



Physical counter-pressure manoeuvres in preventing syncopal recurrence in patients older than 40 years with recurrent neurally mediated syncope: a controlled study from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)[†]

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Received 21 October 2013; accepted after revision 22 April 2014

Aims

Physical counter-pressure manoeuvres (PCM) are effective in young patients with vasovagal syncope and recognizable prodromal symptoms. The aim of this study was to investigate their effectiveness in patients ≥ 40 years with severe neurally mediated syncope (NMS) enrolled in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3).

Methods and results

In the ISSUE-3 study, 63 out of 162 patients had a diagnosis of hypotensive NMS (Types 2, 3, and 4A) documented by implantable loop recorder; of these, 40 were instructed to perform isometric leg and arm PCM therapy. Their mean age was 62 ± 13 years; 47% of patients had a history of some episodes without prodrome. A group of 45 untreated patients acted as controls. The primary endpoint was the time to first syncope recurrence. During follow-up, syncope recurred in 15 PCM patients (37%) and in 24 control patients (53%) ($P = 0.14$). At 21 months, the modelled syncope recurrence rates were 42% [95% confidence interval (CI): 27–61] and 64% (95% CI: 48–80), respectively ($P = 0.27$).

Conclusion

In conclusion, many ISSUE-3 patients affected by hypotensive NMS have syncopal recurrence despite PCM. Older age and the absence of sufficiently long recognizable prodromal symptoms in the ISSUE-3 population might have hampered the effectiveness of PC therapy.

Keywords

Physical counter-pressure manoeuvres • Neurally mediated syncope • Old patients

Introduction

Vasovagal syncope is a common clinical condition, with an estimated lifetime prevalence of 35%.^{1–3} Although the disorder is

episodic in nature, often symptoms occur over many years due to recurrences of episodes of (pre)syncope so it could be considered a chronic disorder with important deleterious effects on the quality of life.⁴

[†]The investigators of PC2 Trial analysis of ISSUE-3 Study are listed in the Appendix.

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What's new?

- Physical counter-pressure manoeuvres (PCM) are effective in young patients with vasovagal syncope and recognizable prodromal symptoms, while Third International Study on Syncope of Uncertain Etiology (ISSUE-3) patients affected by hypotensive neurally mediated syncope have syncopal recurrence despite PCM.
- Physical counter-pressure manoeuvres therapy is not confirmed as a panacea but its use is valuable and we must strive to improve its application in practice.

The pathophysiology of spontaneous vasovagal syncope is not completely known. Vasovagal syncope induced in the laboratory during tilt table testing is triggered by a reduction in the central venous volume because of venous pooling of blood in lower body veins during prolonged standing. A steep fall in cardiac output seems to be the main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. Excessive vagal tone (resulting in bradycardia) and withdrawal of muscle sympathetic nerve tone may frequently also occur in a late phase of the reflex.^{5–9}

Physical counter-pressure manoeuvre (PCM) therapy has been previously proven to be effective in stabilizing blood pressure in patients with autonomic failure^{10,11} and there are published reports on controlling or aborting impending vasovagal syncope by leg crossing and muscle tensing.^{12–14} A comparable effect was also found with isometric arm counter-pressure manoeuvre.¹⁵ The PC trial¹⁶ showed that PCMs are a risk-free, effective, and low-cost treatment method in young patients with vasovagal syncope with prodromal symptoms, and should be recommended in combination with current conventional therapy as first-line treatment in patients presenting with this syndrome. For this reason, PCM are indicated (Class I) for patients with reflex syncope and prodrome in the last European Society of Cardiology (ESC) guidelines for diagnosis and treatment of syncope.¹⁷

Nevertheless, an analysis has shown less efficacy of PCM in patients older > 65 years with vasovagal syncope.¹⁸

The aim of this study was to evaluate the feasibility and efficacy of PCM in the older population of the ISSUE-3 study,¹⁹ after documentation of a likely hypotensive neurally mediated syncope (NMS) by means of implantable loop recorder (ILR).

Methods

The ISSUE-3 study included patients ≥ 40 years old who had suffered ≥ 3 syncopal episodes of likely NMS aetiology in the previous 2 years, which had a severe clinical presentation (because of high frequency and/or high risk) to warrant specific treatment. Assessment of the severity of the clinical presentation was based on the definitions of high frequency or high risk provided by ESC guidelines.²⁰ Specifically, syncope was defined as very frequent when it altered the quality of life of the patient, and at high risk when it was unpredictable (the absence of premonitory symptoms), and thus not amenable to prevention by standard measures (i.e. physical manoeuvre, sitting, squatting, etc.), exposed patients to the

risk of trauma, or occurred during the performance of a 'high-risk' activity (e.g. driving, machine operation, etc.).

All these individuals received an ILR and were followed up. In accordance with the guidelines of the ESC,²⁰ NMS was considered likely when the clinical history was consistent with NMS and competing diagnoses had been excluded. Patients were excluded if they had one or more of the following features: (i) cardiac abnormalities which suggested cardiac syncope described as overt heart failure; ejection fraction < 40%; old or recent myocardial infarction; hypertrophic or dilated cardiomyopathy; clinically significant valvular disease; sinus bradycardia < 50 b.p.m. or sinoatrial block; Mobitz I second-degree atrioventricular block; bundle-branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; Brugada syndrome; arrhythmogenic right ventricular cardiomyopathy; (ii) symptomatic orthostatic hypotension diagnosed by means of standing blood pressure measurement; (iii) non-syncopal loss of consciousness (e.g. epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischaemic attack, intoxication, cataplexy). Patients with carotid sinus syndrome and documented symptomatic bradycardia during carotid sinus massage were also excluded, as this is an accepted indication for cardiac pacing.²⁰

After ILR implantation, all patients were followed up quarterly until the first documented syncopal recurrence, occurrence of a diagnostic arrhythmic event or the end of the study. Events were classified according to the ISSUE classification²¹ as: Type 1 (asystole > 3 s), Type 2 (bradycardia), Type 3 (slight or no rhythm variations), and Type 4 (tachycardia).

For this substudy, those patients who had a Type 2, Type 3, or Type 4A (sinus tachycardia) diagnosis established by means of ILR documentation were selected. These patients were followed in a second phase of the ISSUE-3 study, a multicentre, observational, prospective arm of the study called the PC2 trial where included patients were instructed to perform PCM therapy and lifestyle changes (such as avoiding situations which led to syncope recurrence, i.e. standing still for a long time, crowded places, etc.) described in the previous PC trial.¹⁶ Treatment consisted of isometric leg and arm counter-pressure manoeuvres. Patients were advised to use leg crossing as a preventive measure and to use lower body muscle tensing including 'buttock-clenching' with leg and abdominal muscle tensing, or use hand gripping with a rubber ball or arm tensing in case of the occurrence of symptoms of impending syncope. The patients were instructed to maintain the manoeuvre they chose as long as possible and eventually to move to a second or third manoeuvre if useful. Patients were allowed to choose the manoeuvres and the sequence of their administration. After they received the PCM training, all patients were followed up quarterly during the first 24 months or until the study ended. The patient kept a logbook for registration of symptoms including palpitations, dizziness, pre-syncope, and syncope. The endpoint was the time to first syncope recurrence.

The control group consisted of those patients enrolled in the ISSUE-3 study who, despite an established diagnosis did not receive active treatment for any reason (e.g. centre not participating in the PC2 trial arm of ISSUE-3 study, patient's refusal of treatment, and asystolic NMS patients assigned to the inactive pacemaker arm of the randomized study). The control patients had similar clinical characteristics to those who underwent PCM (Table 1).

The protocol was approved by a research ethics board at each centre and each patient provided signed informed consent. The full study protocol has been previously published.²²

Statistical analysis

Analyses were carried out by means of SAS 9.3. Continuous data are shown as averages \pm SDs or medians (25th–75th percentile), as appropriate, while absolute and relative frequencies were used to describe

Table 1 Baseline patient characteristics

Parameter	PCM n = 40	No PCM n = 45	P-value
Age	62 ± 13	66 ± 12	0.135
Age at first syncope, mean (SD), years	48 ± 19	48 ± 23	0.999
Males	20 (50%)	14 (31%)	0.074
Number of hospitalization due to syncope	2 ± 1	2 ± 1	0.727
Number of pre-syncope during last 2 years	15 ± 13	20 ± 28	0.613
Supine systolic blood pressure	127 ± 17	133 ± 18	0.104
Number of syncope during last 2 years	12 ± 23	8 ± 15	0.187
Number of syncope during lifetime	17 ± 25	11 ± 12	0.325
Number of syncope without prodrome in last 2 years	6 ± 14	3 ± 3	0.571
History of pre-syncope	21 (52%)	24 (55%)	0.851
Without prodrome	19 (47%)	30 (67%)	0.074
Hospitalization for syncope	19 (47%)	25 (56%)	0.458
Typical vasovagal presentation	18 (45%)	24 (53%)	0.443
Typical situational presentation	4 (10%)	13 (29%)	0.034
Minor injuries (contusion, wound, haematoma)	16 (40%)	18 (40%)	1.000
Major injuries (fractures, haemorrhage, neurological complications)	3 (7%)	4 (9%)	1.000
Hypertension	19 (49%)	23 (51%)	0.827
Diabetes	4 (10%)	5 (11%)	1.000
Neurological/psychiatric diseases	1 (2%)	0 (0%)	0.471
Anti-hypertensive drugs	19 (47%)	25 (56%)	0.518
Psychiatric drugs	30 (75%)	40 (89%)	0.153
Any other drugs	31 (77%)	34 (76%)	1.000
Lowest upright systolic blood pressure (SD), mmHg	119 ± 15	123 ± 20	0.289
Mean heart rate, mean (SD), b.p.m.	69 ± 9	71 ± 9	0.523
Structural heart diseases	4 (10%)	4 (9%)	1.000
Echo performed	31 (79%)	29 (64%)	0.128
Any echocardiographic abnormality (e.g. valvular disease)	2 (7%)	3 (11%)	0.655
Ejection fraction (SD), %	63 ± 6	60 ± 5	0.060
LVEDD (SD), %	49 ± 7	50 ± 6	0.619
LVESD (SD), %	33 ± 9	31 ± 5	0.936
Tilt test performed	35 (88%)	37 (82%)	0.483
Positive tilt test	18 (51%)	24 (65%)	0.229
TT asystole	4 (21%)	9 (37%)	0.324
Maximum asystolic pause if TT asystole, mean (SD), s	7 ± 14	5 ± 8	0.700

categorical data. The Shapiro–Wilk test was performed to check the skewness of distributions. Continuous variables were compared by means of the unpaired Student's *t*-test or the non-parametric Mann–Whitney test, depending on data distribution. χ^2 and Fisher's exact tests were used to compare proportions. The time to the first recurrence

of syncope was analysed by means of Kaplan–Meier survival curves, which were compared using the log-rank test.

Results

Study participants were enrolled from July 2006 to November 2010 and follow-up was concluded in November 2012. During the observation period, 162 out of 504 patients had a diagnosis of NMS documented by ILR, which showed an electrocardiogram pattern consistent with a reflex mechanism (i.e. Types 1, 2, 3, and 4A of the ISSUE classification). Among the 162 established NMS patients, 63 had a diagnosis of likely hypotensive NMS (Types 2, 3, and 4A of ILR classification): as per protocol, 40 patients received instruction about PCM and lifestyle changes and were assigned to the PCM study group, 13 patients did not receive PCM instruction and were assigned to the control group, and 10 patients were lost to follow-up (for whom no information was available about received therapy). The control group consisted of the above 13 hypotensive NMS patients who did not receive PCM instruction plus 32 patients with asystolic NMS who did not receive any active treatment (because assigned to the inactive pacemaker arm of the randomized study). The clinical characteristics of the study population are listed in the *Table 1*.

During a mean follow-up of 16 ± 10 months, 39 (46%) patients experienced at least one syncope recurrence, 15 (37%) in the PCM group and 24 (53%) in the no PCM group ($P = 0.14$). Of patients with recurrence in the PCM group, seven had recurrence despite using manoeuvres and seven did not use them (three of them had syncope without prodrome); data are missing for one patient. At 21 months, the modelled syncope recurrence rates were 42% [95% confidence interval (CI): 27–61] and 64% (95% CI: 48–80), respectively ($P = 0.27$) (*Figure 1*) with a relative risk reduction of 34%. In particular, the recurrence rate of the 13 hypotensive patients of the control group was 69% (95% CI: 38–94). The results remained similar when comparing the subgroup of patients with a history of syncope with prodrome, who potentially were more likely to benefit from PCMs: modelled syncope recurrence rates of 45% (95% CI: 25–72) and 73% (95% CI: 47–93), respectively, $P = 0.31$ with a relative risk reduction of 38% (*Figure 1*).

Discussion

The efficacy of PCM in the ISSUE 3 study was limited in patients affected by likely hypotensive NMS documented by ILR. Comparing the patients who were instructed to perform isometric leg and arm PCM, with the untreated patients acting as controls, less patients had recurrence of syncope with PCM (*albeit* not statistically significant) but still many PCM patients had recurrence of syncope despite the therapy.

Leg and arm counter-pressure manoeuvres (leg crossing, hand gripping, and arm tensing) are a risk-free, effective, low-cost, and first-line treatment in patients presenting vasovagal syncope with prodromal symptoms.^{10–15} The multicentre, prospective, randomized PC trial¹⁶ assessed the effectiveness of PCM in daily life in 223 patients, aged 38 ± 15 years, with recurrent vasovagal syncope and recognizable prodromal symptoms. Most patients had positive tilt test results, but the mechanism was not confirmed by ILR. The recurrence-free survival was better in the treatment group

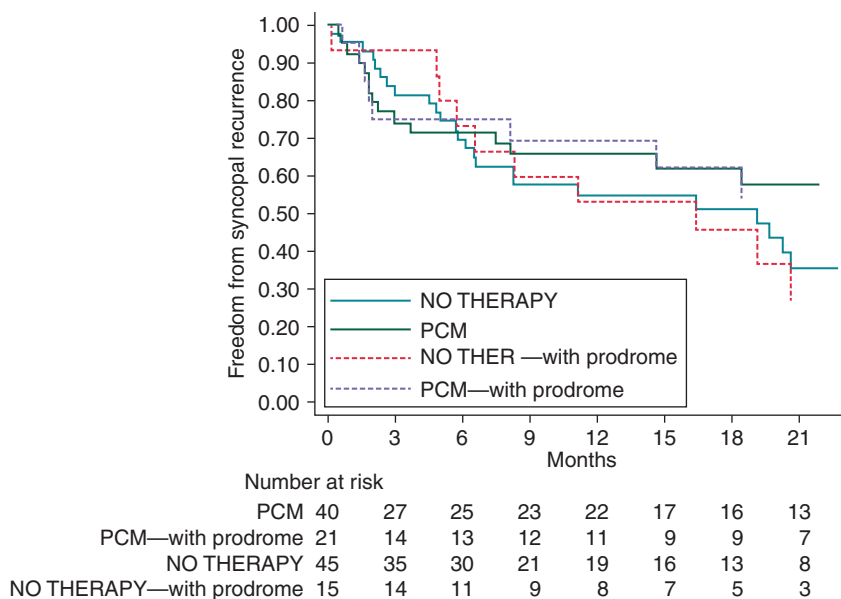


Figure 1 Comparison between Kaplan–Meier curves of freedom from syncope recurrence in patients who performed PCM training and control untreated group of patients. Log rank: $P = 0.274$. The survival curves of the two subgroups of patients with and without a prodrome is superimposed (intermittent line): $P = 0.31$.

(log-rank $P < 0.018$), resulting in a relative risk reduction of 39% and no adverse events were reported. In the previous studies, the mean age of the patient population where PCM have been proven to be effective has ranged from 28 to 55 years old.^{13–16}

PC2 trial population was very different from that of PC trial. PC2 trial was aimed to verify the effectiveness of PCM in patients affected by hypotensive NMS only (asystolic forms excluded), in most cases without any or with very short prodromal symptoms and much older (mean age 66 ± 12 years). The experience of ISSUE-3¹⁹ showed that, in a selected group of patients with severe clinical presentation of certain or suspected neurally mediated reflex syncope and age >40 years, it is necessary to follow a diagnostic process guided by ILR to discover the underlying mechanism. Patients with cardioinhibitory NMS could benefit from pacemaker implantation, but what would the consequences be for patients with the vasodepressive form?

In the present study, PC2 trial was unable to confirm the effectiveness of PCM therapy in older patients affected by likely hypotensive NMS (by means of ILR documentation). Nevertheless, the actuarial relative risk reductions observed in this study (34% in total population and 38% in the subgroups of patients with a history of prodrome) was only slightly lower than that observed in the PC trial, which was 39%. This finding suggests that the effectiveness of PCM was not so different in the two trials, but PC2 patients probably were more severely affected than PC patients because they had to fulfil restrictive inclusion criteria (see the Methods section). The consequence was that they had a higher absolute recurrence rate than PC patients both in the active arm (37 vs. 32%) and also in the control arm (53 vs. 51%). Moreover, although the PC2 trial is the first study considering patients with predominantly hypotensive component to NMS, it is limited in size. The population of the present study was less than half

that of the PC trial; we cannot therefore exclude a Type II error; the difference with the control group could have become significant with a larger sample size.

With these conclusions of our analysis, some points need discussion. First, 50% of patients with recurrence of syncope in the PCM group did not use the PCM; it is possible that young patients could have greater compliance in applying correctly the PCM. It is known that old patients have a decreased muscular mass and muscular strength than younger, which limits the execution of effective PCMs. In the study of Croci *et al.*,¹⁸ which analysed the efficacy of isometric arm counter-pressure manoeuvres in patients with vasovagal syncope, the actuarial predicted recurrence rate of syncope at 1 year was higher in older patients (44% in patients >65 years vs. 5% in patients ≤ 65 years). Even if not statistically significant, our patients aged <55 years had lower recurrence rate than those aged >55 years (34 vs. 46%; $P = 0.536$).

Secondly, among factors that hampered the effectiveness of PCM, there is the absence of sufficiently long recognizable symptoms (prodrome) in the ISSUE-3 population. Even if we did not find substantial differences in outcome between the total population and the subgroups of patients with a prodrome (Figure 1), this is the substantial difference between this study and the other studies in which the PCM were assessed as effective^{12–16}, in most cases there is an absence of clear prodromal symptoms. Another aspect of the patients in this study may be that sufficient time was not dedicated to the task of PCM training. The patients with a short prodrome feel more vulnerable to their attacks than those with longer warning. They require more reassurance confidence building in PCM. This lack of specific attention to the problem may have influenced the results.

It is also necessary to state the fact that patients in the no PCM group were more often females, had less prodrome, and had a typical situational presentation of their syncope episodes.

Furthermore, the ISSUE-3 study, as most trials on syncope patients, used for the primary endpoint the time to first recurrence of syncope. Although the first recurrence is optimal endpoint to compare different treatments for serious outcomes like death or hospitalization, it is not optimal for repetitive, in most cases benign events, such as NMS recurrences. In the context of NMS the most important endpoint may be better assessed from the quality of life, which could give a more definite illustration of the clinical benefit of PCM. Patients adversely affected in terms of quality of life, are those with frequent and/or traumatic recurrences, it is possible to anticipate success of treatment, despite recurrences (once or twice over 2 years), when it is possible to avoid traumatic syncope and reduce the burden of recurrence.

Discussion of the importance and efficacy of PCM remains open. In the future, there could be a randomized, controlled trial including ISSUE-3-like patients, selected by ILR with a 'therapy' group employing a specific and organized protocol of training in PCMs compared with a 'no-Therapy' control group, where all patients are affected by hypotensive NMS (without important asystole documented by ILR).

The debate remains open on the two points which may have hampered the effectiveness of the PCM therapy: the correlation between efficacy of PCM, considering the fact that our analysis has not shown a statistically significant difference between the subgroups under and above 55 years of age and the presence or relative absence of prodromal symptoms, considering that the relative risk reduction in PC2 (34% in total population and 38% in the subgroup of patients with clear prodrome) is only slightly lower than that observed PC trial (all patients with prodrome), with a not statistically significant result possibly due to a possible Type II error as a consequence of the small sample size.

An organized, articulated, well-structured programme of training and learning of PCM therapy may aid provision of more effective therapy.

Lastly, we must consider that the practical use of PCM could have a role in some NMS pacemaker patients. ISSUE-3 showed that 25% of patients, who underwent PM implantation after evidence of profound cardioinhibition documented by ILR, had a recurrence within 2 years despite the PM being switched on. In the case of frequent or debilitating recurrences, PCM could represent the only possible therapeutic opportunity to combat the hypotensive reflex component (hybrid therapy for mixed NMS).

Limitations

As already discussed above, the major limitation of the study is the small number of patients in the respective groups which might indeed induce a Type II error. In addition, since the present study is actually a substudy based on ILR data, this might imply some selection bias.

Even if control patients were not instructed formally to perform PCMs, this therapy has become so well-known and widely applied in clinical practice after the publication of PC trial¹⁶ which we

cannot exclude that also some control patients used PCMs during the study period.

Due to the lack of randomization, the method of selection of the control group has potential bias and resulted to be non-homogeneous. Indeed, it was formed of 13 out of 63 hypotensive NMS patients who did not receive instruction for CPM and of 32 asystolic NMS patients who did not undergo pacemaker therapy. However, these two subgroups of no-PCM were comparable in terms of baseline characteristics and time to first event and have been combined to form a larger control group. Moreover, the control group had baseline characteristics which were fairly comparable with those of the CPM group (Table 1).

Lower annual rates of recurrence occurred in some centres compared with others. This may reflect different strategies used in teaching PCM, which may vary from a rapid demonstration to a well-structured and articulated programme requiring more time, specific tasks, and additional steps.

Conclusions

Many ISSUE-3 patients affected by hypotensive NMS have syncope recurrence despite PCM. It is necessary to consider that this is the only practicable therapeutic strategy in patients affected by hypotensive NMS (Class I recommendation in the guidelines on syncope of the ESC¹⁷ and that much scientific literature supports the use of this therapy, not only in patients with vasodepressive forms of NMS but also in patients with cardioinhibitory forms, in whom there is no indication to implant a pacemaker as the first therapeutic strategy (<40 years old). From this ISSUE-3 substudy, PCM therapy is not confirmed as a panacea but its use is valuable and we must strive to improve its application in practice.

Conflict of interest: M.T. reports receiving modest consultancy fees from Medtronic; R.S. is a consultant to Medtronic, receiving modest fees, and is a paid lecturer for St Jude Medical; A.M. reports receiving modest consultancy fees from Medtronic; S.G., G.D., and A.G. are employees of Medtronic; the other authors have no financial disclosures to make.

Funding

The ISSUE-3 study has been sponsored by Medtronic BRC, Maastricht. M.

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