Role of Baroreflex Sensitivity in Predicting Tilt Training Response in Patients with Neurally Mediated Syncope

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Background

• Neurally mediated syncope (NMS)
  – The most common type of syncope
  – Pathophysiological mechanism remain uncertain
  – Head-up tilt test (HUT) is often used to confirm NMS in patients with a suspicious history of NMS
  – Autonomic nervous system
  – Arterial baroreflex control of heart rate (baroreflex sensitivity, BRS) and vascular tone also play a role
Background

• The role of arterial baroreflex function in the pathophysiology of NMS is controversial.

• Most studies have failed to any clear evidence of alteration in arterial baroreflex control of heart rate

• A few have reported a reduction, or an increase in baroreflex activity
P < 0.0003
|                      | NTG−, n = 39 | HUT+, n = 21 | NTG+, n = 37 | P ANOVA |
|----------------------|--------------|--------------|--------------|---------|
| Gender (M/F)         | 26/13        | 12/9         | 19/18        | 0.39    |
| Age (years)          | 35 ± 13      | 32 ± 14      | 36 ± 12      | 0.55    |
| Body mass index (kg/m²) | 25 ± 4      | 24 ± 3       | 23 ± 4†      | 0.027   |
| Baroreflex sensitivity assessment |           |              |              |         |
| SAP ramps (n/100 heart beats) | 2.4 ± 2.2   | 2.0 ± 1.3    | 2.2 ± 1.7    | 0.75    |
| BEI (%)              | 28 ± 19      | 44 ± 24†     | 48 ± 27†     | <0.001  |
| BRS (ms/mmHg)        | 12.8 ± 5.8   | 15.5 ± 7.4   | 16.8 ± 7.4†  | 0.048   |

![Graph showing changes in BRS (ms/mmHg) over time](image)

**C**

- **HUT+**: ▲
- **NTG+**: □
- **NTG−**: ●

**Legend**: *P = 0.004**
Subjects with tilt-induced VVS showed greater resting BRS

The enhanced reflex tachycardiac response to arterial baroreceptor deactivation at rest may represent a characteristic feature of subjects prone to tilt-induced VVS
**Cumulative proportion free events**

- < 8.5 ms/mmHg
- 8.5-12.4 ms/mmHg
- 12.5-17.6 ms/mmHg
- > 17.6 ms/mmHg

Log-Rank test

\[ p < 0.001 \]

**Tilt test (minutes)**

- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
Reduced BRS during HUT has independent role in predicting the recurrence of syncope

Cox’s multivariate analysis of VVS recurrence during follow-up

| Model   | Hazard ratio (95% CI) | P-value |
|---------|-----------------------|---------|
|         |                       |         |
| Model 1 |                       |         |
| Female gender | 3.19 (1.40–7.28) | 0.006   |
| ≥ 3 syncope events before HUT | 2.95 (1.26–6.87) | 0.012   |
| RR interval² | 0.98 (0.71–1.34) | 0.88    |
| Baseline BRS | 0.94 (0.88–1.00) | 0.058   |
| Model 2 |                       |         |
| Female gender | 3.01 (1.37–6.63) | 0.006   |
| ≥ 3 syncope events before HUT | 3.60 (1.46–8.83) | 0.005   |
| **5 min HUT BRS** | 0.91 (0.84–0.99) | 0.030   |
| Model 3 |                       |         |
| Female gender | 2.86 (1.07–7.61) | 0.036   |
| ≥ 3 syncope events before HUT | 5.49 (1.58–19.08) | 0.007   |
| **5 min NTG BRS** | 0.73 (0.57–0.94) | 0.016   |
| **5 min NTG BEI³** | 1.02 (0.74–1.40) | 0.92    |

Europace 2010;12:1149-1155
Schematic practical decision pathway for the first-line management of reflex syncope

Reflex syncope

Education, life-style measures (Class I)

Severe/recurrent form

Low BP phenotype

Prodromes

Hypotensive drugs

Dominant cardioinhibition

No or very short

Yes

Younger

• Fludrocortisone
• Midodrine (Class IIb)

Counter-pressure manoeuvre (Class IIa)

Tilt training (Class IIb)

ILR-guided management in selected cases (Class I); See section 4.2.4

Stop/reduce hypotensive drugs (Class IIa)

Cardiac pacing (Class IIa/IIb) SeeFigure 10

Older
Tilt Training

• Tilt training by head-up tilt table in hospital
• Home self training
  – Standing against a wall (20cm from the wall for 30 minutes)
The Effect of Orthostatic Training in the Prevention of Vasovagal Syncope and Its Influencing Factors

Hui ZENG,¹ MD, Kanyi GE,¹ Weilun ZHANG,¹ Guang WANG,¹ MD, and Lijun GUO,¹ MD

Home orthostatic self-training is an effective therapy for the prevention of VVS

Int Heart J 2008;49:707-712
Is Home Orthostatic Self-Training Effective in Preventing Neurally Mediated Syncope?

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| Follow up Head-up Tilt Test Between Tilt Training Group and Controls |
|---|---|---|
|                  | Tilt Training (n = 16) | Controls (n = 17) | P   |
| Tilt-duration (min) | 39 (10–45) | 39 (10–45) | 0.913 |
| FU response of head-up tilt test | 9/16 (56%) | 9/17 (53%) | 0.849 |

Home orthostatic self-training was ineffective in reducing the positive response rate of HUT
Home orthostatic self-training was unable to influence the spontaneous syncope recurrence except for vasodepressor type
Repeated tilt testing in patients with 
tilt-positive neurally mediated syncope

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- In-hospital tilt training by tilt table
- The HUT was repeated day after day (one session per day)
- All 222 patients obtained a negative tilt test (mean 2.9 tilt session)
Tilt training increases the vasoconstrictor reserve in patients with neurally mediated syncope evoked by head-up tilt testing

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- The patients with 2 consecutive positive tilt test was enrolled
- In-hospital daily repeated tilt training
- The target was to obtain 2 consecutive negative tilt tests
- Follow-up tilt test was performed at 6 weeks later
Tilt testing appears to restore orthostatic tolerance by increasing the amount of vasoconstriction.
Background

• In-hospital tilt training vs home orthostatic self-training

• Limitation
  – Hospital admission
  – Medical costs
  – Non-response to tilt training
Purpose

• This study aimed to assess the role of BRS in predicting response to tilt training in patients with NMS
Methods

• **Inclusion criteria**
  – Tilt training registry from Mar. 2006 to Mar. 2014
  – HUT positive patients with suggestive clinical history
  – The patients with **two consecutive positive responses** to HUT were enrolled
    • A positive response to the initial diagnostic HUT and a positive response to the first session of tilt training

• **Exclusion criteria**
  – Any other cause of syncope
  – Structural heart disease

• **Retrospectively reviewed**
Methods

• **Tilt test protocol**
  - Supine position (10 min)
  - Passive head-up tilt 70° (30min)
  - Isoproterenol 1ug/min ~ 5ug/min (each 3 min)

• **Tilt training**
  - Tilt tests were repeated day after day
    • two sessions per day

• **Data acquisition**
  - During sequential head-up tilt test, beat to beat arterial blood pressure was continuously measured non-invasively by Finometer® PRO
Methods

• Arterial baroreflex sensitivity
  – Cross-correlation baroreflex sensitivity (xBRS) method

• Data analysis
  – Before passive HUT (5 min)
  – After passive HUT (5 min)
  – Before syncope or study end (5 min)

• Tilt training response
  – Three consecutive negative tilt test
Methods

- Diagnostic tilt test
- Tilt training at hospital (N=111)
  - Session 1
    - Session 1 negative (N=41)
    - Data loss (N=13)
  - Study population (N=57)
    - Responder (N=52)
    - Non-responder (N=5)
# Results

- **Baseline clinical characteristics**

|                                | Patients (N = 57) |
|--------------------------------|-------------------|
| Age (years)                    | 33.9 ± 13.5       |
| Male gender                    | 26 (45.6)         |
| Height (cm)                    | 167.9 ± 9.2       |
| Weight (kg)                    | 63.1 ± 11.1       |
| BMI (kg/m²)                    | 22.4 ± 3.4        |
| Frequency of syncope before diagnosis | 5.2 ± 5.5        |
| Type of VVS                    |                   |
| Mixed                          | 14 (24.6)         |
| Cardioinhibitory               | 3 (5.3)           |
| Vasodepressive                 | 40 (70.2)         |
| Phase of positive diagnostic HUT |                 |
| Passive                        | 22 (38.6)         |
| Isoproterenol                  | 35 (61.4)         |
| Duration of initial diagnostic HUT (min) | 30.1 ±12.4     |

VVS, vasovagal syncope; HUT, head-up tilt test
Baseline clinical characteristics of the study groups

|                                | Responder group (N = 52) | Non-responder group (N = 5) | P value |
|--------------------------------|--------------------------|----------------------------|---------|
| Age (years)                    | 32.9 ± 13.3              | 44.4 ± 13.2                | 0.071   |
| Male gender                    | 25 (48.1)                | 1 (20.0)                   | 0.62    |
| Height (cm)                    | 168.6 ± 8.9              | 160.7 ± 10.0               | 0.067   |
| Weight (kg)                    | 63.4 ± 10.9              | 60.6 ± 14.2                | 0.604   |
| BMI (kg/m²)                    | 22.3 ± 3.4               | 23.2 ± 3.0                 | 0.466   |
| Frequency of syncope before diagnosis | 5.2 ± 5.7                | 5.0 ± 3.0                  | 0.439   |
| Type of VVS                    |                          |                            |         |
| Mixed                          | 13 (25.0)                | 1 (20.0)                   | 0.323   |
| Cardioinhibitory              | 2 (3.8)                  | 1 (20.0)                   |         |
| Vasodepressive                 | 37 (71.2)                | 3 (60.0)                   |         |
| Phase of positive diagnostic HUT |                          |                            |         |
| Passive                        | 19 (36.5)                | 3 (60.0)                   | 0.364   |
| Isoproterenol                 | 33 (63.5)                | 2 (40.0)                   |         |
| Duration of initial diagnostic HUT (min) | 30.3 ± 12.7         | 28.6 ± 9.9                 | 0.597   |
| Total number of tilt training session | 5.5 (4.0 – 6.8)      | 6.0 (5.0 – 8.0)            | 0.265   |
| Total time of tilt training (min)   | 214.0 (175.8 – 263.5)   | 237.0 (144.5 – 301.5)      | 0.854   |
| Mean time of tilt training (min)      | 39.7 ± 6.0              | 34.5 ± 5.6                 | 0.071   |
BRS and hemodynamic data during the first session of the tilt training (1)

|                                | Tilt training responder group (N = 52) | Tilt training non-responder group (N = 5) | P value |
|--------------------------------|---------------------------------------|------------------------------------------|---------|
| **Supine position**            |                                       |                                          |         |
| BRS (ms/mmHg)                  | 18.17 ± 10.09                         | 7.99 ± 5.84                              | 0.008   |
| SBP (mmHg)                     | 108.2 ± 13.5                           | 133.3 ± 35.2                             | 0.094   |
| DBP (mmHg)                     | 57.1 ± 10.0                            | 64.7 ± 21.6                              | 0.555   |
| MBP (mmHg)                     | 77.6 ± 10.1                            | 92.6 ± 26.1                              | 0.186   |
| HR (bpm)                       | 63.5 ± 8.9                             | 64.8 ± 15.0                              | 0.732   |
| SVR (dyn·s/cm²)                | 1148.8 ± 257.5                         | 1138.1 ± 536.6                           | 0.250   |
| **After upright posture**      |                                       |                                          |         |
| BRS (ms/mmHg)                  | 6.78 ± 4.02                            | 4.74 ± 1.88                              | 0.120   |
| SBP (mmHg)*                    | 103.2 ± 13.5                           | 119.6 ± 20.0                             | 0.024   |
| DBP (mmHg)*                    | 61.5 ± 9.4                             | 71.4 ± 6.4                               | 0.010   |
| MBP (mmHg)*                    | 77.6 ± 10.3                            | 90.9 ± 11.8                              | 0.016   |
| HR (bpm)*                      | 81.1 ± 12.0                            | 76.1 ± 13.6                              | 0.339   |
| SVR (dyn·s/cm²)*               | 1269.1 ± 237.3                         | 1648.2 ± 449.1                           | 0.091   |
- BRS and hemodynamic data during the first session of the tilt training (2)

|                         | Tilt training responder group (N = 52) | Tilt training non-responder group (N = 5) | \( P \) value |
|-------------------------|----------------------------------------|------------------------------------------|---------------|
| Before syncope develop  |                                        |                                          |               |
| BRS (ms/mmHg)           | 5.89 ± 4.17                            | 5.03 ± 3.07                              | 0.540         |
| SBP (mmHg)              | 94.1 ± 13.0                            | 108.2 ± 20.5                             | 0.079         |
| DBP (mmHg)              | 57.2 ± 8.8                             | 64.8 ± 6.9                               | 0.036         |
| MBP (mmHg)              | 70.4 ± 9.3                             | 81.4 ± 12.0                              | 0.042         |
| HR (bpm)                | 98.8 ± 20.5                            | 85.6 ± 8.5                               | 0.164         |
| SVR (dyn⋅s/cm\(^5\))    | 1210.7 ± 277.2                         | 1548.3 ± 409.7                           | 0.065         |

**BRS value ≥ 8.945 in supine position – n(%)**

|                         |                                        |                                          |               |
|-------------------------|----------------------------------------|------------------------------------------|---------------|
|                         | 45 (86.5)                              | 1 (20.0)                                 | 0.004         |

HUT, head-up tilt test; BRS, baroreflex sensitivity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; SVR, systemic vascular resistance
- Changes of BRS and SVR before and after tilt training

|                             | Tilt training responder group (N = 52) | Tilt training non-responder group (N = 5) | P value |
|-----------------------------|----------------------------------------|------------------------------------------|---------|
| Supine position             |                                        |                                          |         |
| BRS (ms/mmHg)*              | 1.11 ± 11.93                           | 2.79 ± 4.55                              | 0.489   |
| SVR (dyn·s/cm^5)            | -29.3 ± 363.7                          | -34.9 ± 605.4                            | 0.880   |
| After tilt table up         |                                        |                                          |         |
| BRS (ms/mmHg)†              | 0.71 ± 3.56                            | 0.76 ± 1.94                              | 0.772   |
| SVR (dyn·s/cm^5)‡           | -47.7 ± 299.3                          | -303.1 ± 588.4                           | 0.390   |
| Before syncope develop      |                                        |                                          |         |
| BRS (ms/mmHg)§              | -2.37 ± 4.35                           | -1.25 ± 3.21                             | 0.656   |
| SVR (dyn·s/cm^5)‡           | -88.3 ± 396.7                          | -171.3 ± 580.3                           | 0.670   |

BRS, baroreflex sensitivity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; SVR, systemic vascular resistance
### Multivariate analysis of tilt training Non-response

|                     | Hazard ratio (95% CI) | \( p \) value |
|---------------------|-----------------------|---------------|
| **Model 1**         |                       |               |
| BRS < 8.945 in the supine position | 23.10 (1.2 – 443.59) | 0.037         |
| MBP after upright posture       | 1.07 (0.96 – 1.18)   | 0.227         |
| Frequency of syncope before initial HUT | 1.12 (0.87 – 1.43) | 0.377         |
| Total number of tilt training session | 1.04 (0.50 – 2.17) | 0.907         |
| **Model 2**         |                       |               |
| BRS < 8.945 in the supine position | 29.62 (1.64 – 534.14) | 0.022         |
| MBP before syncope      | 1.07 (0.94 – 1.22)   | 0.312         |
| Frequency of syncope before initial HUT | 1.08 (0.85 – 1.38) | 0.544         |
| Total number of tilt training session | 0.95 (0.42 – 2.15) | 0.895         |
| **Model 3**         |                       |               |
| BRS < 8.945 in the supine position | 46.55 (1.66 – 1308.64) | 0.024         |
| Female gender         | 0.59 (0.03 – 12.86)   | 0.739         |
| Frequency of syncope before initial HUT | 1.11 (0.88 – 1.40) | 0.388         |
| Total number of tilt training session | 1.13 (0.54 – 2.39) | 0.742         |
Summary

- Female gender, frequency of syncope before tilt training, type of VVS, phase of positive diagnostic HUT, total number of tilt training session were not different between the two groups.

- Changes of BRS and SVR before and after tilt training between two groups were not different.

- Low BRS value (especially <8.945 ms/mmHg) in supine position was associated with tilt training non-response.
Conclusion

• BRS in supine position before head-up tilt could be a predictor for determining the response to tilt training in patients with NMS who are being considered for in-hospital tilt training
THANK YOU
FOR YOUR ATTENTION