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Impaired hemodynamic response to tilt, handgrip and Valsalva manoeuvre in patients with takotsubo syndrome

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ABSTRACT

Purpose: Long-term β-adrenolytics treatment in takotsubo syndrome (TTS) patients is based on the premise, that TTS is strongly associated with sympathetic nervous system overactivity. The aim of the study was to establish hemodynamic response to tilt, handgrip and Valsalva manoeuvre in patients with takotsubo syndrome compared to healthy subjects (CONTROL) and patients after ST Elevation Myocardial Infarction (STEMI).

Material and method: Echocardiographic examination was performed at rest, ECG and continuously non-invasively measured arterial blood pressure were used for evaluation of hemodynamic responses to Valsalva manoeuvre, static handgrip (HG) followed by post-exercise ischemia, and tilt. Ten healthy women, 20 with TTS and 20 after STEMI, mean age 64 ± 8.5 years, participated in the study.

Results: Pressor response to Valsalva manoeuvre and tilt in TTS group was diminished in comparison to CONTROL and close to that of STEMI. During HG, increase of SBP was the lowest in TTS group. Data indirectly suggest that it was due to deficient stroke volume in TTS and STEMI patients during these manoeuvres; though echocardiographic findings at rest did not reveal any significant differences between groups.

Conclusions: Our data show that despite apparent resolution of the immediate effects of TTS, impaired response to cardiovascular challenge, similar to that in STEMI patients, persisted. As the manoeuvres applied mimic daily life situations, causes of impairment should be searched for and potential health risk evaluated.

1. Introduction

Takotsubo syndrome (TTS) is a clinical syndrome, characterized by transient regional wall motion abnormalities of left or right ventricle in the absence of obstructive coronary artery disease. The reasons for susceptibility of the individual patient remain unknown, however exaggerated adrenergic response to emotional or physical stimuli may be the underlying mechanism. The hypothesis that such exaggerated adrenergic response is underlying mechanism of TTS seems to be confirmed by the finding that typically two- to threefold higher plasma catecholamine level compared to patients presenting with acute myocardial infarction were found immediately after the episode of TTS. Several days later this level declined however remained substantially higher than that in patients with myocardial infarction (Wittstein et al., 2005). In the recovery phase the level of plasma catecholamine was not different from that in control subjects (Christensen et al., 2016).

Episodes of TTS most often appear in postmenopausal women and are preceded by stressful event (Peters et al., 2015). Lavi et al. demonstrated that cardiac vagal tone and baroreflex sensitivity decrease significantly in postmenopausal women and in addition, cardiovascular β-adrenoreceptor responsiveness decreases, whereas α-1 adrenoreceptor responsiveness increases (Lavi et al., 2007). Therefore, sympathetic activity replaces parasymphathetic one as the main regulator of cardiovascular system in this group. Furthermore, systemic baroreflex buffering ability is significantly reduced in postmenopausal women. These changes would affect cardiovascular responses during acute stress and would increase both heart rate and vasoconstriction. Lyon et al. have proposed that β1 (positive inotropic effects with norepinephrine) and β2 (negative inotropic effects with high concentrations of circulating epinephrine) adrenergic receptors are unevenly distributed through the myocardium. A relative abundance of β2 receptors in the apical myocardium could explain the tendency for apical suppression with basal sparing (*i.e.*, the takotsubo morphology) during the high adrenergic states with increased levels of circulating

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epinephrine (Lyon et al., 2008). Changes in the sensitivity or density of local myocardial adrenergic receptors from base to apex during menopause could help explain the pathophysiology in this group.

As it is hypothesised that TTS is strongly associated with autonomic nervous system dysfunction, various studies attempting to assess sympathetic and parasympathetic activity have been undertaken. Analysis of the autonomic tests performed in TTS patients showed that they are predisposed towards prolonged sympathetic activation, catecholamine stunning and suppressed parasympathetic modulation of the heart, in response to stressors, long after the initial TTS episode (Norcliffe-Kaufmann et al., 2016).

Contribution of the sympathetic activity in the cardiovascular reaction on Valsalva manoeuvre, handgrip test, and tilt is substantial (Zygmunt and Stanczyk, 2010). Some studies have shown that in patients with TTS these reactions are intensified, which suggests association with increased responsiveness of the sympathetic nervous system (Norcliffe-Kaufmann et al., 2016).

Despite the lack of convincing evidence for the effectiveness of long-term β-adrenolytics treatment in TTS patients, they are widely used, so it is worth knowing whether this affects their hemodynamic responses to manoeuvres that evoke strong sympathetic activation. Therefore we designed the study in which TTS patients medicated with β-adrenolytics were asked to perform Valsalva manoeuvre, handgrip combined with post-exercise ischemia and tilt. Their hemodynamic responses were compared with control subjects and post myocardial infarction patients, both groups also medicated with β-adrenolytics. It gave the possibility to compare TTS group with two other groups of subjects, one with apparently intact cardiovascular system and other with impaired one, in order to find out whether hemodynamic responses of TTS subjects are normal in line with apparent recovery of cardiac function at rest. It must be stressed that as the use of β-adrenolytics affects the sympathetic nervous system activity the cardiovascular response to autonomic tests will be altered. It is therefore reasonable to define these stimuli as functional tests and not autonomic tests.

2. Material and methods

The investigation consisted of performing a echocardiographic examination and a set of tests in a group of 50 women: 20 with takotsubo syndrome (TTS group), 20 after ST Elevation Myocardial Infarction (STEMI group) and 10 healthy subjects (CONTROL group) mean age 64 (± 8.5 years). The diagnosis of takotsubo syndrome was made according to revised Mayo Clinic criteria (Prasad et al., 2008). However, in each patient angiography was performed in order to exclude obstructive coronary disease. In case of clinical doubts MRI was used to exclude myocarditis. In every patient resolution of the left ventricle dysfunction was confirmed in control echocardiography after 4–12 weeks.

None of the patients were treated with vasodilators. Most patients in TTS and STEMI groups were treated with ACE-I (95% in both groups). Moreover, there were 4 patients after STEMI and 2 patients after TTS using diuretics. All patients after STEMI were treated with acetylsalicylic acid. None of these medications were withheld before testing. None of the patients were treated with α-adrenolytic, anticholinergic, antihistamine, analgesic and antidepressant drugs.

All subjects were medicated with β-adrenolytics at doses ranging from 2.5 to 5 mg of bisoprolol. The average dose of bisoprolol was similar in all groups.

Patients were asked to abstain from smoking, drinking coffee or consume alcohol for 12 h before the test, as well as performing excessive effort 48 h before the test. Each patient signed an informed consent form, and the study was approved by the institutional review board of the Medical University of Warsaw. The study complied the Declaration of Helsinki.

Transthoracic echocardiographic examination was performed in the morning (between 8:00 and 9:00 am) in the echocardiography laboratory in 1st Chair and Department of Cardiology, Medical University of Warsaw (certified with grade C accreditation of the Section of Echocardiography of the Polish Cardiac Society) using Epic 7 Ultrasound Machine (Philips Medical Systems, Andover, Massachusetts, United States) or iE33 (Philips Medical Systems, Andover, Massachusetts, United States). All examinations were performed according to European Association of Cardiovascular Imaging guidelines by one experienced echocardiographer. Systolic function of the left ventricle was calculated using Simpson method. Diastolic function was evaluated according to mitral inflow, annular e' velocity, average E/E' ratio, left atrial maximum volume index and peak tricuspid regurgitation volume.

Before the beginning of tests patients were staying in supine position for 10 min. Tests were applied in following order: Valsalva manoeuvre, static handgrip (HG) followed by post-exercise ischemia (PEI) and tilt. Valsalva manoeuvre, HG and PEI were performed in supine position. Valsalva manoeuvre with respiratory effort lasting 15 s, was performed at a level of 40 mm Hg of air pressure in the lungs. After 5 min of rest, HG lasting 2 min was performed with a hand-held dynamometer with a force of 30% of MVC (maximal voluntary contraction). It was immediately followed by 2-minute PEI obtained by inflating sphygmomanometer cuff 20 mm Hg above the systolic pressure observed near the end of HG. After 5-minute rest, tilt to 60° lasting 5 min was applied.

ECG was registered continuously with Monitor EKG (FX2000P Emtel, Poland). Blood pressure was registered continuously and non-invasively with a Portapres (FMS, Amsterdam, Holland). The finger cuff was placed on a finger of the non – working limb.

During tests (except Valsalva manoeuvre) subjects maintained constant (15 breaths/min) breathing rate by adjusting it to a signal from a light emitting diode. During the Valsalva manoeuvre subjects maintained elevated air pressure in lungs and mouth by attempting to exhale into a mouthpiece with a closed air outflow. The air pressure in mouth was measured with pressure sensor MPX 2050GP (Motorola, Schaumburg, IL, USA).

Handgrip was performed with the hand dynamometer DR4-CA (JBA Zb. Staniak, Warsaw, Poland). In order to enable subject to maintain constant force of 30% MVC, the force signal was continuously recorded and displayed to the subject. Post-exercise ischemia was produced with a sphygmomanometer cuff, the air pressure in the cuff was continuously measured by an MPX 2050GP pressure sensor (Motorola, Schaumburg, IL, USA) and recorded.

Tilt test was performed on tilt table with regulation of the slope angle (SP-1/E, Tech Med, Poland).

All the signals were analogue, they were digitised at a sampling rate of 200 Hz, using WinAcq data acquisition system (Absolute Aliens Oy, Turku, Finland) and computer-stored by WinCPRS software (Absolute Aliens, Turku, Oy, Finland).

For statistical analysis two-way ANOVA for repeated measurements was applied. The first factor was *group*, the second factor was *time*. A value of $p < 0,05$ was taken as the threshold for statistical significance. A Newman-Keuls *post hoc* was performed when significant effects or their interaction were detected. Nonparametric tests (Wilcoxon's signed rank and Kruskal–Wallis tests) were used if the assumptions of ANOVA were not met.

3. Results

Basic characteristic of the patients and echocardiographic results are presented in Table 1.

3.1. Hemodynamic responses to Valsalva manoeuvre, handgrip, post exercise ischemia and tilt

3.1.1. Valsalva manoeuvre

In case of STEMI and TTS groups SBP clearly declined in the first

Table 1
Basic characteristic of the patients and echocardiographic results.

	TTS	STEMI	Control
Age (years)	67.2 (55–82)	62.9 (41–78)	60.1 (47–71)
Time from the disease episode (months)	51 (3 – 123)	41 (14–94)	NA
EF (%)	61.6 (57–69)	56.4 (27–70)	63.6 (60–68)
LVDD (mm)	47 (40–54)	47 (40–60)	45 (40–52)
E/A	0.9 (0.6–1,9)	1 (0.7–2)	1,2 (0.9–1.5)
E/E'avg.	9.5 (6.5–12,3)	12 (7.7–22.8)	10.3 (8.8–11.5)

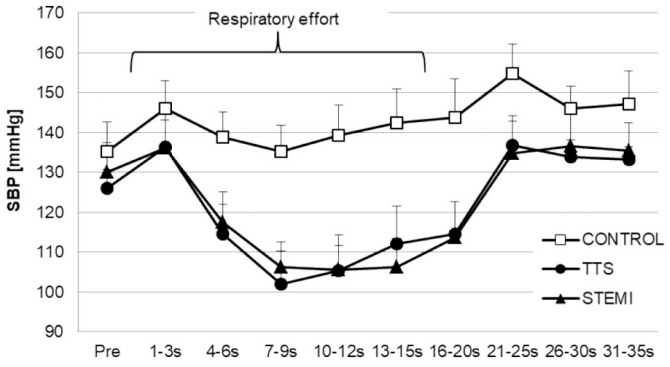

Fig. 1. Time course of SBP during Valsalva manoeuvre. Values are means ± SE. Values shown on the figure are averaged SBP during last minute before test, 3-s periods of test during respiratory effort, and 5-s periods of test after this effort.

part of the respiratory effort, then started to rise slightly. This rise accelerated immediately after the end of the respiratory effort and reached level close to baseline without overshoot (Fig. 1). In contrast, in CONTROL group, SBP slightly declined and then started to rise up during respiratory effort which was followed by small overshoot.

Statistical analysis pertains to the period of baseline and 15-s respiratory effort. In this period the effect of group factor attained statistical significance. There were no such effect in recovery period. As a result the effect of group factor calculated for these two periods combined lost statistical significance. Therefore, taking into account the changes taking place in the first period enabled us to discover the significant impact of the group factor.

There was initial rise of DBP (CONTROL: 15.9 ± 7.3 mm Hg, TTS: 14.0 ± 13.6 mm Hg, STEMI: 10.5 ± 12.7 mm Hg) and SBP (CONTROL: 10.7 ± 21.7 mm Hg, TTS: 10.2 ± 14.9 mm Hg, STEMI: 6.1 ± 19.2 mm Hg) in all groups, which may be attributed to increase in intrathoracic air pressure generated during Valsalva manoeuvre. DBP continued to rise in CONTROL group more steeply than in TTS and STEMI. Despite evident difference between groups, main effect of factor *group* as well as interaction between *time* and *group* factors were close to but did not attain significance level ($p = 0.08$ and $p = 0.06$ respectively).

Pulse pressure declined significantly ($p < 0.000001$ main effect of factor *time*) throughout the Valsalva manoeuvre, most steeply in its mid-phase. Of note is lack of initial rise, similar to that observed in SBP and DBP. The lack of initial PP rise conforms with the conjecture, that initial rise of SBP and DBP was caused by the rise of intrathoracic air pressure (Niewiadomski et al., 2014; Niewiadomski et al., 2012). It is evident that decline of PP is deeper in TTS and STEMI than in CONTROL, however neither main effect of factor *group* nor interaction *group* x *time* attained significance.

Jointly, different courses of DBP and PP changes in CONTROL groups *vs.* two other groups resulted in significantly different courses of SBP change in CONTROL *vs.* TTS and STEMI groups. The different time-courses of SBP changes between groups resulted in significant ($p < 0.00001$) main effect of *time* and significant ($p < 0.05$) *time* x *group* interaction.

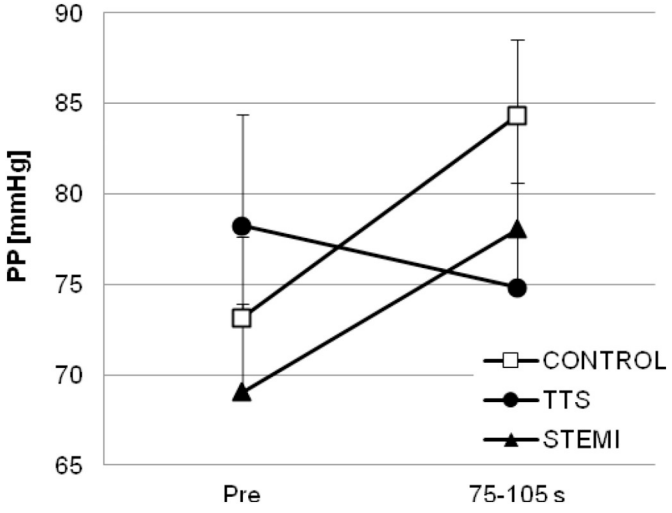

Fig. 2. Time course of PP during handgrip. Values are means ± SE. Values shown on the figure are averaged PP during last minute before handgrip and 75–105 s of test.

During Valsalva manoeuvre HR increased significantly ($p < 0.00001$), HR was lower throughout Valsalva manoeuvre in CONTROL group in comparison with TTS and STEMI ones, but the main effect of *group* factor did not attain significance ($p = 0.17$).

3.1.2. Handgrip

Handgrip caused distinct rise of HR; two-way ANOVA showed significant main effect of *time* ($p < 0.00001$) and no effect of *group*. DBP also rose, and the effect of time was significant ($p < 0.0001$) as revealed by Wilcoxon's test. There was no effect of *group* according to Kruskal-Wallis test. In case of SBP, which also rose during handgrip, ANOVA revealed that beside significant effect of time there was almost significant ($p = 0.085$) interaction between *time* and *group*, explicable in light of much less steeper increase of SBP in TTS group (from 139.1 ± 29.3 mm Hg to 145.4 ± 28.2 mmHg) as compared with CONTROL and STEMI groups (from 135.1 ± 27.7 mm Hg to 155.9 ± 29.6 mmHg, from 127.6 ± 25.9 mm Hg to 143.5 ± 28.1 mm Hg, respectively). Significant ($p < 0.005$) interaction between *time* and *group* factors, along with significant ($p < 0.005$) effect of *time* was seen in PP (Fig. 2). This interaction reflected the fact that PP in TTS group insignificantly decreased whereas in two other groups significantly ($p < 0.05$) increased.

3.1.3. Post-exercise ischemia

During PEI heart rate declined in comparison to HG, however remained slightly but significantly ($p < 0.05$) elevated over baseline as was revealed by Wilcoxon's test. Otherwise hemodynamic response was similar to that during handgrip: DBP, SBP and PP during PEI remained significantly ($p < 0.001$ - Wilcoxon's test, $p < 0.00001$- ANOVA, $p < 0.00005$ - ANOVA respectively) elevated in comparison to baseline. Though in TTS group increases of SBP and PP were evidently smaller than in remaining groups, *time* x *group* interaction did not reach significance level ($p = 0.11$, $p = 0.088$ respectively). Similar results were obtained when one-way ANOVA was applied to SBP and PP increments; ΔSBP and ΔPP were evidently smaller in TTS group than in CONTROL and STEMI ones, however the difference did not reach significance level ($p = 0.11$, $p = 0.088$ respectively).

3.1.4. Tilt

During tilt HR increased in all groups (Fig. 3). This increase was gradual, evident already in the first minute of tilt and achieving plateau in the second. Heart rate increases as well as increments of HR (ΔHR)

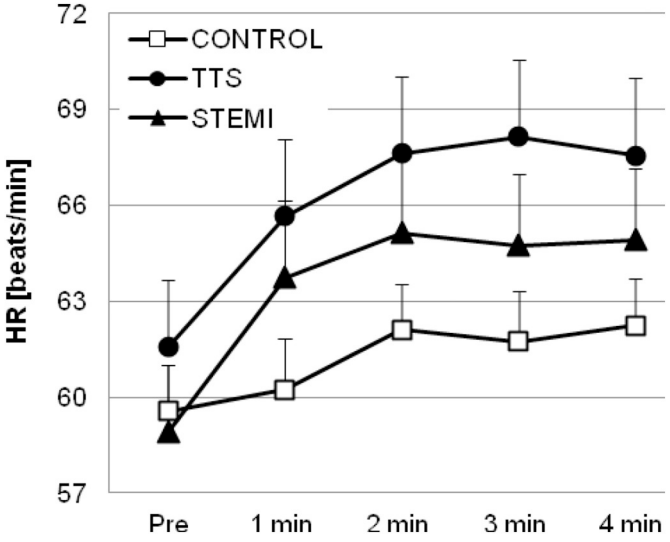

Fig. 3. Time course of HR during tilt test. Values are means ± SE. Values shown in the figure are averaged HR during last minute before tilt and 1, 2, 3, and 4 min of test.

were lower in CONTROL group than those in other two groups. ANOVA of ΔHR showed a significant ($p < 0.000001$) main effect of factor *time* and significant ($p < 0.05$) main effect of factor *group*. *Post hoc* analysis showed that values of ΔHR were significantly ($p < 0.0002$) greater in second, third and fourth minutes of tilt in comparison to values in first minute and were significantly ($p < 0.05$) greater in TTS and STEMI groups in comparison to CONTROL group, but not significantly different between TTS and STEMI groups.

In contrast to HR, which was attenuated in CONTROL group, when compared to TTS and STEMI groups, pressor reaction to tilt was delayed and somewhat weaker in these two latter groups, when compared to CONTROL. This was evident when SBP increments over baseline (ΔSBP) were analyzed (Fig. 4). ANOVA of ΔSBP revealed significant ($p < 0.0002$) main effect of factor *time* and significant ($p < 0.002$) interaction between *time* and *group* factors. In CONTROL group ΔSBP achieved almost maximal value (13.4 ± 16.9 mm Hg) already in the first minute of tilt, whereas in TTS group ΔSBP became negative in first (−1.7 ± 26.3 mm Hg) and the second minute of tilt (−2.4 ± 27.1 mm Hg), turned positive in the third and fourth minute (6.3 ± 24.3 mm Hg), however remained smaller than in CONTROL

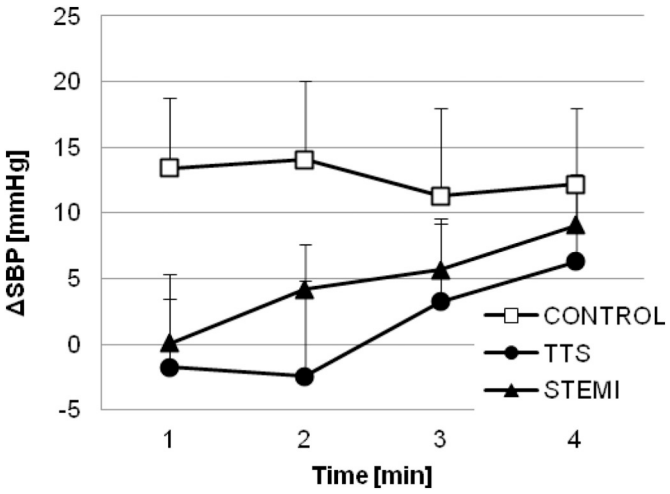

Fig. 4. Time course of SBP increments (ΔSBP) during tilt test. Values are means ± SE. Values shown in the figure are averaged ΔSBP during 1, 2, 3, and 4 min of test.

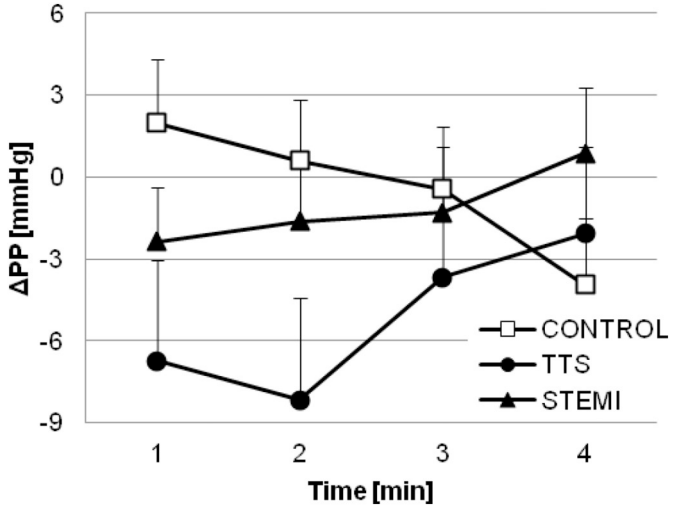

Fig. 5. Time course of PP increments (ΔPP) during tilt test. Values are means ± SE. Values shown on the figure are averaged ΔPP during 1, 2, 3, and 4 min of test.

(12.2 ± 18.2 mm Hg). Also in STEMI group ΔSBP rose gradually, starting from almost zero in the first minute and remaining lower than in CONTROL group throughout the tilt. *Post hoc* analysis confirmed that also in TTS and STEMI groups ΔSBP significantly ($p < 0.05$) increased with time.

Time courses of changes of DBP increments (ΔDBP) in three groups were similar to those of ΔSBP: in CONTROL group already in the first minute ΔDBP attained its almost maximal value (11.4 ± 15.8 mm Hg) and retained it throughout subsequent minutes of tilt. Both in TTS and STEMI groups ΔDBP rose gradually from 5.0 ± 15.8 mm Hg (TTS) and 2.4 ± 10.0 mm Hg (STEMI) up to 8.4 ± 16.0 mm Hg and 8.2 ± 14.1 mm Hg, respectively. Accordingly ANOVA revealed that main effect of factor *time* and interaction *time* x *group* was close to significance level ($p = 0.08$).

The most striking difference between groups was demonstrated with changes of pulse pressure increments (ΔPP) (Fig. 5). In CONTROL group these increments were positive in the first (2.0 ± 7.4 mm Hg) and second minute, negative in the third and fourth (−3.9 ± 7.7 mm Hg) minute. In TTS group ΔPP were negative during whole tilt (first minute: −6.7 ± 13.7 mm Hg, fourth minute: −2.1 ± 11.9 mm Hg) and in STEMI slightly negative from the first (−2.4 ± 8.4 mm Hg) to third (−1.3 ± 10.3 mm Hg) minute. However as ΔPP's SD was often greater than the mean, ANOVA detected no significant effects.

In summary, pressor response in TTS group was diminished in comparison to CONTROL and close to that of STEMI. In particular, this is evident in time course of SBP response to tilt and Valsalva manoeuvre. In case of handgrip, increase of SBP was the lowest in TTS group and the difference between groups was almost significant. Probably differences in SBP were caused by different PP responses to tests. In case of tilt PP initially decreased in TTS group whereas it increased in CONTROL group, in case of handgrip it declined in TTS group whereas it increased both in CONTROL and STEMI groups, and finally in case of Valsalva manoeuvre PP declined more in TTS and STEMI groups than in CONTROL group.

4. Discussion

It seems, that the long term consequences of TTS may be first detected when tests which challenge cardiovascular system like maximal exercise test are applied (Lazzeroni et al., 2017). Beside dynamic exercise also static exercise (HG), Valsalva manoeuvre and tilt can be regarded as challenges to cardiovascular system (Kivowitz et al., 1971; Wortmann et al., 1992).

We observed similarly changed time course of SBP in TTS and STEMI groups in which in most of the patients more than one year elapsed from the acute episode. In the only other study of Norcliffe-Kaufmann et al., where blood pressure changes were examined during tilt, no differences between TTS and control groups were found (Norcliffe-Kaufmann et al., 2016). The discrepancy between their and our study may for instance stem from differences in protocol, as in Norcliffe-Kaufmann et al. study patients were examined after washout of β-blockade. However, of note is the fact that SBP changes in control groups in Norcliffe-Kaufmann et al. and our study did not differ, what may mean that TTS patients are specifically sensitive to β-blockade. We were unable to find relevant studies on tilt test in post-myocardial infarction (MI) patients.

In our study during HG SBP rose much less steeply in TTS group than in other two groups. This may be explained by the fact that though DBP was increasing during HG in both groups in similar way, in TTS group PP was declining whereas in CONTROL and STEMI PP was increasing during HG. To our knowledge no study has been published in which pressor response to HG has been studied in takotsubo patients. As to post-MI patients receiving β-blockade Detollenaere et al. observed almost twice as large increase of SBP in patients 6 weeks after MI in comparison to control (Detollenaere et al., 1993). Baccelli et al. observed increase in BP in patients who sustained MI 4–5 weeks prior to the study and who were not receiving any medication that might affect cardiac rhythm or contractility (Baccelli et al., 1978).

It should be realized that maintaining pressure increase during HG may pose considerable strain on left ventricle in cardiac patients. For instance in NYHA class III patients, blood pressure increased during HG in similar way as in control, however because of reduced contractility reserve this required increased end-diastolic pressure (in accordance with Frank-Starling mechanism), and could produce episodes of congestive heart failure or pulmonary oedema in susceptible patients (Kivowitz et al., 1971).

A marked decrease in blood pressure in the TTS and STEMI groups was observed during the Valsalva test but not in CONTROL group, contrary to results obtained by Norcliffe-Kaufmann et al. (Norcliffe-Kaufmann et al., 2016). They found that during the Valsalva manoeuvre, both TTS and control groups had a similar decrease in SBP during straining phase. It is questionable whether their results could be compared with ours, firstly because the body position in which Valsalva manoeuvre was performed is not clearly stated by these authors. If the body position differed between their and our study this could essentially influence the time course of blood pressure changes during the Valsalva manoeuvre. It has been found that SBP decline occurring in phase II is less conspicuous in supine than in sitting and standing position (Ten Harkel et al., 1990; Singer et al., 2001; Rasmussen et al., 2017). A second reason which may explain the discrepant results was the lack of β-blockade in Norcliffe-Kaufmann et al. study (Norcliffe-Kaufmann et al., 2016). Again, as in case of previous tests we were unable to find relevant studies on Valsalva manoeuvre in post-MI patients.

It follows that indeed the results obtained during these tests indicate that functional response is clearly impaired in the TTS group and, although to a lesser extent, in the STEMI group. Moreover, the results of echocardiography recorded at rest do not predict this type of phenomenon. This means that despite the apparent resolution of the effects of the acute event in TTS, long-lasting effects of this event persist, which, however, become apparent only during functional tests. This agrees with the result of Lazzeroni et al. that despite rapid recovery of left ventricular pump function, some kind of impairment of heart function is still present which may be associated with unfavourable prognosis of TTS patients (Lazzeroni et al., 2017).

As we already pointed out, the differences in pressor response to tilt, handgrip and Valsalva manoeuvre may derive from reduced PP. It is supposed, that magnitude of PP depends on stroke volume (SV) and properties of the arterial tree, thus we hypothesise that underlying cause of impaired pressor response to tests applied is diminished SV in TTS subjects (Dart and Kingwell, 2001). This may indicate a weakening of the cardiac pump function in this group of patients, evident however in situation of challenge to cardiovascular system.

5. Conclusions

To our knowledge it is the first study which revealed impaired pressor response to tilt, handgrip and Valsalva manoeuvre in TTS patients. The potential importance of this study derives from the fact that these tests mimic, in controlled way, frequent situations of everyday life. Impaired pressor response may be caused by weakening pump function of the heart, not indicated by results of comprehensive echocardiographic examination performed at rest. As deteriorated cardiac function may have far reaching consequences, even leading to further damage to heart muscle, further studies are needed to gain insight in causes of altered arterial pressure response to above mentioned tests, specifically the possible detrimental effect of β-blockade, which may aggravate already existing defects.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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