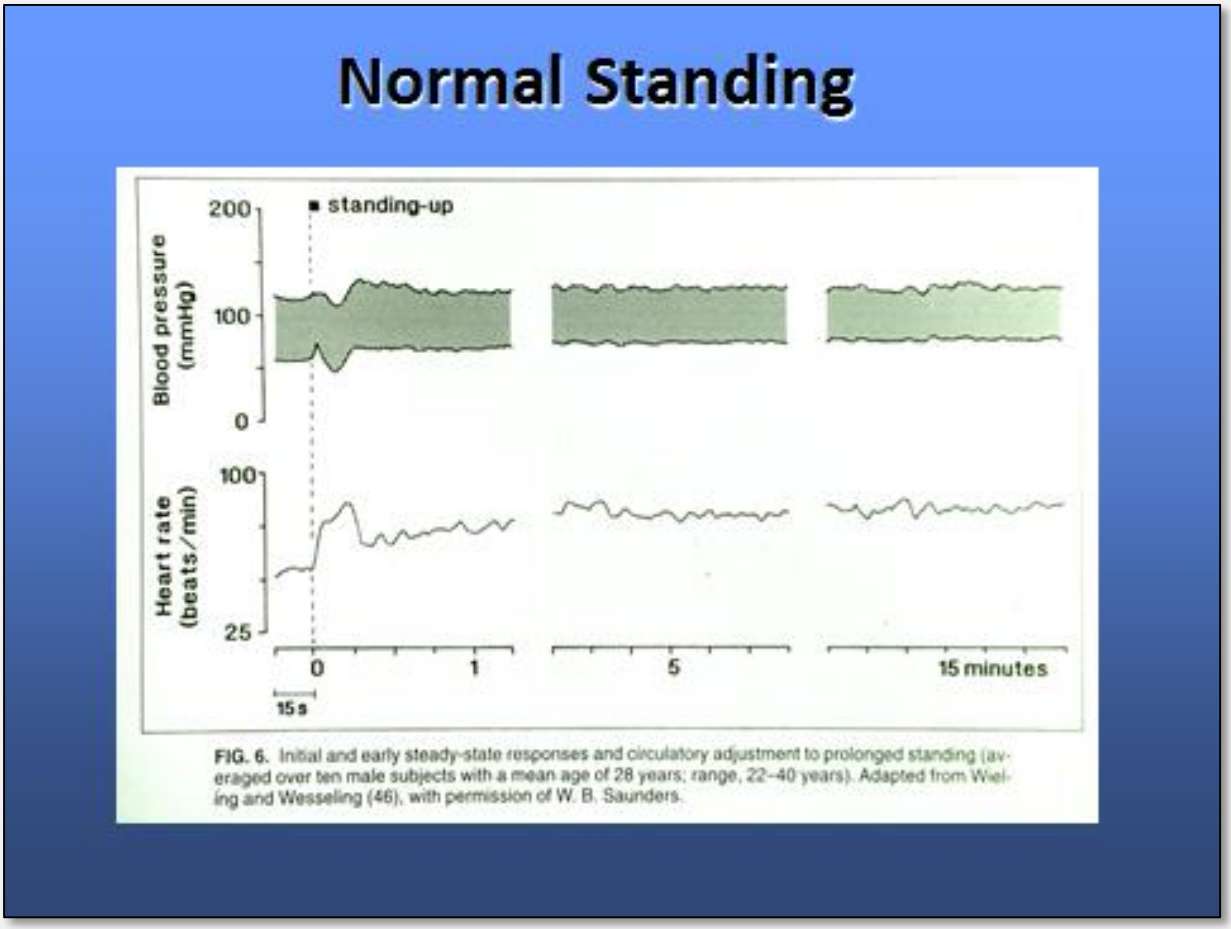
I. Pathophysiology in ME: Orthostatic Intolerance



This slide shows the pulse and blood pressure of a healthy person standing for 15 minutes. These values actually stay the same for much longer, up to 90 minutes in normal persons[1]. But this is not so in ME[2].

Orthostatic Intolerance is really quite simple. It is the state of being intolerant to orthostasis or the upright posture. Standing is the most upright position but sitting can also be affected by OI. Ultimately it is due to a reduction of blood flow to the brain. When blood flow to the brain is reduced, fainting is the usual result, but fainting almost never happens in ME, something that has never been explained. It is likely, but never proven, that people faint frequently before getting ME. Fainting is called 'syncope', and the stage just before fainting is called 'pre-syncope'. One attractive theory about ME is that it is a constant state of pre-syncope.

When a healthy person faints after standing too long on a hot day, the rest of the day they have severe fatigue. Presumable this is because there requires a recovery period after the sudden decreased blood flow which caused the faint. The same thing happens after a concussion. A good rule of thumb is that the fatigue after a head injury or faint should be gone

after a good night's sleep, a sleep that is 'restorative', again, something that does not occur in ME.

Here is a good way to tell if you have orthostatic intolerance. You are walking around the supermarket for fifteen minutes and you are doing alright. The act of walking helps to circulate blood to your brain by the muscle contractions in your legs. Then you stand at the check-out counter and the person in front of you has lots of coupons. You stand still for ten minutes and then you feel that you have to lie down. The standing still causes blood to pool in the legs and less gets to the brain. This is orthostatic intolerance.

Or, a nice hot shower in the morning to wake you up makes you go back to bed. The heat from the shower will dilate the blood vessels of the body, particularly the legs, and less blood is left over to get to the brain. Or a big pasta meal causes the gut vessels to open and you get exhausted. This is post-prandial fatigue, because the increased blood to the gut to digest the meal means less to the brain.

A way of testing this in the office is to have the patient lie down on the examination table for fifteen minutes with pulse and blood pressure being taken. Then the patient stands quietly beside the table (but not resting on it) and the nurse takes pulse and blood pressure every five minutes. It is essential that there be no movement during this time. The patient stands for as long as possible until collapse. Actually, the patient should lie down just before the syncope, and most good nurses can predict this.

A healthy person can stand like this for 90 minutes. Soldiers can stand still, at attention for many hours. But a person with ME can stand, on average fifteen minutes in my experience, although this has a wide variation. This bedside test I call the "poor man's tilt table test." Actually, I think it is better than a full tilt table test because it more closely replicates what happens during everyday life.

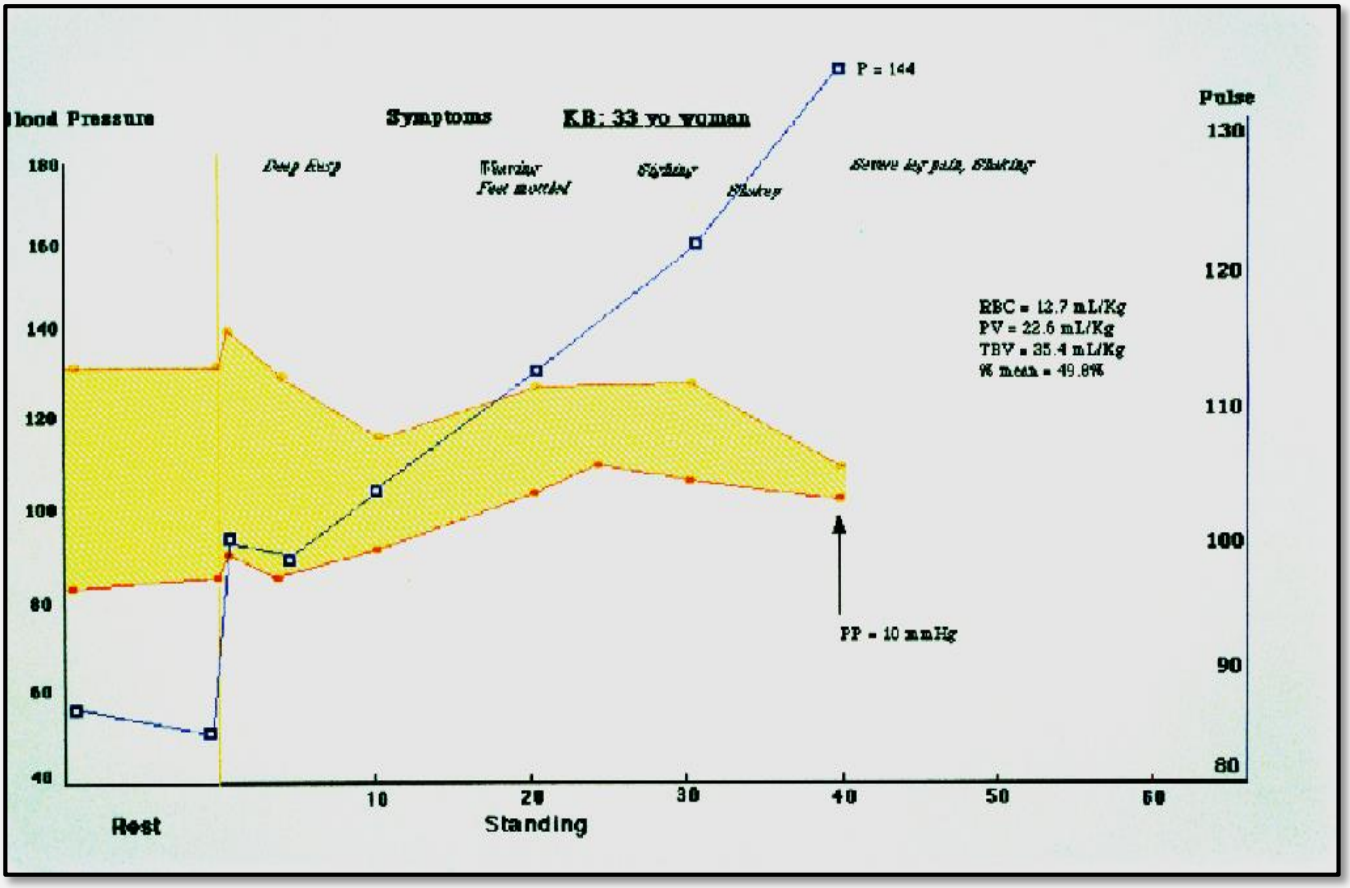
There are five different types of orthostatic intolerance that occur during this test: 1) postural orthostatic tachycardia syndrome or POTS. This is defined by the pulse going up 28 beats per minute or more during quiet standing. 2) Orthostatic narrowing of the pulse pressure or ONPP. The pulse pressure is the difference of the lower BP number subtracted from the upper number. In order to circulate blood well, there needs to be a pulse pressure of at least twenty. A healthy person with a BP of 120/80 has a pulse pressure of 40 mm Hg. 3) Orthostatic hypotension (OH) is where the blood pressure drops significantly on standing. 4) Diastolic hypertension (DH) is where the lower BP number goes up because of blood vessels constrict in an attempt to compensate for standing. It is pretty rare in ME. And 5) delayed orthostatic hypotension where the blood pressure drops after standing for five or ten minutes. All of these types of orthostatic intolerance cause a decrease, (or further decrease) of blood flow through the brain.

For the clinician, looking at the symptoms of someone at the ten minute mark is very instructive. The patients are wobbly, in obvious pain, pale, and sometimes will slur their speech. Their cognitive functions are impaired. However, despite the discomfort, they continue standing,

sometimes when their pulse and blood pressure predict that they could not be standing. Seeing a patient whose pulse is 140 or blood pressure falling toward zero yet they are still standing is a mark of how often this happens to them – they are used to it. Ignorant physicians say that ME patients are wimps, yet no one would not be able to stand in these circumstances.

A word of caution – this test can be followed by significant post-exertional malaise (PEM), particularly if the patient passes out during the test.

POTS

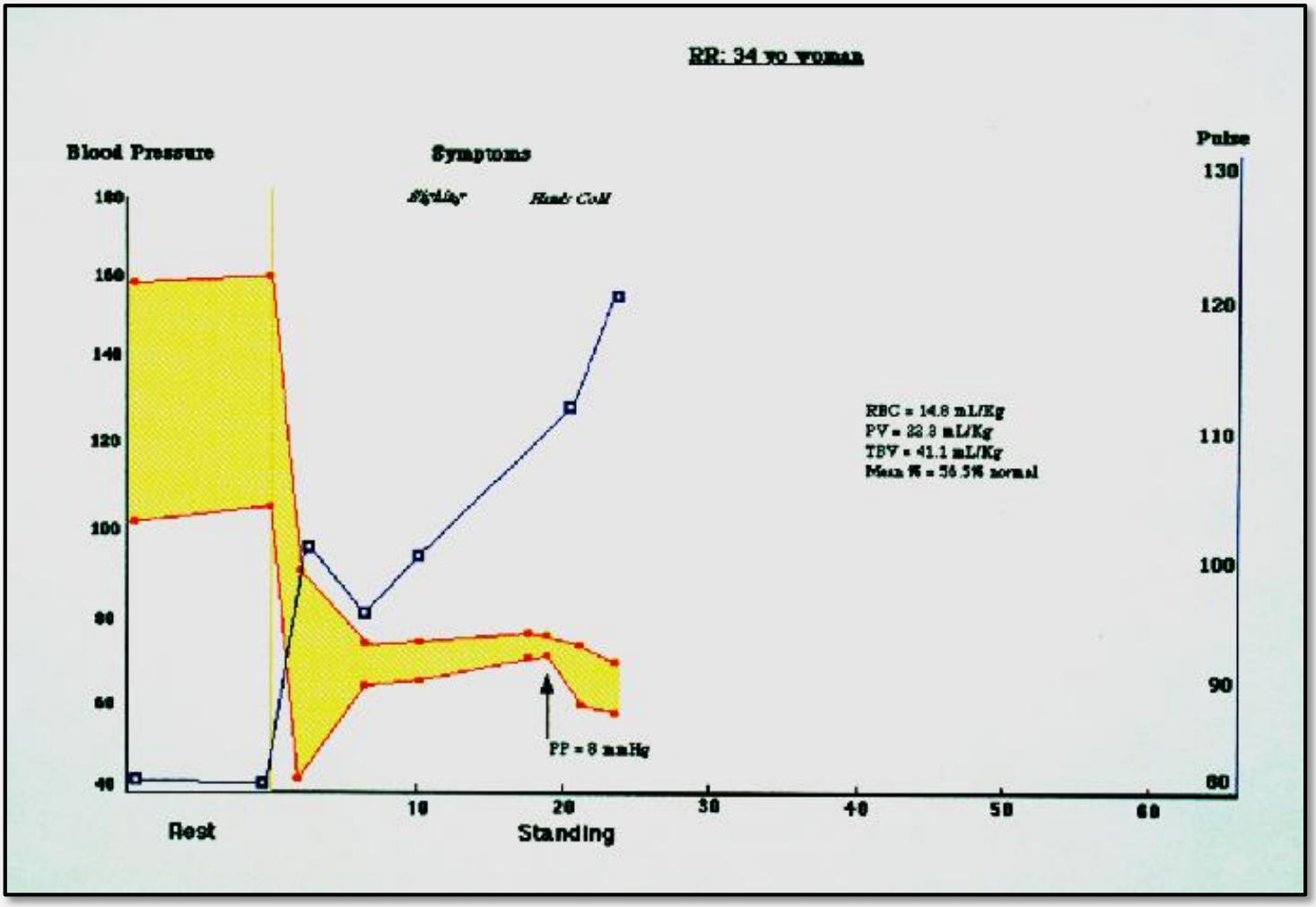


In this slide the yellow area is a continuous blood pressure reading with the scale on the left, while the blue line is the pulse with the scale on the right side. The blood volume of this patient is printed in the right side, a subject that we will come to later. Actually there are three abnormalities here: POTS and orthostatic narrowing of the blood pressure. The blood volume is abnormal and was measured about a week before this standing test was done.

At the end of the rest period the blood pressure was 130/84 which is normal and the pulse was 84, also normal. Many persons with ME will have a resting tachycardia, sometimes around 110 beats/min. At ten minutes the pulse is up to 105 and continues up to 140 bpm, at which time the test was terminated 40 minutes after beginning. The blood pressure stayed OK for a bit but by ten minutes was 125/100 showing slight diastolic hypertension and some narrowing of the pulse pressure. By the test termination at 40 minutes, the pulse pressure was

down to 10 mm Hg. The important thing here is that you cannot circulate blood in your brain with a pulse of 140 and a pulse pressure of 10 mm Hg.

At the time of the test termination she looked terrible. She looked like she always looked after standing still for 40 minutes. And the numbers suggest that she should have been in an intensive care unit somewhere. Someday, when ME becomes recognized, it will be illegal to do this test in the office. But I have done it in well over 100 persons in my office; no one has had any dangerous or worrisome complications like stroke or heart attacks. This sort of thing happens to them every time they stand still in the grocery store checkout line.



This slide portrays POTS (pulse up 40 bpm from resting), orthostatic narrowing of the BP (to 9 mm Hg), and orthostatic hypotension (fall of systolic blood pressure from 160 to 90 immediately upon standing). Many of the kids in the fludrocortisone studies[3] probably had graphs that looked like this. Obviously, this woman felt light headed upon standing but this was ignored. Her physician wanted to treat her for hypertension with diuretics.

Note the blood volume numbers, again done a week or two before this test. Her blood volume was 56.5% of a normal person's volume. For anyone with hypertension with his or her ME, it is essential to do a blood volume test because of the irony of 'hypovolemic hypertension'. Most normal persons with hypertension have 'hypervolemic hypertension' and the treatment is

to reduce salt in the diet and treat with diuretics or fluid pills. Actually the blood volume test was developed for exactly this reason around 1960.

The responses to standing are said to be controlled by the autonomic nervous system[4], although this is an over-simplification. In ME there are four abnormalities that contribute to orthostatic intolerance: 1) low blood volume[5], 2) decreased cardiac output when standing[6], 3) abnormal venous enervation in the legs leading to reduced venous return[7], and 4) increased end-arteriolar pressure[8]. These abnormalities overlap, but they all contribute to reduced blood flow in the brain.

By the way, the body, originally controlled by the primitive 'lizard-brain' knows what to do when the blood flow is poor; it shunts blood to the important organs: the heart, lungs and kidneys. The brain was an evolutionary afterthought.

In the next segment of this series I will address the blood volume.

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Dr David Bell graduated from Harvard College and gained an MD degree at Boston University. Postdoctoral training in paediatrics was completed with subspecialty training in Paediatric Behaviour and Developmental Disorders.

In 1978 he began work at the University of Rochester and then began a private practice in the town of Lyndonville, New York. In 1985 nearly 220 persons became ill with an illness subsequently called chronic fatigue syndrome in the communities surrounding Lyndonville, New York. This illness cluster began a study of the illness which continues today.

Dr David Bell is the author or co-author of numerous scientific papers on CFS, and, in 2003 was named Chairman of the Advisory Committee for Chronic Fatigue Syndrome of the Department of Health and Human Services. Publications include A Disease of A Thousand Names, (1988) and The Doctor's Guide to Chronic Fatigue Syndrome, (1990). Dr Bell is currently performing ME/CFS research into the XMRV retrovirus.