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Effect of physical countermaneuvers on orthostatic hypotension in familial dysautonomia

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Abstract Familial dysautonomia (FD) patients frequently experience debilitating orthostatic hypotension. Since physical countermaneuvers can increase blood pressure (BP) in other groups of patients with orthostatic hypotension, we evaluated the effectiveness of countermaneuvers in FD patients.

In 17 FD patients (26.4 ± 12.4 years, eight female), we monitored heart rate (HR), blood pressure (BP), cardiac output (CO), total peripheral resistance (TPR) and calf volume while supine, during standing and during application of four countermaneuvers: bending forward, squatting, leg crossing, and abdominal compression using an inflatable belt. Countermaneuvers were initiated after standing up, when systolic BP had fallen by 40 mmHg or diastolic BP by 30 mmHg or presyncope had occurred.

During active standing, blood pressure and TPR decreased, calf volume increased but CO remained stable. Mean BP increased significantly during bending forward (by 20.0 (17–28.5) mmHg; P = 0.005) (median (25^{th} – 75^{th} quartile)), squatting (by 50.8 (33.5–56) mmHg; P = 0.002), and abdominal compression (by 5.8 (–1–34.7) mmHg; P = 0.04) – but not during leg-crossing. Squatting and abdominal compression also induced a significant increase in CO (by 18.1 (–1.3–47.9) % during squatting (P = 0.02) and by 7.6 (0.4–19.6) % during abdominal compression (P = 0.014)). HR did not change significantly during the countermaneuvers. TPR increased significantly only during squatting (by 37.2 (11.8–48.2) %; P = 0.01). However, orthopedic problems or ataxia prevented several patients from performing some of the countermaneuvers. Additionally, many patients required assistance with the maneuvers.

Squatting, bending forward and abdominal compression can improve orthostatic BP in FD patients, which is achieved mainly by an increased cardiac output. Squatting has the greatest effect on orthostatic blood pressure in FD patients. Suitability and effectiveness of a specific countermaneuver depends on the orthopedic or neurological complications of each FD patient and must be individually tested before a therapeutic recommendation can be given.

Key words physical maneuvers · familial dysautonomia · syncope · autonomic failure · impedance cardiography

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Introduction

Familial dysautonomia (FD) is a rare autosomal recessive genetic disease that affects autonomic, sensory and motor function [2]. One of the most prominent clinical features of autonomic dysfunction in FD is orthostatic hypotension (OH) [2]. Patients with FD show no increase in plasma noradrenaline [1] or vascular resistance [7] upon standing, suggesting an inadequate sympathetic response to postural change. Pharmacological and dietary treatment, including fludrocortisone, midodrine, and increased fluid and salt intake, have been instituted to counteract the effects of orthostatic hypotension in FD but are not completely effective [2, 3].

Physical countermaneuvers are non-invasive techniques that can be used by healthy individuals and patients with autonomic failure to maintain blood pressure while standing [5, 20, 22]. Some of the more common countermaneuvers include leg-crossing, squatting and bending forward accompanied by compressing the abdomen with crossed arms and are rather effective in minimizing postural blood pressure drops [22, 23]. Furthermore, abdominal compression, achieved by means of an inflatable binder, has been shown to be particularly effective in the treatment of orthostatic intolerance in children and patients with autonomic failure [16, 19]. In the FD population, the effects of various countermaneuvers on standing blood pressure have not yet been studied.

The mechanisms by which physical countermaneuvers stabilize blood pressure depend on the selected maneuver. Squatting, leg-crossing and bending forward increase the extravascular pressure, thereby limiting venous blood pooling [9, 11, 22, 23]. Squatting may also increase total peripheral resistance [5, 14]. Abdominal compression, squatting and bending forward can mobilize blood from the splanchnic vascular bed and enhance the venous return of blood to the heart [9, 19, 23]. Bending forward also decreases the hydrostatic pressure difference between the heart and brain [23].

Previously we showed that the failure of peripheral vasoconstriction, rather than an excessive venous pooling of blood to the legs, mainly contributes to orthostatic hypotension in FD patients [7]. Consequently, countermaneuvers that enhance peripheral vasoconstriction might be most effective in FD patients and would provide a simple and non-invasive technique of stabilizing blood pressure in these patients. Efficient countermaneuvers might provide a simple technique to stabilize BP in FD patients during unexpected situations of pronounced acute orthostatic hypotension. Therefore, we assessed systemic cardiovascular responses to bending forward, squatting, leg-crossing and inflation of an abdominal binder to evaluate, which of the countermaneuvers are most effective in our group of FD patients.

Methods

We studied 17 patients with familial dysautonomia (9 men, 8 women) aged 26.4 ± 12.4 years (mean ± standard deviation (SD)). Their height was 153.7 ± 10.5 cm (mean ± SD) and their weight was 46.1 ± 10.4 kg (mean ± SD). The diagnosis of FD had been established using standard criteria, including Ashkenazi Jewish ancestry, absent or diminished deep tendon reflexes, absence of overflow tears, absence of fungiform papillae of the tongue and absent axon flare response after intradermal histamine injection [2]. All FD patients had typical mutations of the *IKBKAP* gene [15]. Most of the patients showed other signs typically seen in FD, including delayed motor development, failure to thrive, increased sweating, orthostatic intolerance, skin blotching, trunk and limb ataxia, spinal and joint deformations [2].

All FD patients who were taking medication known to affect the cardiovascular system (e. g. fludrocortisone, midodrine) were asked to discontinue the medication for 18 hours prior to the procedures. Patients who were unable to comply with this requirement for medical reasons were not included in the study. Additionally, the participants were asked to refrain from caffeine and alcohol for 24 hours before the testing. All patients were studied at least 3 hours after their last meal.

The study protocol was approved by the Institutional Research Board of New York University School of Medicine and written informed consent was obtained from each subject prior to testing according to the Declaration of Helsinki.

Procedures

A medical history was taken and a detailed neurological examination was performed in all FD patients. The subjects initially rested in a supine position for at least 40 minutes to ensure cardiovascular stability.

We continuously monitored electrocardiographic RR-intervals (5-lead ECG), heart rate (HR) and non-invasive beat-to-beat systolic (SBP), diastolic (DBP) and mean (MBP) blood pressure at the left radial artery using applanation tonometry (Colin Pilot™, San Antonio, TX, USA). Arterial tonometry has been validated against intra-arterial BP measurements during various states, including orthostatic stress [13].

Cardiac stroke volume (SV) was measured by impedance cardiography (Cardioscreen®, Medis GmbH, Ilmenau, Germany), via electrodes attached to the neck and thorax. This technique has been described previously and has been extensively validated against other methods, e. g. echocardiography and thermodilution, under various physiological conditions, including orthostatic stress [4, 8]. Cardiac output (CO) was calculated as the product of heart rate and stroke volume. Total peripheral resistance (TPR) was calculated as mean arterial pressure (MAP) divided by CO.

Using impedance plethysmography, we determined calf volume changes from the relative changes in calf impedance [6, 7]. Recording electrodes were placed on the lateral malleolus and lateral aspect of the knee to define a calf segment. To calculate the initial volume of the calf, we measured the distance between the electrodes and measured calf circumferences at 3 cm intervals. An impedance monitor (Cardioscreen®, Medis GmbH, Ilmenau, Germany) supplied a 1 mA, 50 Hz current which was passed between electrodes placed 5 cm outside the recording electrodes. Changes in the impedance of the calf segment enclosed by the recording electrodes were measured and stored for analysis [6, 7].

Recordings were made at supine rest, during active standing and during each of the four physical countermaneuvers. SV measurements, CO and TPR calculations were not performed during bending forward, because this maneuver may have significantly influenced the impedance values solely due to the straining of the thorax. Calf volume changes were not determined during squatting and leg crossing, as these maneuvers are associated with a mechanical deformation of

the calves. For each countermaneuver, the patients initially rested supine for 15 minutes, then performed an active stand. The countermaneuver was performed after systolic blood pressure had fallen by at least 40 mmHg or diastolic blood pressure had fallen by at least 30 mmHg or as soon as presyncopal signs and symptoms, such as lightheadedness, nausea, blurred vision or dilated pupils had occurred. Each countermaneuver was maintained for at least 30 seconds after blood pressure had stabilised. During the countermaneuvers, care was taken to maintain the tonometer for blood pressure measurement at the level of the heart and to minimize any movement artifacts. The following countermaneuvers were performed in a randomized order:

- *Bending forward* Subjects were instructed to bend forward while standing and to cross their arms over their abdomen. This maneuver translocates blood from the splanchnic capacitance vessels towards the heart. Bending forward also decreases the hydrostatic height between the heart and the brain [23].
- *Squatting* Patients were asked to quickly squat down from the standing position. By this, blood is squeezed from the veins of the legs and of the splanchnic vascular bed which increases cardiac filling pressure and cardiac output [9]. Squatting also increases total peripheral resistance in patients with autonomic failure [5].
- *Leg crossing* Patients were instructed to cross one leg in direct contact with the other while standing actively on both legs and pressing the calves and thighs of both legs against each other. This maneuver mechanically compresses the veins of the legs and thus increases central blood volume [10, 20, 22].
- *Abdominal compression* A 16 cm broad band, comprising an outer layer of hard polyester cloth and an inner inflatable elastic cuff, was placed around the patients' waist at the level of the umbilicus and inflated to 20 mmHg, thus compressing the abdomen [16, 19].

Data acquisition and analysis

The signals of electrocardiographic RR-interval and arterial blood pressure were digitized at a sampling rate of 300 Hz, fed to a computer and stored for off-line analysis. A computer program identified the peak of each R wave and constructed time series of RR-interval, SBP, DBP and MBP. The impedance signals were fed to a second computer and analyzed using commercially available software (Multiscreen 4.1, Medis GmbH, Ilmenau, Germany) to obtain beat-to-beat values of stroke volume and leg volume.

The responses to active standing were determined from the mean values recorded during the last 30 seconds of active standing before initiation of the first randomized countermaneuver and compared to the mean values recorded during the last 3 minutes of supine rest. Responses of SV, CO, TPR and calf volume to active standing were expressed as percent changes from the supine baseline.

The effect of a countermaneuver was evaluated by comparing the hemodynamic variables recorded during the 30 seconds immediately after stabilization of blood pressure by the countermaneuver to the mean values recorded during the last 30 seconds of active standing, before initiation of the countermaneuver [10]. Furthermore, relative changes in hemodynamic parameters during the countermaneuvers were calculated as percent changes from the preceding standing values [16, 22].

Statistical analysis

Results are reported as medians and interquartile range between the 25th and the 75th percentile, unless otherwise indicated. Responses to active standing and to each of the countermaneuvers were evaluated using the Wilcoxon signed rank test. To assess differences in the effects of the countermaneuvers, we compared relative changes in mean blood pressure between the four countermaneuvers. Comparisons between the responses to each of the four countermaneuvers were made using the Friedman test with Dunn's post-tests, where a significant P value was found. P-values were all two-sided and the level of statistical significance was set at $P < 0.05$.

Results

Response to active standing

Mean values of the cardiovascular variables during supine rest and active standing are shown in Table 1. Active standing resulted in substantial decreases in blood pressure that fulfilled standard criteria of orthostatic hypotension [21]. SBP fell by 53.4 (–83––45.8) mmHg ($P = 0.0003$), DBP by 39.3 (–53.3––33) mmHg ($P = 0.0003$) and MBP by 45.3 (–67––38) mmHg ($P = 0.0003$).

Fifteen of the 17 patients experienced at least mild orthostatic dizziness that occurred within the first three minutes of standing. In three subjects, the cardiac and calf impedance signals during standing were inadequate for further analysis. In the remaining 14 patients, stroke volume, cardiac output, and HR did not change significantly during standing. However, there was a significant decrease in total peripheral resistance and a significant, although small, increase in calf volume (Table 1).

Effects of countermaneuvers

Only seven of the 17 patients were able to perform all four countermaneuvers, although 16 patients could per-

Table 1 Medians and the interquartile ranges of the hemodynamic parameters recorded during the last 3 minutes of the supine rest and during the last 30 seconds of active standing. Significant differences between active standing and supine rest are indicated by * (Wilcoxon signed rank test; $P < 0.05$)

	SBP	DBP	MBP	HR	SV	CO	TPR	Calf vol.
Supine	148.5 (134.7–170.3)	94.0 (77.25–103.3)	118.0 (95–127.7)	76.9 (71.1–86.1)	100	100	100	100
Active standing	86.0* (56–95)	49.0* (38–56)	65.0* (53–74)	81.8 (74.2–86.3)	–3.9 (–25.8–2.8)	–0.9 (–18.6–6.1)	–37.5* (–51––30.7)	+1.3* (1–2.05)

SV, CO, TPR and calf volume values are expressed as percent changes from the supine baseline
SBP systolic blood pressure (mmHg); *DBP* diastolic blood pressure (mmHg); *MBP* mean arterial pressure (mmHg); *HR* heart rate (bpm); *SV* stroke volume (%); *CO* cardiac output (%); *TPR* total peripheral resistance (%); *Calf vol.* calf volume (%)

form at least 2 countermaneuvers. Only three patients were able to bend forward independently, seven patients squatted adequately and eight patients performed leg crossing without assistance. Ten patients needed physical support when bending forward, three patients when squatting and four patients when leg-crossing. Owing to ataxia and orthopedic problems of the spine or knees with limited movement range, four patients were unable to bend forward and seven patients could not squat adequately. Five patients lost their balance during leg-crossing. Three patients had respiratory problems during abdominal compression; the remaining 14 patients did not need any assistance during abdominal compression. In 14 of the 15 patients who experienced orthostatic dizziness, application of at least one of the countermaneuvers was associated with a reduction of these symptoms, as reported verbally by the patient.

Only those patients, who were able to perform the maneuvers either independently or with assistance, were included in further analysis of hemodynamic changes. Stroke volume, cardiac output, total peripheral resistance and calf volume values are not included for the three patients in whom we were unable to obtain adequate signals.

Systolic blood pressure increased during bending forward (by 23.0 (11.5–32) mmHg; $p = 0.0005$), squatting (by 49.0 (21.5–57.5) mmHg; $p = 0.002$), leg crossing (by 8.3 (–1.4–16.8) mmHg; $p = 0.01$) and abdominal compression (by 27.0 (8.9–41) mmHg; $p = 0.001$). Diastolic blood pressure rose by 12.0 (8.5–20) mmHg ($p = 0.0005$) during bending forward, by 38.0 (12.5–48.5) mmHg ($p = 0.004$) during squatting and by 11.6 (–8.1–31.2) mmHg ($p = 0.02$) in response to leg crossing, but was unchanged during abdominal compression (+2.0 (0–4.3) mmHg; $p = 0.30$).

Fig. 1 shows the changes in MBP elicited by the four countermaneuvers for the individual patients. Bending forward caused a significant increase in mean blood pressure (by 20.0 (17–23.5) mmHg; $P = 0.005$), with 8 of the 13 patients showing an increase of at least 20 mmHg. Squatting also significantly increased MBP (by 50.8 (33.5–56) mmHg; $P = 0.002$), with 8 of the 10 patients showing an increase of at least 30 mmHg, where 5 of the 10 patients had MBP increases of more

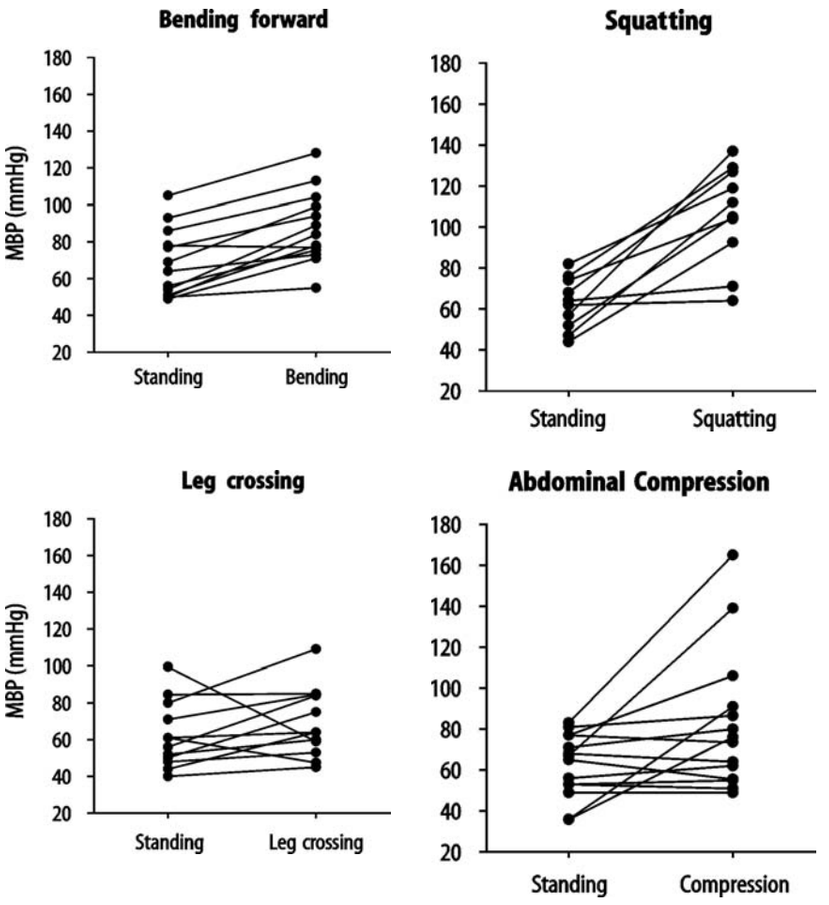

Fig. 1 Individual responses of mean arterial pressure (MBP) during the four countermaneuvers

than 50 mmHg. Leg crossing did not result in a significant increase in MBP (P = 0.11), although 4 of the 12 patients who performed the maneuver did show MBP increases of more than 20 mmHg. Inflation of the abdominal binder resulted in a significant increase in blood pressure (by 5.8 (–1–34.7) mmHg; P = 0.04), but there was considerable variability in the responses between the patients. While 5 of the patients showed an increase in MBP of at least 20 mmHg during abdominal compression, the remaining 9 patients showed MBP increases of less than 10 mmHg or even a decrease in blood pressure.

Squatting was the most effective countermaneuver at increasing blood pressure. In the 7 patients who performed all four countermaneuvers, the MBP increase during squatting was significantly greater than during bending forward, abdominal compression and leg crossing (P = 0.014).

Fig. 2 shows the changes in CO elicited by squatting, leg crossing and abdominal compression for the individual patients. Squatting induced a significant increase in CO (by 18.1 (–1.3–47.9) %; P = 0.02) with 7 of the 10 patients showing an increase of at least 10 %. In contrast, leg crossing did not significantly increase CO (P = 0.36) with only 3 of the 9 patients, who performed the maneuver and in whom we obtained adequate impedance signals, showing CO increases of at least 10 %. Inflation of the abdominal binder resulted in a significant increase in CO (by 7.6 (0.4–19.6) %; P = 0.014). Seven of the 11 patients, who tolerated the abdominal compression and had adequate impedance signals, showed an increase of more than 10 %. Heart rate did not change significantly during any of the countermaneuvers, while stroke volume increased significantly during squatting (10.6 (–7.3–49.7) %, P = 0.01) and abdominal compression (7.6 (0.4–19.6) %, P = 0.014) but not during leg-crossing (P = 0.82). Calf volume did not change significantly during either of the maneuvers in which it was measured (bending forward P = 0.52; abdominal compression P = 0.13).

Changes in TPR induced by squatting, leg crossing and abdominal compression in the individual patients are shown in Fig. 3. Only squatting resulted in a significant increase in TPR (by 37.2 (11.8–48.2) %; P = 0.01) with 8 of the 10 patients showing an increase of at least 10 %, while in 7 of these patients, TPR increased by more than 35 %. Conversely, TPR increases were not significant during abdominal compression (by 18.4 (–0.6–54) %; P = 0.09) or leg crossing (by 10.3 (–21–20.2) %; P = 0.65). However, abdominal compression caused TPR to increase substantially by at least 35 % in 4 of the 11 patients, while leg crossing only elicited a TPR increase of this magnitude in one patient.

Discussion

In all of the FD patients, active standing caused substantial reductions in orthostatic blood pressure without reflex tachycardia or peripheral vasoconstriction. Three of the physical countermaneuvers – squatting, bending forward and abdominal compression – were successful at ameliorating the postural drops in blood pressure, although there was considerable variation in the effectiveness of the countermaneuvers between individual patients. Not every patient was physically able to perform each countermaneuver without assistance, but most of the patients could adequately perform at least one of the maneuvers. These findings suggest that the overall effectiveness of physical countermaneuvers is rather limited in the FD population compared with other groups of patients [5, 16, 20, 23]. However, in some FD patients a particular countermaneuver may be useful for averting an episode of posturally-related syncope.

For the patients who were able to perform it, squat-

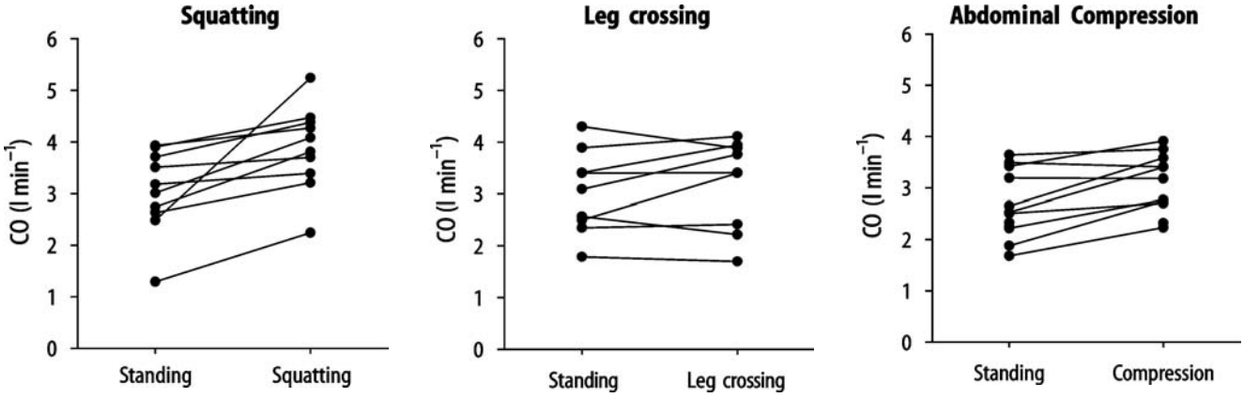

Fig. 2 Individual responses of cardiac output (CO) during squatting, leg crossing and abdominal compression. Data of the patients in whom we were unable to obtain adequate impedance signals are not shown

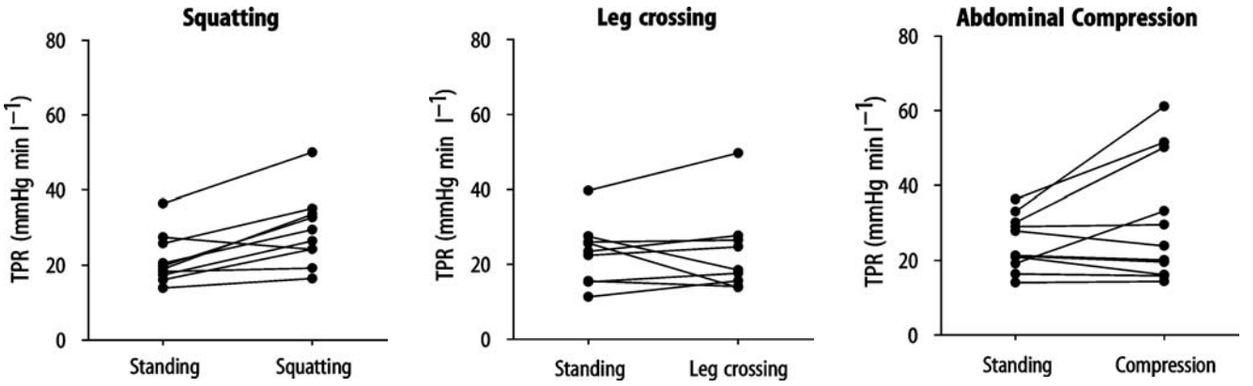

Fig. 3 Individual and mean responses of total peripheral resistance (TPR) during squatting, leg crossing and abdominal compression. Data of the patients, in whom we were unable to obtain adequate impedance signals, are not shown

ting seemed to be the most effective countermaneuver as it resulted in the greatest and most consistent increases in blood pressure. Squatting also enhanced cardiac output and total peripheral resistance. The increase in cardiac output was presumably due to compression of splanchnic veins and arterioles, thus mobilizing the abdominal reservoir of blood and enhancing the venous return of blood to the heart [12]. The increased total peripheral resistance during squatting is consistent with findings in other patients with autonomic failure [5] and was probably a mechanical effect, because FD patients have impaired reflex peripheral vascular responses [7, 17, 18]. Since an absent peripheral vasoconstriction is the most important contributor to orthostatic hypotension in FD [7], we might expect that any maneuver that increases total peripheral resistance – like squatting – would be particularly valuable in these patients.

Despite squatting being the most effective countermaneuver in terms of ameliorating the extent of orthostatic hypotension, several of the FD patients had some difficulty in performing the maneuver. In these patients another countermaneuver might be more useful. For example, bending forward and abdominal compression significantly increased blood pressure in our FD patients. Both these countermaneuvers involve compression of the splanchnic blood vessels, while bending forward also reduces the vertical distance between the heart and the brain. The effects of abdominal compression were rather inconsistent, with five patients showing increases in mean blood pressure of at least 20 mmHg and the remaining patients showing little or no change in blood pressure. Abdominal compression is also cumbersome, requiring the patient to wear a binder and inflate it when required. However, in patients who are susceptible to severe and frequent episodes of orthostatic hypotension, and in whom the maneuver is effective, abdominal compression might be beneficial as a means of last resort. The blood pressure response to bending forward was more consistent and increased in most patients. A disadvantage of bending forward was that, as with squatting, many FD patients had difficulty in performing the maneuver or required assistance.

In contrast to the other countermaneuvers, leg crossing was relatively ineffective at increasing blood pressure. Nevertheless, four patients did show considerable increases in blood pressure of at least 20 mmHg during the maneuver. In other studies in autonomic failure and syncope patients [20, 22], leg crossing substantially and significantly increased both cardiac output and blood pressure, which was not the case in our FD population. In patients with FD, venous pooling in the legs does not contribute to a large extent to their orthostatic hypotension [7]. In fact, we found that during active standing, the average increase in calf volume in our patients was only about 1.3 %. This compares to an increase of 4.6 % after 10 min of head-up tilting in a previous study by our group [7]. In the current study, muscle pump activation during active standing, as well as the shorter time period, might have limited the amount of venous pooling. The reduced venous pooling during active standing is consistent with our finding that the decrease in cardiac output was negligible. The efficacy of leg crossing in other autonomic failure patients or patients with syncope is attributed to its effects on decreasing the excessive venous pooling in the lower extremities that is a contributing factor to blood pressure falls in these patients [20, 22]. In FD patients, the absence of a significant effect of leg-crossing on blood pressure might have been a consequence of their limited venous pooling.

Our study does contain a few limitations, which we have to consider when interpreting the results. Although impedance cardiography has been well validated against other techniques of measuring cardiac output [4, 8], movement artifacts and changes in body geometry during the countermaneuvers might have introduced some technical errors. For this reason, we excluded impedance

measurements during bending forward, as this maneuver seemed to impose a strain on the thorax. Squatting might also have strained the thorax somewhat, although all the patients who performed the maneuver were able to maintain their trunk in a vertical plane. Nevertheless, we are cautious about our interpretation of the results derived from impedance measurements during the countermaneuvers. In any case, we were more interested in the blood pressure changes as these results are of most clinical relevance. Blood pressure was assessed by arterial tonometry, which has been validated against intra-arterial recordings [13], although not during physical countermaneuvers. However, we took every effort to ensure that the sensor remained at heart level and to minimize movement artifacts. Therefore, we are confident in the accuracy of our blood pressure measurements.

A major difficulty in this study was that many patients were unable to perform the countermaneuvers or required assistance to perform them. This was not unexpected considering the neurological, orthopedic and other complications associated with FD. Our findings may therefore have been biased by the fact that in our analysis we could only include patients who actually were able to perform the maneuvers. However, the purpose of our study was not only to evaluate quantitatively the hemodynamic changes, but to assess the overall clinical applicability of physical countermaneuvers in the FD population. In that respect, we did find that in nearly all of the patients, at least one countermaneuver could be performed that was effective at augmenting blood pressure. Even in the patients who could adequately perform the maneuvers, different countermaneuvers were effective in different patients. In the clinical setting we would therefore advise evaluation of several countermaneuvers for each patient to determine the best maneuver for that patient. The patient – and the relatives – can then learn to apply the most appropriate countermaneuver to cope with situations of orthostatic hypotension. We normally instruct our FD patients to try to avoid situations that might precipitate a syncopal episode, such as standing still for a long time. In the event of posturally-related dizziness, we suggest that the patients should sit or lie down until the symptoms have passed. Only where that is not possible, we would recommend that patients use a countermaneuver as a last resort. In this case, the patient should apply that particular maneuver that was tested to be most suitable and effective in this individual patient.

To summarize, countermaneuvers may be helpful in FD patients if properly selected and applied. In contrast to the usefulness of countermaneuvers in other disorders of orthostatic intolerance [5, 16, 20, 22, 23], their efficacy in the FD population is limited because of orthopedic problems, ataxia, and the specific pathophysiology of orthostatic hypotension in FD.

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