Vasovagal Syncope
A Neuroendocrine Disorder?

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Syncope: Definition

A syndrome in which loss of consciousness is:

- relatively sudden onset
- temporary (usually <1-2 min)
- self-terminating
- usually rapid recovery

Due to inadequate cerebral perfusion

Most often due to a fall in systemic arterial pressure
Syncope Classification

Cardiovascular Causes

- Neuro-Enocrine
  - VVS
  - CSS
  - Adenosine related
  - Situational
    - Cough
    - Post-micturition, etc.
  - Situational

- Orthostatic
  - Drug-Induced
  - ANS Failure
    - Primary
    - Secondary

- Cardiac Arrhythmia
  - Bradycardia
    - Sinus pause/arrest
    - AV block
  - Tachycardia
    - VT, SVT
    - LQTS, Brugada, etc.

- Structural Cardio-Pulmonary
  - Aortic Stenosis
  - HCM
  - Pulmonary Hypertension
  - Pulmonary Embolism
  - Aortic Diss.
  - MI

60% 15% 10% 5%

Unexplained Causes ≈10%

After Moya A et al, ESC Syncope Guidelines, Eur Heart J 2009; 30: 2642
Since 1980, techniques have been developed that are applicable to the study of VVS. These include the Finapres (finger arterial pressure), Modelflow (calculation of stroke volume from arterial waveform), measurement of regional impedance to assess regional blood distribution, microneurography of peroneal nerve to indicate sympathetic outflow to skeletal muscle, monitoring of cerebral oxygen saturation (by NIRS), endocrine assessments of epinephrine, norepinephrine, vasopressin (AVP), atrial natriuretic peptide (ANP), renin, pancreatic polypeptide (PPP) and endothelin-1 (biomarker) and coagulation parameters (vWF and fibrinogen). Combinations of these techniques have allowed a greater understanding of the mechanisms involved in VVS.

Jardine DL et al Heart Rhythm in press 2017
Syncope Tilt-Induced: Pathophysiology

- Pre-Tilt Phase 0: Supine
  - Some biomarker abnormalities exist prior to tilt. These are notably elevated levels of Endothelin-1, AVP, ANP, Renin, epinephrine, norepinephrine and pro-coagulation markers.
  - Low endothelin-1 and adrenomedullin may point to asystole in older patients.
  - A few subjects show BP oscillation during this phase, a phenomenon as yet not fully characterised in neuroendocrine terms. However, raised epinephrine levels are expected to be associated. Furthermore, this finding has a PPV for tilt-induced syncope close to 100%.
  - Raised levels of vWF and Fibrinogen, in Phase 0, have been demonstrated in those whose tilt tests are positive.

Syncope Tilt-Induced: Pathophysiology

• **Tilt Phase 1: Early stabilisation-Haemodynamic**
• The adjustments from supine to head up tilt at 0-2 minutes, in this example, show a rapid increase in Thoracic Impedance (decrease in Central Blood Volume) resulting in decreases in Stroke Volume and Cardiac Output despite an increase in Heart Rate.

• Mean Arterial Pressure is maintained by an increase in Systemic Vascular Resistance.

• By this mechanism, Mean Arterial Pressure remains stable for >20 minutes despite a progressive fall in Cardiac Output.

Jardine DL et al The pathophysiology of the vasovagal response. Heart Rhythm 2017 in press
Syncope Tilt-Induced: Pathophysiology

• **Tilt Phase 1: Early stabilisation-Neuroendocrine**
  • Vasopressin rises early and is likely responsible for the rise in systemic vascular resistance.
  • Rise in epinephrine (more prominent in young than old and linked to asystole) occurs early and rises steeply later but if present early blood pressure oscillation may also be present. Modest rise in norepinephrine (mostly from adrenal) which only parallels heart rate change, possibly linked to vasodepressor response later.
  • ANP may fall and is related to subsequent syncope.
  • Renin may begin to fall, particularly in positive tilts.

Syncope: Pathophysiology

Jardine DL et al
The pathophysiology of the vasovagal response.
Heart Rhythm 2017 in press
Syncope: Pathophysiology

• **Tilt Phase 2: Circulatory instability or early pre-syncope-haemodynamics**

• At 28-32 minutes, in this example, the addition of -20 mm Hg Lower Body Negative Pressure to head-up tilt causes further decreases in Central Blood Volume and Cardiac Output. Systolic blood pressure and pulse pressure decrease slightly, and BP oscillation increases indicating a marked increase in sympathetic activity.

• Mean Arterial Pressure is maintained by a further increase in Systemic Vascular Resistance. Probably caused by the associated rise in epinephrine.

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Syncope: Pathophysiology

• Tilt Phase 2: Circulatory instability or early pre-syncope neuroendocrine changes

• BP oscillation is quite common and associated with high epinephrine levels (more in younger).

• Norepinephrine is raised but only modestly: epi/norepi ratio is smaller in older.

• ANP and Renin tend to fall. Minor endocrine changes in those who will not have syncope

Syncope: Pathophysiology
Regional impedance and volume

Syncope: Pathophysiology

• **Tilt Phase 3: Terminal hypotension or late pre-syncope haemodynamics**

At 38-40 min, in this example, increase in Lower Body Negative Pressure further to -40 mmHg induces a fall in Heart Rate and Cardiac Output. Sympathetic withdrawal and fall in epinephrine

Although Systemic Vascular Resistance decreases, it remains far above supine control, Blood Pressure oscillation disappears and a classical vasovagal faint occurs.

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Syncope: Pathophysiology

• Tilt Phase 3: Terminal hypotension or late pre-syncope neuroendocrine changes

At 38-40 min, in this example, increase in Lower Body Negative Pressure further to -40 mmHg induces a fall in Heart Rate (vagal discharge) confirmed by pancreatic polypeptide release. Sympathetic withdrawal shown by peroneal microneurography and fall in both epinephrine (BP oscillation disappears) and norepinephrine which parallels heart rate fall.

Jardine DL et al
The pathophysiology of the vasovagal response.
Heart Rhythm 2017 in press
Syncope: Pathophysiology
Cerebral Oximetry

• **Tilt Phase 4: Recovery**

  - After tilt-down and cessation of Lower Body Negative Pressure, there is a rapid recovery of Blood Pressure and heart rate to baseline levels followed by an overshoot. Consciousness is restored.

  • Pancreatic Polypeptide remains raised for a few minutes

Syncope: Pathophysiology

Syncope: Pathophysiology

Vasovagal syncope is a complex reaction and although much of the variation between individuals may relate to study methods, age is most important. For example, during phase 2, Cardiac Output falls in nearly all patients whereas isolated vasodilatation only occurs in younger patients.

The mechanism of circulatory instability in younger patients is variable: for example, some have splanchnic shunting with increased cardiac output while others have splanchnic pooling with decreased cardiac output. The second mechanism is thought to apply to all older adults but has not yet been fully demonstrated.

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Syncope: Pathophysiology

In all patients, the mechanism for terminal hypotension is a fall in cardiac output due to lack of venous return, with or without a fall in systemic vascular resistance due to sympathetic withdrawal.

The mechanism of recovery is more likely the effect of increased venous return on stroke volume [Frank-Starling relationship] than the reversal of the cardioinhibitory reflex.

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Vasovagal syncope is a neuroendocrine disorder

Conclusions

VVS is very complex.

Only now are we getting to grips with this complexity using modern non-invasive techniques.

There remains much to learn.

The hope was that understanding the mechanisms better would permit effective therapeutic intervention but this remains an unachieved goal.