regional wall motion was semiquantitatively scored by two experienced blinded observers according to the recommendations of the American Society of Echocardiography[13] (1 = normal, 2 = hypokinesia, 3 = akinesia) and a wall motion score index (WMSI) was calculated by the sum of the score of all segments divided by the total number of segments. Myocardial contractility defect length was also assessed by measuring the endocardial length of wall motion abnormality (wall motion defect length, WMDL) in each apical view, averaged, and then expressed as (WMDL/LV endocardial length) $\times$ 100.[12].

Myocardial opacification at MCE was visually assessed in each of the 16 myocardial segments and semiquantitatively scored as previously described.[12] Single perfusion score was assigned to each myocardial segment on the basis of the degree of opacification at the peak contrast effect.[14] Scores were graded as 1 = normal, 2 = reduced, or 3 = absent opacification. Contrast score index (CSI) was calculated by the sum of MCE score in each segment divided by the total number of segments. Myocardial perfusion defect length was also assessed by measuring the endocardial length of perfusion abnormality (contrast defect length, CDL) and then expressed as (CDL/LV endocardial length) $\times$ 100.[12]

Left ventricular volumes were calculated by the modified Simpson biplane method and LV ejection fraction (LVEF) was derived from the formula: (end-diastolic volume − end-systolic volume/end-diastolic volume) $\times$ 100. Myocardial contractility and perfusion were also re-evaluated at 1-month follow-up in both groups of patients.

All patients gave written informed consent to participate to the study for research and publication purposes and to all procedures associated with the study. The study complied with the Declaration of Helsinki and was approved by our institutional Ethics Committee.

Reproducibility

To assess intraobserver variability of MCE analysis, 20 MCE studies obtained in five ABS and five STEMI patients were independently reviewed by the same observer (A.R.D.C.) 60 ± 14 days after initial scoring. Both readers (A.R.D.C. and L.G.) were blinded to the clinical diagnosis (ABS vs. STEMI) of all patients. Interobserver variability was assessed by comparing the reading of two observers (A.R.D.C. and L.G.). Intraobserver and interobserver variability of CSI analysis was 2.2 ± 1.9 and $4.2 \pm 2.7\%$ (absolute difference), with a *K*-value for

agreement of 0.91 and 0.95, respectively. Intraobserver and interobserver variability of WMSI analysis was 3.3 ± 2.1 and 4.7 ± 3.1% (absolute difference), with a *K*-value for agreement of 0.89 and 0.93, respectively. For LV volume analysis, intra- and interobserver variability was 3.5 ± 1.5 and 5.2 ± 2.5%, with a *K*-value for agreement of 0.90 and 0.94, respectively.

Statistical analysis

As all measured parameters showed a normal distribution, data are presented as mean ± SD. Categorical variables were compared by Fisher's exact test. Continuous variables of different study conditions within the same study group were compared by two-way ANOVA for repeated measures followed by Bonferroni's adjustment, whereas comparisons between groups were performed by unpaired Student *t*-test. A two-sided *P*-value lower than 0.05 was always required for statistical significance. Statistics were performed by using the statistical software package SPSS version 15.0.

Results

Characteristics of the study population

Clinical characteristics of the two groups are presented in *Table 1*. ABS patients were all female, were less smokers, and generally tended to have less cardiovascular risk factors than STEMI patients. Clinical presentation was similar to STEMI patients and followed recent emotional or physical stress in the majority of ABS patients. ST-segment elevation was present in 11 of the 15 ABS patients. The majority of STEMI patients showed single vessel disease (LAD), whereas the two other patients also had a critical stenosis of right and circumflex coronary artery, respectively, that were both successfully treated the day after primary PCI. Left ventricular outflow tract obstruction (mean gradient <20 mmHg) was present in three ABS patients. Mean peak cTnT and CK-MB value levels were significantly lower in ABS when compared with STEMI patients ($P < 0.001$ for both). At 1-month follow-up, ECG in all ABS patients was completely normalized.\

Regional myocardial perfusion

All ABS patients showed a perfusion defect within the dysfunctional myocardial region (*Figure 1A*), that was transmural in the majority of ABS patients (11 of 15). The extent of perfusion defect significantly decreased during adenosine infusion (*Figure 1B*) with regard to both CSI (1.48 ± 0.17 vs. 1.28 ± 0.17, $P < 0.001$, *Figure 2A*) and CDL (22.7 ± 5.9 vs. 14.8 ± 7.1% of LV endocardial length, $P < 0.001$; *Figure 2C*) in all patients, promptly returning to baseline resting conditions after cessation of adenosine infusion. At 1-month follow-up, myocardial perfusion significantly improved when compared with baseline (CSI 1.00 ± 0.02, $P < 0.001$ vs. baseline, *Figure 2A*; CDL 0.7 ± 2.0% of LV endocardial length, $P < 0.001$ vs. baseline, *Figure 2C*), being completely normal in 13 ABS patients.

Patients in the STEMI group showed a baseline perfusion defect similar to ABS patients (transmural in 12 of 15 patients; CSI 1.58 ± 0.23, $P = 0.21$ vs. ABS, *Figure 2B*; CDL 23.7 ± 8.3% of LV endocardial length $P = 0.68$ vs. ABS, *Figure 2D*), which did not change during adenosine infusion with regard to both CSI (1.56 ± 0.22, $P = 0.76$ vs. baseline, *Figure 2B*) and CDL (23.1 ± 8.5% of LV endocardial length, $P = 0.83$ vs. baseline, *Figure 2D*). At 1-month follow-up, no significant differences in myocardial perfusion were

Table 1 Clinical characteristics

	ABS	STEMI	*P*-value
n	15	15	
Age	68 ± 14	61 ± 11	0.14
Female, *n* (%)	15 (100)	12 (80)	0.22
Caucasian, *n* (%)	15 (100)	15 (100)	1
Acute chest pain, *n* (%)	13 (87)	15 (100)	0.48
Recent physical or emotional stress	10 (67)	1 (7)	<0.01
ST-segment elevation, *n* (%)	11 (73)	15 (100)	<0.01
Single vessel disease (LAD), *n* (%)	0 (0)	13 (87)	<0.001
Final TIMI flow 3, *n* (%)	14 (93)	11 (73)	0.33
LV hyperthophy, *n* (%)	5 (33)	6 (40)	1
LV outflow obstruction, *n* (%)	3 (20)	0 (0)	0.22
Peak enzyme levels			
TnT (ng/mL)	0.75 ± 0.69	13.22 ± 11.51	<0.001
CK-MB (ng/mL)	20.29 ± 13.10	326.51 ± 202.01	<0.001
Cardiovascular risk factors			
Dyslipidaemia, *n* (%)	6 (40)	8 (53)	0.05
Hypertension, *n* (%)	6 (40)	9 (60)	0.47
Diabetes, *n* (%)	1 (7)	2 (13)	1
Smoke, *n* (%)	3 (20)	10 (67)	0.02
IHD familiarity, *n* (%)	5 (33)	8 (53)	0.46

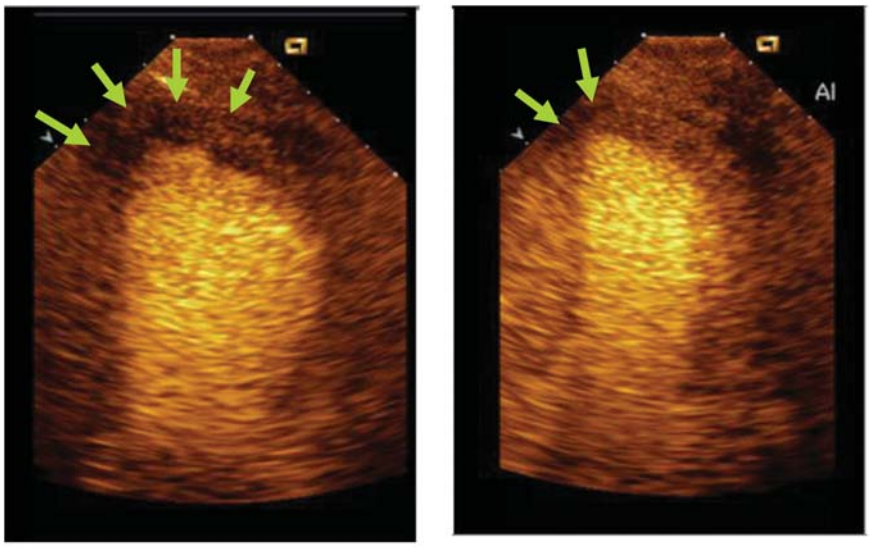

Figure 1 Myocardial contrast echocardiography. (*A*) A clear perfusion defect is present at baseline within LV apical myocardium (arrows). (*B*) During adenosine, a significant decrease in the extent of the perfusion defect is evident.

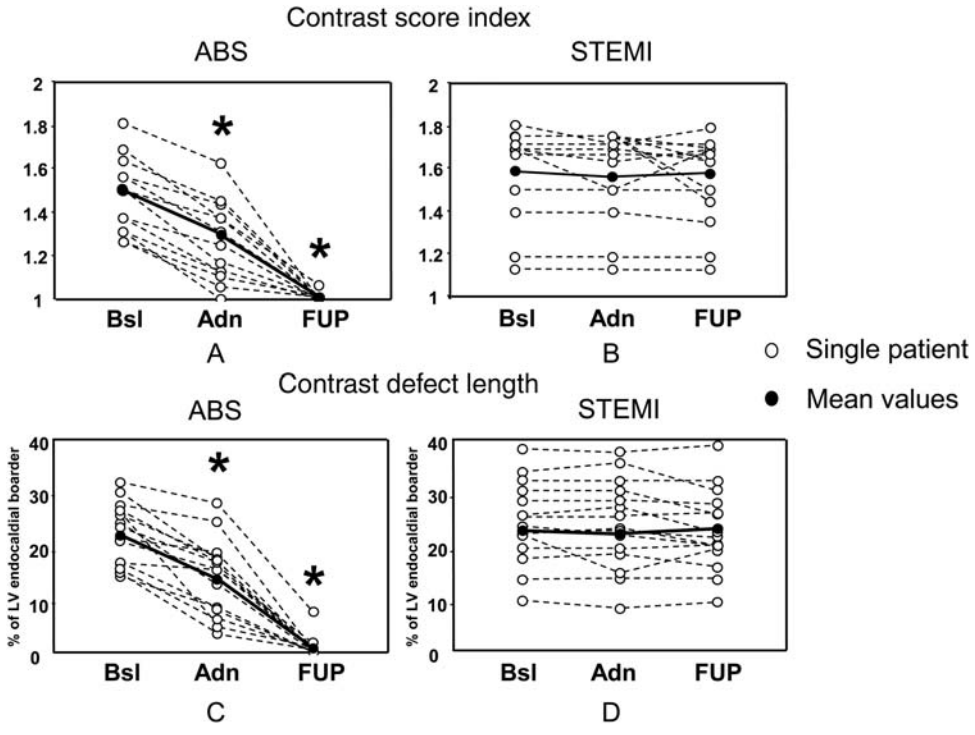

Figure 2 Myocardial perfusion. Contrast score index (CSI) (*A* and *B*) and contrast defect length (CDL) (*C* and *D*) at baseline (Bsl), at peak of 90 s adenosine infusion (Adn) and at 1-month follow-up (FUP) in ABS and STEMI patients. *$P < 0.001$ vs. bsl.

observed when compared with baseline in STEMI patients (CSI 1.58 ± 0.23, $P = 1$ vs. baseline, *Figure 2B*; CDL 24.2 ± 8.3% of LV endocardial length, $P = 0.71$ vs. baseline, *Figure 2D*).

Regional myocardial dysfunction

In all ABS patients, regional myocardial dysfunction, as shown by both left ventriculography and transthoracic echocardiography,

involved LV apex and spared LV basal segments. Specifically, in five ABS patients myocardial dysfunction was limited to LV apex, in five it was extended to all mid-ventricular segments, in two it involved mid-ventricular anterior and inferior interventricular septum and LV inferior wall, in one mid-ventricular antero-lateral wall, and in two anterior or inferior interventricular septum, respectively.

At baseline, no significant difference between haemodynamic variables were present between ABS and STEMI groups (mean blood pressure 84 ± 12 vs. 85 ± 13 mmHg, $P = 0.58$, respectively; heart rate 63 ± 11 vs. 62 ± 11 b.p.m., $P = 0.42$). During adenosine mean blood pressure decreased (79 ± 11 and 80 ± 12 mmHg, $P = 0.02$, respectively) and heart rate increased (71 ± 13 and 73 ± 11 b.p.m., $P < 0.01$, respectively) to a similar extent in both groups ($P = 0.47$ and $P = 0.57$ between groups, respectively).

At baseline, in both ABS and STEMI patients, regional myocardial dysfunction was significantly larger than myocardial perfusion defect (in ABS patients WMDL 35.7 ± 12.8 vs. CDL 22.7 ± 5.9% of LV endocardial length, $P < 0.001$; in STEMI patients WMDL 41.3 ± 12.8 vs. CDL 23.7 ± 8.3% of LV endocardial length, $P < 0.001$).

Regional wall motion abnormalities temporarily decreased during adenosine infusion in ABS patients with regard to both WMSI (from 1.79 ± 0.24 to 1.51 ± 0.28, $P < 0.001$, *Figure 3A*) and WMDL (from 35.7 ± 12.8 to 26.2 ± 13.0% of LV endocardial length, $P < 0.001$, *Figure 3C*), promptly returning to baseline values immediately after cessation of adenosine infusion. Conversely, in STEMI patients, adenosine challenge did not change the extent of myocardial dysfunction with regard to both WMSI (from 1.93 ± 0.22 to 1.92 ± 0.23, $P = 0.93$, *Figure 3B*) and WMDL (from 41.3 ± 12.8 to 42.0 ± 12.2% of LV endocardial length, $P = 0.88$, *Figure 3D*). When compared with baseline condition, during adenosine infusion left ventricular end-diastolic volume (LVEDV) showed no significant difference in both groups (in ABS from 101 ± 20 to 100 ± 16 mL, $P = 0.85$, *Figure 4A*; in STEMI from 99 ± 22 to 101 ± 22 mL, $P = 0.86$, *Figure 4B*), whereas left ventricular end-systolic volume (LVESV) significantly decreased only in ABS (in ABS from 56 ± 11 to 50 ± 13 mL, $P = 0.03$, *Figure 4C*; in STEMI from 55 ± 17 to 56 ± 17 mL, $P = 0.87$, *Figure 4D*). Consequently, LVEF improved only in ABS group (from 45 ± 7 to 50 ± 7%, $P = 0.01$, *Figure 5A*), whereas no changes were observed in STEMI patients (from 45 ± 9 to 44 ± 10%, $P = 0.94$, *Figure 5B*).

At 1-month follow-up, a significant improvement in regional myocardial contractility, paralleling the improvement in myocardial perfusion, was observed in ABS patients (WMSI 1.03 ± 0.05, $P < 0.001$ vs. baseline, *Figure 3A*; WMDL 1.7 ± 3.9% of LV endocardial length, $P < 0.001$ vs. baseline, *Figure 3C*), but not in STEMI patients (WMSI 1.85 ± 0.24, $P = 0.41$ vs. baseline, *Figure 3B*; WMDL 38.1 ± 12.0, $P = 0.48$ vs. baseline, *Figure 3D*). Similarly, while no change was present with regard to LVEDV in both groups (in ABS 93 ± 12 mL, $P = 0.16$ vs. baseline; in STEMI 109 ± 37 mL, $P = 0.32$ vs. baseline), a significant decrease with regard to LVESV was evident in ABS patients and not in STEMI group (in ABS 36 ± 7 mL, $P < 0.001$ vs. baseline, *Figure 4C*; in STEMI 57 ± 26 mL, $P = 0.74$ vs. baseline). Consequently, at 1-month follow-up, LVEF significantly improved only in ABS (61 ± 3, $P < 0.001$ vs. baseline, *Figure 5A*) but not in STEMI patients (48 ± 10%, $P = 0.33$ vs. baseline, *Figure 5B*).

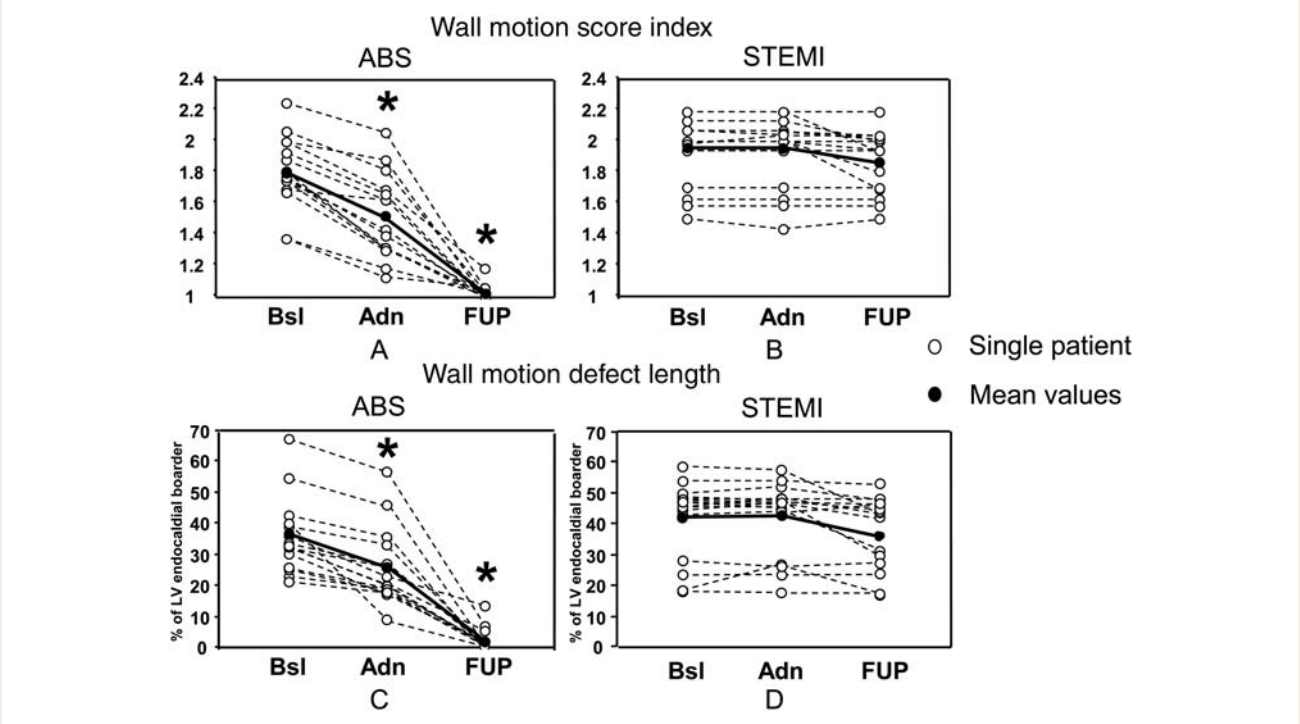

Figure 3 Myocardial dysfunction. Wall motion score index (WMSI) (*A* and *B*) and wall motion defect length (WMDL) (*C* and *D*) at baseline (Bsl), at peak of 90 s adenosine infusion (Adn) and at 1-month follow-up (FUP) in ABS and STEMI patients. *$P < 0.001$ vs. bsl.

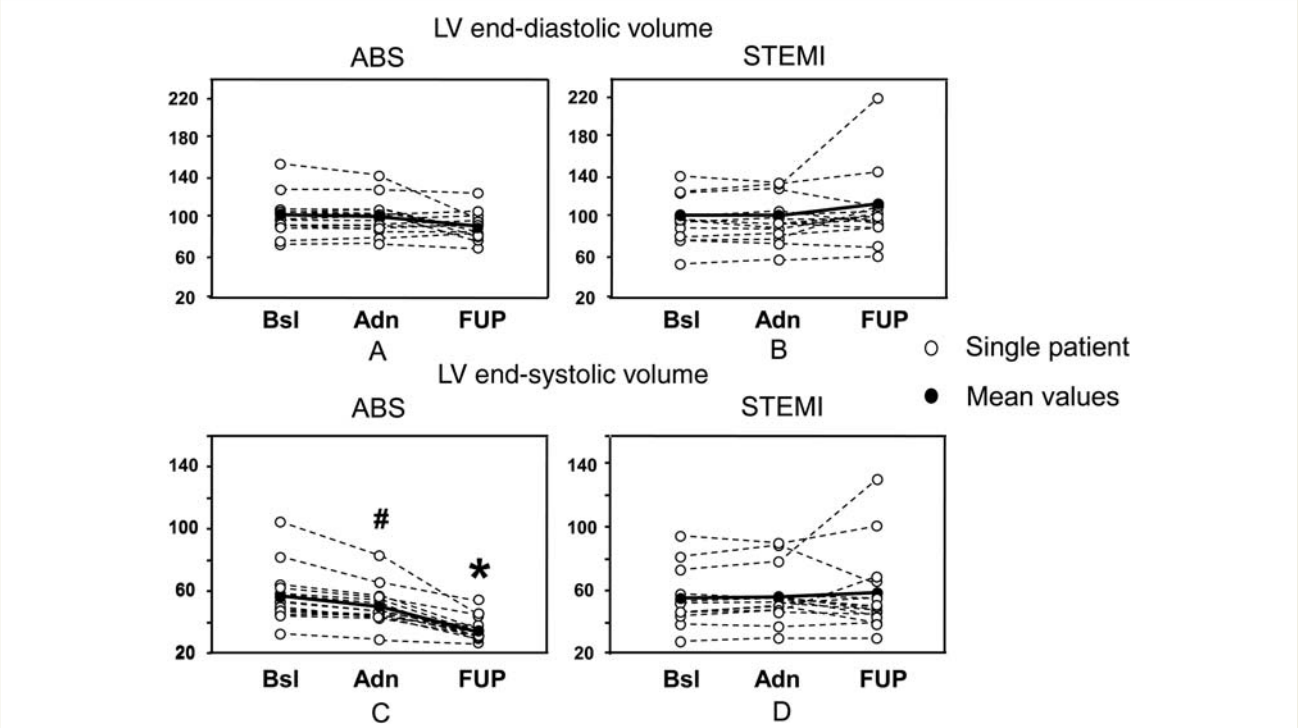

Figure 4 Left ventricular volumes. Left ventricular end-diastolic volume (LVEDV) (*A* and *B*) and left ventricular end-systolic volume (LVESV) (*C* and *D*) at baseline (Bsl), at peak of 90 s adenosine infusion (Adn), and at 1-month follow-up (FUP) in ABS and STEMI patients. $^{\#}P < 0.05$ vs. bsl; $^{*}P < 0.001$ vs. bsl.

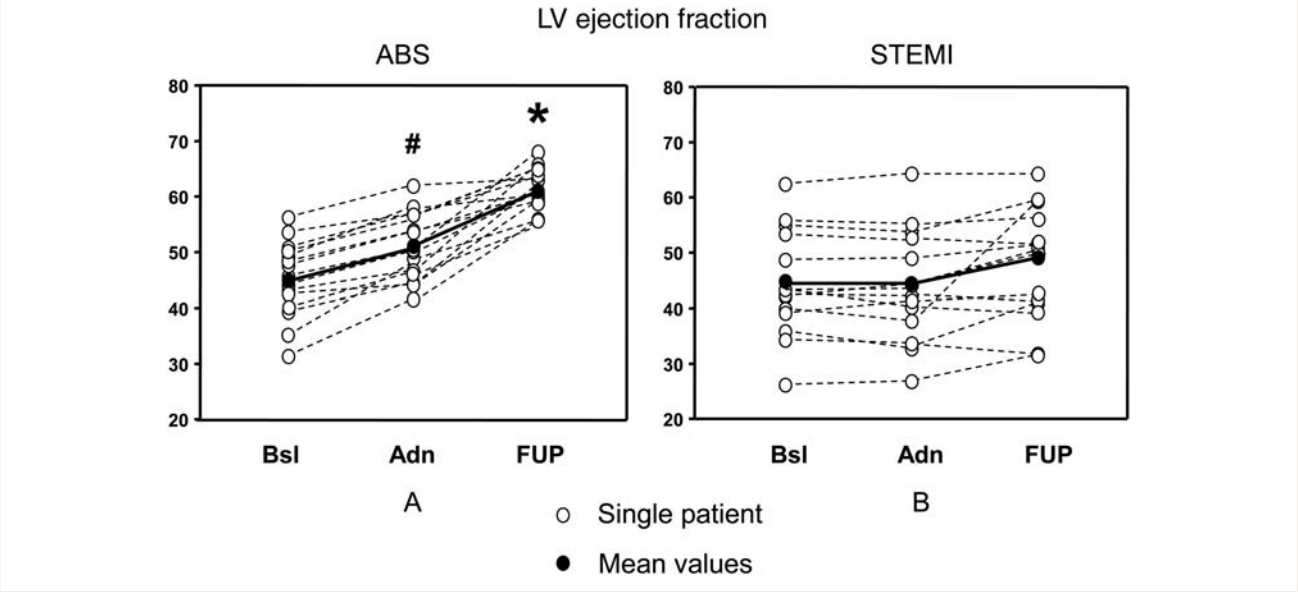

Figure 5 Left ventricular ejection fraction (LVEF). Left ventricular ejection fraction at baseline (Bsl), at peak of 90 s adenosine infusion (Adn), and at 1-month follow-up (FUP) in ABS (*A*) and STEMI patients (*B*). $^{\#}P < 0.05$ vs. bsl; $^{*}P < 0.001$ vs. bsl.

Discussion

This study provides novel insight into the pathogenesis of the emerging clinical entity of ABS. For the first time, we demonstrate that, irrespectively of its aetiology, reversible coronary microvascular dysfunction is the common pathophysiological determinant of this syndrome. In fact, in ABS patients, a clear perfusion defect was evident at MCE within the dysfunctional myocardial area. As opposed to STEMI patients, in ABS such perfusion defect was transiently reduced by adenosine and recovered at 1-month follow-up. Moreover, myocardial dysfunction was strictly related to microvascular perfusion defect, since adenosine-induced recovery of coronary microvascular perfusion was associated to significant improvement in regional myocardial dysfunction.

Clinical characteristics

At the initial clinical presentation, ABS is usually indistinguishable from an ACS, usually resembling STEMI. However, in the presence of angiographically normal coronary arteries associated with regional myocardial dysfunction, usually apical and characteristically involving more than one single coronary artery branch territory, the diagnosis of ABS can be postulated. Then, normalization of myocardial dysfunction at follow-up substantiates the definitive diagnosis of ABS.

This syndrome is relatively rare, occurring in 1.2–2.0% of all patients with a clinical presentation of ACS.[2,3] Our experience confirms the high prevalence of post-menopausal female gender and recent physical or emotional stress reported in previous studies.[3,6,7] Given the high frequency of physical or emotional stress preceding ABS symptoms onset, catecholamine-induced myocardial toxicity has been postulated as possible pathogenesis of ABS.[15] Although elevated catecholamines levels have been found in ABS patients[6] and the higher beta-receptors expression in the apical myocardium is well recognized,[16,17] this pathogenetic mechanism is still under debate. Temporal occlusion of epicardial coronary arteries, either by epicardial vessel spasm or by spontaneously lysed thrombus, has been hypothesized to explain reversible myocardial dysfunction associated with angiographically normal coronary arteries typical of ABS. However, the high frequency of spontaneous or pharmacologically induced coronary macrovascular spasm observed in Japanese patients has not been confirmed in western population.[1] The hypothesis of spontaneously lysed thrombus cannot be reconciled with the multiterritorial distribution of myocardial dysfunction in ABS and usually intact coronary vessel wall at intravascular ultrasound. Reversible myocardial dysfunction presenting as ACS and associated with unobstructed coronary arteries is also a clinical feature of myocarditis. In this regard, some cardiotropic viruses have been occasionally reported to be associated with ABS.[18] Left ventricular outflow tract obstruction, a feature previously described in ABS,[3,19] was present in a minority of our ABS patients (3 of 15), more likely as a consequence of the hypercontractility of LV base.

A possible role of coronary microvascular dysfunction has been indirectly suggested by the presence of reduced TIMI frame count in the majority of ABS patients at urgent coronary angiography[9] and by the spontaneous improvement of coronary flow reserve, as assessed by transthoracic Doppler, at 1-month follow-up.[10,11]

Coronary microvascular dysfunction as common pathogenetic mechanism in Apical Ballooning Syndrome

In all our ABS patients, a microvascular perfusion defect was present within dysfunctional myocardium. Such defect was significantly temporarily reversed by adenosine challenge and entirely resolved at 1-month follow-up. Thus, coronary microvascular constriction appears to be the common pathophysiological mechanism in ABS. The causes of such microvascular constriction may be multiple. In patients in whom ABS is associated to physical or emotional stress, it is likely that catecholamines may play a role. Moreover, the occurrence of the syndrome in post-menopausal women may support the hypothesis of stress-mediated vasoconstriction enhanced by estrogens depletion.[20] However, our study was not designed to address this issue that thus needs to be specifically addressed in future studies.

In order to further support the hypothesis that functional changes of coronary microcirculation are peculiar of ABS, we compared data of ABS patients with those of STEMI patients. We found that, despite the extent of myocardial perfusion defect was similar in the two study groups at baseline, a significant improvement of myocardial perfusion during adenosine infusion and at follow-up occurred only in ABS patients, whereas no changes were observed in STEMI patients. The finding that microvascular perfusion defect returned to baseline soon after adenosine challenge reveals the largely functional nature of coronary microvascular dysfunction in ABS, as adenosine vasodilates constricted microvessels. Conversely, in STEMI patients, microvascular perfusion defect is largely due to anatomical changes of coronary microvessels that are largely insensitive to adenosine administration and remain unchanged over time. Our data are consistent with those recently published by Rigo *et al.*[11] showing that ABS patients exhibit a reduced coronary flow reserve, as assessed by transthoracic Doppler in multiple coronary epicardial vessels, compared with normal population. These results are in line with our findings, showing that ABS is the result of coronary microvascular dysfunction.

This is not a case–control study aiming at comparing ABS with acute myocardial infarction. We designed an observational study on ABS and we then compared the presence, extent, pharmacological, and temporal changes of microvascular dysfunction observed in ABS patients with that observed in a group of STEMI patients. Accordingly, we intentionally selected as control group STEMI patients with microvascular damage at rest (no-reflow) after successful PCI, as these patients exactly resemble ABS patients at baseline MCE. We are well aware that this subgroup of STEMI patients is not representative of the entire STEMI population, since, as we and others have demonstrated,[21,22] post-PCI STEMI may be associated with different microvascular flow patterns such as reflow or no-reflow, either reversible or irreversible.

Regional myocardial dysfunction

Multiterritorial and usually apical myocardial dysfunction is a typical feature of ABS. We confirmed the presence of this pattern of myocardial dysfunction in all our ABS patients. Akynesia or hypokinesia was always localized at LV apex, usually extended from anterior to

inferior or lateral myocardial segments. It involved exclusively apical and mid-myocardial segments, whereas basal segments were always spared and often hypercontractile in the acute phase. Complete functional recovery of dysfunctional segments at 1-month follow-up was also consistent with the known characteristics of the syndrome.

An interesting and novel finding of our paper is that, along with the improvement of microvascular perfusion, in ABS patients adenosine infusion induces a transient recovery of myocardial dysfunction in the same area. It is conceivable that adenosine potent vasodilator effect resolves coronary microvascular constriction and the restoration of flow within dysfunctional but viable myocardium elicits contractile reserve. As alternative hypothesis, adenosine-induced microvascular vasodilation and consequent regional increase in blood volume might also produce a secondary increase in myocardial thickness resembling as regional improvement in contractile function. However, this has never been clearly demonstrated to be followed by an effective increase in myocardial thickening of dysfunctional hypoperfused wall. Finally, adenosine has been shown to have a cardioprotective effect independently of perfusion changes,[23] which might be considered as possible determinant of improvement in myocardial function in our ABS patients. However, the observed contractile recovery paralleled the improvement in myocardial perfusion, both occurring within 90 s of adenosine infusion. Therefore, it appears unlikely that an eventual cardioprotective adenosine effect could have played a role in such limited period of time. Our finding of adenosine-mediated improvement of myocardial perfusion and function appears to be peculiar of ABS due to the transient resolution of coronary microvascular vasoconstriction. This specific response to adenosine is strikingly different from that observed in other conditions, such as epicardial coronary artery disease or cardiac syndrome X, where pharmacological vasodilation that occurs at macrovascular or microvascular level, respectively, induces the phenomenon of coronary flow steal, thus resulting in decrease of myocardial perfusion.[24,25]

In both STEMI and ABS, the extent of myocardial dysfunction 3 ± 2 days after symptoms onset was larger than that of coronary microvascular perfusion defect. Thus, in both conditions, it is likely that the dysfunctional but perfused borderzone is the result of stunned myocardium following ischaemia–reperfusion cycle. Recovery of dysfunction after adenosine-induced improvement of flow seems to support the hypothesis of post-ischaemic stunned myocardium in the borderzone of ABS patients. However, only serial evaluation of perfusion and function after the acute event may clarify whether myocardial dysfunction is in fact caused by microvascular vasoconstriction in these patients, the former recovering only after the latter. The pathophysiology and natural history of myocardial dysfunction in the borderzone of a necrotic area in STEMI patients is more complex. Pure stunned myocardium recovers spontaneously in few days, while patchy necrosis may be present in this area but it may compromise contraction in the acute phase and prevent recovery at follow-up.[26]

Study limitations

The study cohort described in this study is relatively small. However, ABS is a rare disease so that large studies in such population are difficult to collect and might require a very long time so that only multicentre studies might add additional information. As the reported results were consistent in all patients, we feel confident in the value of the data. Although ABS may present as a NSTEMI, we did not include NSTEMI patients in the control group, because these patients usually do not have evident microvascular dysfunction at rest demonstrable with MCE.

We performed MCE 3 ± 2 days after symptoms onset in both groups of patients. However, in a disease characterized by spontaneous progressive improvement over time, it is likely that we underestimated the extent of microvascular and myocardial damage. Further studies are needed to estimate the early extent of coronary microvascular and myocardial dysfunction and its time course.

In our ABS group, both perfusion and function entirely recovered at follow-up. However, the possibility of finding persistent subclinical microvascular dysfunction should be taken into account in larger studies and a second adenosine challenge may be tested in order to detect possible decrease in microvascular flow reserve. Furthermore, although we fulfilled our goal to evaluate the presence of reversible microvascular dysfunction within regional myocardial dysfunction, we cannot exclude that subtle microvascular dysfunction exist in the remote, normally contracting myocardium.

We did not perform quantification of rate of rise and volume of microvascular perfusion utilizing MCE-specific algorithm. Although this analysis could have given additional information regarding the amount of flow in perfused territories, we were primarily interested in the quantification of the extent of true perfusion defect and of its changes.

Clinical implications

The results of this study may have important clinical implications. In fact, we demonstrate, for the first time, the key pathogenetic role of myocardial vasoconstriction in the pathogenesis of ABS. Although its clinical manifestation usually spontaneously resolves over time, ABS is not always a benign disease. In fact, as previously reported, ABS patients may experience in the acute phase life threatening arrhythmias, severe LV dysfunction and even cardiogenic shock, collectively accounting for 4% of cases.[3] Furthermore, recurrence has been described with a frequency of 3.5%.[3] The demonstration of a common pathogenetic mechanism represented by coronary microvascular constriction might become a therapeutic target. Vasodilators of coronary microcirculation like calcium channel blockers, endothelin antagonists, and adenosine are potential therapeutic agents to test in prospective randomized trials.

Conclusions

In this study, we demonstrate for the first time that, irrespectively of the underlying aetiology, ABS is sustained by a common pathogenetic mechanism that is multiterritorial reversible coronary microvascular vasoconstriction. Regional myocardial dysfunction, typical of the disease, appears to be secondary to microvascular dysfunction. These findings make of ABS a unique model of pure

and clinically relevant coronary microvascular dysfunction and let to categorize ABS from a syndrome to a distinct disease.

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