Drawing a long bow – the relationship between orthostatic intolerance and disorders of elasticity

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Today

- Orthostatic intolerance
  - Mechanisms.
  - Manifestations.
  - Diagnosis
- Disorders of elasticity
  - Mechanism
  - Classification
  - Diagnosis
- Links between OI & elasticity & …& …
Caveat

Scientific publications
Hypertension compared to ME/CFS

- Hypertension
- ME/CFS

<table>
<thead>
<tr>
<th>Year</th>
<th>Publications / Year</th>
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<tr>
<td>1975-1979</td>
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<tr>
<td>2000-2014</td>
<td>70000</td>
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</table>
• Migraines?
• Migraines that have ever caused you to vomit?
• Migraine right now?
• Total loss of vision when upright?
• Insomnia that lasted the entire night?
• Difficulty swallowing?
A coat of many colours

- ME/CFS is not just a fatigue syndrome
- ME/CFS patients are tough!
Orthostatic intolerance

- What is OI? -- definitions
- Maintaining BP during orthostasis – physiology
- How to recognise OI – symptoms & signs
- Who has OI? -- epidemiology
- What interferes with BP control? -- pathology
- How can we fix OI? -- therapy
To cope with orthostasis, the plumbing system needs to be:

1. Clever
2. Powerful
3. Fast

600 ml of blood lost into splanchnic circulation

Change during orthostasis
## Syndromes of orthostatic intolerance

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Postural hypotension</strong></td>
<td>A fall of $&gt; 20/10$ mmHg during upright posture</td>
</tr>
<tr>
<td><strong>Orthostatic intolerance</strong></td>
<td>Symptoms that are relieved by recumbence</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>Faint, collapse, swoon, blackout, keel over,</td>
</tr>
<tr>
<td><strong>Postural orthostatic tachycardia syndrome</strong></td>
<td>Symptoms &amp; a rise of $&gt; 30$ bpm during upright posture</td>
</tr>
<tr>
<td><strong>Inappropriate sinus tachycardia syndrome</strong></td>
<td>Symptoms &amp; sustained rapid heart rate</td>
</tr>
<tr>
<td><strong>Neurally mediated hypotension</strong></td>
<td>A fall in blood pressure which no other cause can be identified</td>
</tr>
<tr>
<td><strong>Dysautonomia</strong></td>
<td>‘Dys’ (dysfunction) &amp; ‘autonomia’ (autonomic nervous system)</td>
</tr>
<tr>
<td>**Etc… **</td>
<td></td>
</tr>
</tbody>
</table>
### Keeping it simple!

<table>
<thead>
<tr>
<th>Orthostasis (word):</th>
<th>• Postural change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic intolerance (symptom):</td>
<td>• Development of symptoms during upright standing relieved by recumbence</td>
</tr>
<tr>
<td>Syncope (phenomenon):</td>
<td>• Transient loss of consciousness caused by inadequate cerebral perfusion</td>
</tr>
<tr>
<td>Postural hypotension (sign):</td>
<td>• &gt;-20/-10 mm Hg within 3 minutes of standing</td>
</tr>
</tbody>
</table>
When things go wrong:
Diagnosing orthostatic intolerance
“Dr, I’m sick”

Could this be orthostatic intolerance?
4 steps to diagnosing orthostatic intolerance

1. Confirm symptoms are related to gravity
2. Identify manifestations of inadequate circulation
3. Identify the buddy conditions of OI
1. A causal role for gravity

- Sudden postural change
- Prolonged upright posture
  - Kitchen / bathroom / dining table / society
- Heat / alcohol / food intolerance
- Exercise intolerance
- Altitude & immersion
  - Planes, mountains and swimming pools
2. Manifestations of inadequate circulation

(a) Inadequate brain blood flow
(b) Excess adrenaline
(c) Syncope
(a) Five symptoms of inadequate brain blood flow

- Light-headedness
  - presyncope / faintness / “blood draining out of me”

- Word finding difficulties
  - Expressive dysphasia

- Poor concentration

- Visual changes

- Neck & shoulder pain
(b) Excessive adrenaline
Six symptoms of excess adrenaline

• Vasoconstriction
  • Cold peripheries
  • Raynaud’s phenomenon
  • Chilblains
• Tremor
• Piloerection
  • Goosebumps
• Sweating
• Pupillary dilation
  • Photophobia
• Tachycardia
  • Palpitations
  • Chest pain
    • praecordial catch
• Alertness, agitation, apprehension, anxiety, panic
  • Situational
(c) Syncope

Vigorous cardiac contraction

Reduced blood for heart to pump

5-HT

Bezold Jarich reflex

↓ sympathetic tone

Hypotension
Sweating

↑ Parasympathetic tone

Belching
Flatus
Nausea
Vomiting
Diarrhoea
3. Buddy conditions of OI (FEFOGMANG)

- Familial
  - Anaemia, Glandular fever, CFS, Postviral fatigue etc
- Elasticity
- Fatigue
  - Post-prandial bloating, pain, belching, fatigue
  - Diarrhoea/constipation (irritable bowel syndrome)
- Orthostatic intolerance
- Gut dysmotility
- Migraines
  - Asthma, eczema, hayfever,
  - Anaphylaxis / Allergies
- Atopy
- Nocturnal disruption
  - Sleep disorder
  - Restless legs / nocturnal urination
- Genitourinary
  - Painful heavy menstruation
  - Urinary incontinence
“You have orthostatic intolerance”

“Are you sure this isn’t anxiety?”
Anxiety disorder

- Low sugar
- Low blood pressure
- Low O₂
- Fearful stimulus
- Pain

Adrenaline

- Palpitations
- Sweating
- Trembling
- ‘Butterflies’
- Anxiety Agitation, panic
- Vasoconstriction Cold digits Raynaud’s
- Pupillary dilation Eye pain

Right adrenal gland
Kidney

ft adrenal gland
Kidney
Treatment

• Education, education, education
• Sodium intake
  • 10 g sodium daily
• Water intake
  • Preferred over solute drinks
• Compression garments
  • Skins, 2XU, Spanx
• Volume expansion
  • Pharmacological:
    • Fludrocortisone
    • Licorice root
  • Saline infusion
  • Erythropoietin
• Vasoconstriction
  • Adrenergic
    • Midodrine
    • Phenylephrine
  • Serotonergic
    • Dihydroergotamine
• Vitamin therapy
Orthostatic intolerance summary

- A component of a larger condition
- Diagnosed by identification of
  - Gravity dependent symptoms
  - Symptoms of inadequate circulation
  - Associated conditions
- Treatment
  - Education, exercise, non-drug therapy, drugs,
  - Counselling
Joint hypermobility

- What determines joint hypermobility?
- Classification of disordered joint hypermobility
- Assigning a diagnosis
Connective tissue: The determinant of elasticity

- Relatively inert tissue that ‘connects’ cells
- Composed of
  - Collagen
  - Elastin
  - Proteoglycans
  - Other substances
- Variably expressed in different tissues
  - tendons, ligaments, muscle, skin
Elasticity – a normal variant

Dance like cave-man

Dance like swans

Too floppy to dance
Disorders of elasticity
Edvard Ehlers & Henri-Alexandre Danlos


  *(Tendency to skin haemorrhage and loosening of articulations)*


  *(A case of skin laxity with chronic bruising of the elbows and knees)*
WORLD AUTHORITY ON SKIN DISORDERS . . .

DR. EDVARD EHLERS
says... "I invariably prescribe yeast"

It is many years since my teacher and friend, Dr. L. Bruun of Paris, taught me to use fresh yeast for staphylococcal infections of the skin. Since then I have invariably prescribed yeast in all cases of furunculosis (skin abscess) as well as in rebellious cases of acne. The effect of yeast upon furunculosis is surprising and inconstantable. It is often slightly laxative.

Dr. Bruun-

The most romantic figure in Danish medicine—Dr. Edvard Ehlers—having medical research in the tropics has brought him decorations from half the governments of Europe.

Hospitals for children born sick into the world, established by him throughout Denmark, have almost eliminated infant deaths from one especially dread disease.

Holder of degrees from the universities of Paris, Strasbourg and Copenhagen—what Dr. Ehlers says of the health properties of yeast is drawn from years of experience as a skin specialist of world-wide reputation. Many doctors now agree that unsightly, embarrassing and unpleasant skin eruptions are associated with chugging of the intestinal tube.

In furunculosis the effect of yeast is inconstantable," Dr. Ehlers says, and then adds, "the yeast treatment must be continued for several months, until the elimination of harmful bacteria is complete."

In a recent survey in the United States, half the doctors reporting said they prescribed fresh yeast. Fleischmann’s Yeast is fresh. Unlike dried or killed yeast it contains millions of living, active yeast plants. As these pass daily through your intestinal tract they combat harmful poisons, purify the whole system. Eat three cake daily, before or between meals. To get full benefit you must eat it regularly and over a sufficient period of time. At all grocers and many leading hotels, lunch counters and soda fountains. Buy 2 or 3 days’ supply at a time. It will keep in a cool, dry place. Write for latest booklet on Yeast in the diet. Health Research Dept. G-27, The Fleischmann Company, 70 Washington St., New York, N. Y.

90 per cent of the start here . . .
Here is where yeast works

As this picture shows, two, the Klondike yeast is made by numbingly cold yeast plants as they come out of the fermenting vat. The exacting process gives the yeast its great vitality through your body. By eating Fleischmann’s Yeast you can keep your mental and physical health. You can improve the health conditions which come only from a child, active nature.

FLEISCHMANN’S YEAST
for Health

Copyright 1925 by The Fleischmann Company.
Disorders of Connective Tissue

Summary

- Joint hypermobility is common
  - 1:20 of the general population

- Joint hypermobility can be normal and asymptomatic
  - e.g. Dancers, athletes, musicians, singers

- Syndromes of joint hypermobility
  - Relatively common - 1:5000 have EDS
  - Difficult to define
    - Criteria are strict, but ancient & narrow
    - Overlap between syndromes
    - Evolving and inadequately researched field
    - Dependent upon clinical measurement of joint mobility
Diagnosing Joint Hypermobility syndromes
“Dr, I’m sick”

Could this be joint hypermobility?
Diagnosing joint hypermobility

1. Identifying manifestations of excessive tissue elasticity
2. Measuring joint hypermobility
3. Assigning a diagnostic category
1. Tissue manifestations of excessive elasticity

- **Musculo-skeletal**
  - Recurrent sprains/subluxations/dislocations, pain, flat feet, TMJ pain, osteoporosis

- **Skin**
  - Velvety skin, cutanea lastica, accentuated palmar reticulum, striae, papyraceous scarring

- **GUT:**
  - Prolapse, cervical incompetence

- **Cardio-vascular**
  - Varicose veins, haemorrhoids, easy bruising, mitral valve prolapse, aortic root dilation, aneurysmal disease

- **Structural**
  - Hernias

- **Facio-maxillliary**
  - Crowded teeth & periodontal disease

- **Ocular**
  - Astigmatisms
Skin laxity
2. Measuring joint hypermobility
Beighton score

≥ 5 = hypermobility
5 point score (Joint hypermobility)

1) Can you now (or could you ever) place your hand flat on the floor without bending your knees?

2) Can you now (or could you ever) bend your thumb to touch your forearm?

3) As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?

4) As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?

5) Do you consider yourself double jointed?

• Answer Yes to 2 of 5:
  – sensitivity 84%
  – specificity 89%

*Int J Clin Pract 2003*
Assigning a diagnosis

- **Joint Hypermobility**
  - Beighton Score >4/9

- **Ehlers-Danlos Type III (Joint hypermobility syndrome)**
  - Beighton Score >4/9 + symptoms (Brighton Criteria)

- **Ehlers-Danlos Type 1**
  - Joint & skin & specific gene disorder

- **Ehlers-Danlos Type 4**
  - Joints & premature aneurysms

- **Marfan Syndrome**

- **Stickler Syndrome**

- **Loeys-Deitz Syndrome**

- **etc**
The big question:

Which causes what?
Change during orthostasis

More than 600 ml of blood lost
Joint hypermobility

- Chronic pain syndrome
- Chronic fatigue syndrome
- Orthostatic intolerance
- Extra-skeletal stretch
- Genito-urinary dysfunction
- Myalgia
- Gut dysmotility
- Allergy
- Ankylosing spondylitis
Anorexia nervosa – a new association with joint hypermobility
Global hypothesis

That patients with anorexia nervosa have a genetically determined increase in joint mobility
Prevalence and familial patterns of gastrointestinal symptoms, joint hypermobility and diurnal blood pressure variation in eating disorders

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²Department of Psychiatry, University of Melbourne, Heidelberg, Victoria, Australia
³Eating Disorders Unit, The Melbourne Clinic, Richmond, Victoria, Australia
⁴Victorian Spinal Cord Service, Austin Health, Victoria, Australia
Methods

• Subjects:
  – Sequential inpatients admitted to Eating Disorders Unit
  – First degree relatives
  – Control group
    – Common measurements compared from separate parallel study

• Measurements:
  – Medical interview
  – Assessment of joint mobility
  – Postural and ambulatory blood pressure
  – Questionnaires (Migraine, Fatigue, Orthostatic intolerance)
## Participant details

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited</td>
<td>30</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Female (n)</td>
<td>29 (97%)</td>
<td>20 (69%)</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.4</td>
<td>44.7</td>
<td>38.6</td>
</tr>
<tr>
<td></td>
<td>(16 to 54, median 21.5)</td>
<td>(10-65, median 50)</td>
<td>(17-63, median 33.5)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>18.0</td>
<td>21.7</td>
<td>24.7</td>
</tr>
<tr>
<td>Mean days from admission</td>
<td>36</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ambulatory monitoring</td>
<td>16</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Postural BPs</td>
<td>19</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Questionnaires</td>
<td>28</td>
<td>20</td>
<td>-</td>
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*mean days from admission when monitoring & postural BPs were done*
## Diagnosis of “Joint hypermobility”

<table>
<thead>
<tr>
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<th>Patients (30)</th>
<th>Relatives (29)</th>
<th>Controls (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-point &gt;2*</td>
<td>19 (63%)</td>
<td>10 (35%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Beighton &gt;4</td>
<td>7 (23%)</td>
<td>4 (14%)</td>
<td>0</td>
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* p<0.05
## Joint Hypermobility

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=30)</th>
<th>Relatives (n=29)</th>
<th>Controls (n=16)</th>
<th>Kruskall-Wallis p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beighton Score</strong></td>
<td>2.57 ± 0.36</td>
<td>1.79 ± 0.30</td>
<td>0.56 ± 0.26</td>
<td>15.9</td>
</tr>
<tr>
<td>Dunn's test</td>
<td>N.S.</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td><strong>Questionnaire</strong></td>
<td>1.93 ± 1.23</td>
<td>1.49 ± 1.38</td>
<td>0.44 ± 0.90</td>
<td>16.6</td>
</tr>
<tr>
<td>Dunn's test</td>
<td>N.S.</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td></td>
</tr>
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</table>
Conclusion

• Joint mobility is increased in the 1st degree relatives of patients with anorexia nervosa, independent of age and gender
• Joint hypermobility in anorexia nervosa may be an indication of a familial disorder of connective tissue elasticity
• Abnormal connective tissue may play a role in the pathogenesis of eating disorders
Summary

• Orthostatic intolerance
  – A buddy condition of CFS, joint hypermobility, gut dysmotility, sleep disorder, atopy

• Joint hypermobility
  – An indication of a systemic disorder of organ structure

• CFS
  – Potentially a component of a more widespread disorder
Autonomic dysfunction in Hypermobility disorders

- Collagen types I and III highly expressed in the connective tissue of blood vessels and articular ligaments

- Abnormal CT in dependent blood vessels -> excessive distension of veins -> increased venous pooling -> haemodynamic symptoms
Classification of EDS

Classical (former types I & II)  COL5A (AD)
Hypermobility (type III)  gene unknown (AD)
Vascular (type IV)  COL3A1 (AD)
Kyphoscoliosis (type VI)  PLOD1 (AR)
Arthrochalasia (type VIIA and VIIB)  COL1A (AD)
Dermatospraxis (type VIIC)  procollagen-N-protein (AR)

Other forms: X-linked EDS (type V)  (XL)
  Periodontitis (type VIII)  (AD)
  Fibronectin-deficient (type X)  ?
  Familial Hypermobility syndrome (XI)  (AD)
  Progeroid EDS  ?
POTS – an OI exemplar

- Heart rate increase of >30 beats per minute within 10 minutes of standing or head up tilt
- OR
- Heart rate > 120 bpm within 10 minutes of standing or heat up tilt
- Consistent symptoms of orthostatic intolerance
Changes in blood pressure and heart rate during postural change

Systolic BP (mm Hg)

Pulse (bpm)

Time (mins)
Characteristics of POTS

- Female
- Young
- Slim (BMI = 23)
- Normal resting blood pressure and heart rate

Associated symptoms
- Light-headedness/dizziness (100%)
- Exercise intolerance (83%)
- Fatigue (67%)
- Blurred vision (61%)
- Chest discomfort (61%)
- Cleanliness (56%)
- Anxiety (56%)
- Nausea whilst standing (50%)
- Tremulousness (50%)
- Flushing (44%)
- Headache while standing (44%)
- Palpitations (39%)

Associated findings
- Mitral valve prolapse (50%)
- Irritable bowel syndrome (22%)
- Chronic fatigue syndrome (17%)
- Inflammatory bowel disease (17%)
A coat of many colours

- POTS is not just a blood pressure syndrome
- POTS patients are tough!
The autonomic nervous system

- **Parasympathetic system**
  - Relaxing/digestive function
  - Neurotransmitters = Acetylcholine

- **Sympathetic system**
  - Fight or flight
  - Neurotransmitters
    - Acetylcholine
    - Noradrenaline
    - (Adrenaline)
Maintaining blood pressure during upright posture

1. Muscle pump returns blood to the heart
2. Autonomic nervous system increases cardiac output
3. Autonomic nervous system constricts blood vessels and thereby ensures blood flow is maintained to vital organs