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EDITORIAL

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Syncope, falls and cobalamin deficiency in the old population

Syncope and falls in the elderly, besides their effects on the sufferer, are an enormous economic burden on the society, since they are not only responsible for about 6 % of all hospital admissions but also the main causes of hip fractures; they, in turn, are the leading causes of death and permanent handicap in old people. For example, some 500,000 hip fractures are recorded annually in the United States and Europe and about 1.5 million worldwide [1], with an estimated mortality rate of 25 %. This figure is estimated to approximately double to 2.6 million by the year 2025, and 4.5 million by the year 2050 [1]. The total annual cost of hip fractures will increase from approximately 7.2 billion dollars currently to 16 billion dollars in the year 2040 [2]. The work-up of syncope and falls is also associated with high costs of between $ 5000 to $ 16000 per diagnosis [3, 4], since expensive investigations such as CTs or MRIs of the head, 24-hour ECGs, EEGs, and ECG event recorders including implantable loop recorders are usually in need. In the last few years it has become increasingly evident that cobalamin deficiency may be a common cause of syncope and falls in the elderly, a fact which is not mentioned in textbooks or even in the most recent editions of on-line services of internal medicine [5] or neurology. Also, wrongly in the absence of anaemia, cobalamin deficiency is rarely thought of; besides, most doctors incorrectly assume that serum B12 estimations are sufficient to diagnose the condition, which is clearly not the case [6, 7].

The first case of anaemia caused by B12 deficiency was described by J. S. Combe in 1824 [8], B12-deficiency anaemia associated with adrenocortical insufficiency ("Anaemia-disease of the supra-renal capsules") was first observed by Thomas Addison [9] and "progressive pernicious anaemia" was systematically described by Anton Michael Pirmer [10] of Switzerland in 1872. Already then the combination of two clinical manifestations, i. e. the bone marrow disturbance with altered red cell morphology and kinetics, and the severe neurological deficit, was noticed. Meat, eggs and dairy products are the only source of cobalamin, of which about 10 to 20 μg/day are provided by a normal Western diet; this is quite close to the 5 to 10 μg of the daily minimal requirement. Total body stores of cobalamin amount to 2 to 5 mg, of which 50 % are stored in the liver. Even after complete lack of intake or resorption of cobalamin it therefore takes years to develop clinical B12-deficiency. Cobalamin is liberated by hydrochloric acid and pepsin from its dietary protein sources, bound in the intestinum to an endogenous protein, the "R-factor" from which it is later released by pancreatic proteases, and then bound to another 45 kDa protein, the intrinsic factor. The thus formed complex is then taken up by ileac receptors, from which B12 is transferred into the blood. It is obvious that an intact gastric, pancreatic and ileac function is necessary for the vitamin to be taken up by the human body.

Cobalamin is necessary for the formation of methionine from homocysteine and for the formation of tetrahydofolate. Its lack causes a decrease in methionine levels with concomitant increases of homocysteine, and the lack of tetrahydrofolate causes delayed DNA synthesis and nuclear maturation, which is the cause of disturbed red cell maturation. It is the lack of methionine that leads to subacute combined degeneration of the spinal cord and often severe symmetrical neuropathy, predominantly affecting the legs with paraesthesias, ataxia, weakness, spasticity, paraplegia and incontinence. Central symptoms include irritability, memory loss and dementia. Up to 25 % of all neurological cases

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of cobalamin deficiency occur in the absence of haematological disturbances. In our unit we have seen a few cases of severe B12-deficiency with B12 levels of zero causing severe dementia and yet normal red cell counts and morphology were present.

In single case reports it was noted that cobalamin deficiency was not only associated with peripheral but also autonomic neuropathy [11–14]. Beitzke et al. [15] performed a systematic investigation of haemodynamics and autonomic nervous system functions in a group of patients with cobalamin deficiency and compared them to normal subjects and patients with established diabetic neuropathy. They found marked autonomic disturbances including lack of rise of total peripheral resistance, lack of modulation of sympathico-vagal balance and lack of modulation of baroreceptor reflex sensitivity after passive head-up tilt; the magnitude of these changes was comparable to that observed in long-standing diabetes with autonomic neuropathy as established by the Ewing battery [16].

It is not generally appreciated that the diagnosis of autonomic failure can often only be made by modern technology[a], an example of which is shown in the accompanying figures: Fig. 1 (top) shows a normal haemodynamic and autonomic response to passive head-up tilt in a healthy subject, and Fig. 2 in a patient with autonomic neuropathy due to cobalamin deficiency. Whereas in normal subjects a marked heart rate variability, a rise of heart rate and of total peripheral resistance with fall of stroke volume can be seen after the tilt, there is not only much less variation of heart rate and of blood pressure, but also a lack of response of peripheral resistance to the sympathetic stimulation in patients with cobalamin deficiency. As can be seen, immediately after head-up tilt, a short-lived fall of BP is seen with continuous blood pressure recording. Since heart rate response to tilt is preserved and since concomitant oscillometric blood pressure measurements do not detect these short-lived falls of blood pressure (Fig. 3) the patient would have been classified wrongly as healthy performing the investigation with the equipment which is worldwide the usual standard for performing tilt testing, namely a conventional ECG tracing combined with intermittent oscillometric or auscultatory blood pressure measurement. Conventional blood pressure measurements need between 30 and 60 seconds, depending on heart rate; clinically relevant drops of blood pressure, which might cause falls, are thus not detectable if their duration is 15 s or less. The autonomic neuropathy can also be detected by power spectral analysis of heart rate and continuous blood pressure, since the physiological increase of sympathetic tone (the 0.1 Hz band of systolic blood pressure) and decrease of parasympathetic tone (the 0.3 Hz band of heart rate variability) with rise of sympathico-vagal balance after tilt as seen in normal subjects (Fig. 1), is lacking in B12-deficiency (Fig. 2). The simple inspection of these completely non-invasive real time recordings[a] therefore allows the diagnosis of autonomic neuropathy or autonomic failure without further analysis. This modern equipment does not only improve the sensitivity of tilt- or of autonomic testing but also saves valuable time of the doctor.

In this issue, Moore et al. [17] report a study in a small group of eight patients with cobalamin deficiency and orthostatic hypotension, who were investigated before and after treatment with cobalamin over 6 months. The authors found that the orthostatic hypotension improved considerably after such a relatively short period of treatment. This is surprising given the slow response or even irreversibility of other neurological disturbances observed in long-standing cobalamin deficiency. The prompt response to cobalamin treatment could suggest that autonomic nerves have more regenerative potential than sensory or motor nerves or the central nervous system. Eight patients with "idiopathic" orthostatic hypotension served as a control group, who were left untreated over the period of 6 months. Autonomic failure in elderly persons is commonly caused by ischemic encephalopathy (with or without parkinsonian syndromes!), pure autonomic failure or autonomic peripheral neuropathy (in old age often due to amyloidosis). Autonomic failure is rewarding to treat symptomatically with the available options albeit the underlying disease can usually not be treated. These options include: physical measures, mineralocorticoids and non-steroidal anti-inflammatory agents to increase extracellular and intravascular volume, oral potassium supplements to improve baroreceptor function [18, 19], α-adrenergic agonists (like midodrine) to increase vessel tone or ADH analogues in the evening to increase body water (in cases associated with nocturia and weight loss of more than 1 kg during the night). Orthostatic hypotension is however difficult to treat if both episodes of hypertension and hypotension are observed in the same patient as is very commonly the case. In these cases the above substances directed against hypotension (except potassium supplements and ADH analogues) will aggravate hypertension. In this situation our own experience suggests the combined use of centrally acting antihypertensives such as moxonidine or rilmenidine combined with the above mentioned measures directed against hypotension. Systematic controlled studies for this difficult condition are however lacking.

The study by Moore et al. [17] demonstrates the exciting possibility of not only offering symptomatic therapy, but also therapy directed toward the cause of a commonly overlooked disease. This improvement of orthostatic hypotension was also observed in the first

[a] Task Force™ Monitor, www.cnsystems.at

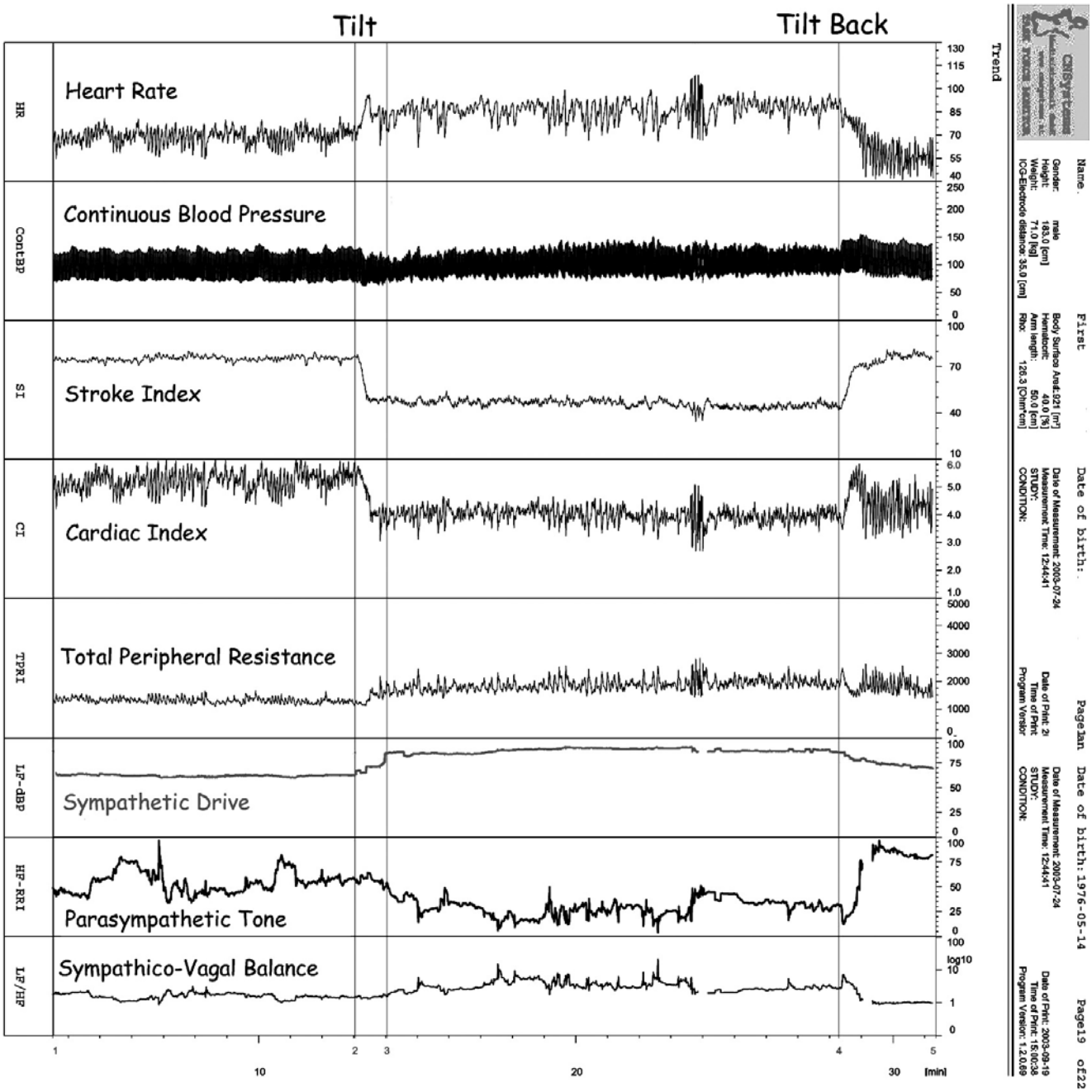

Fig. 1 Non-invasive recording of heart rate, beat to beat blood pressure, stroke volume, total peripheral resistance, and the power spectral analysis of heart rate interval and of blood pressure in a normal subject during passive head-up tilt (HUT). Also shown is the band plot of the 0.1 Hz band of blood pressure (sympathetic activity) and the 0.3 Hz band of the heart rate interval (parasympathetic tone). The recording was performed with the Task Force™ Monitor of www. cnsystems.at. Stroke volume decreases and heart rate and peripheral resistance rise in response to HUT. The band plot of the power spectral analysis shows marked sympathetic activation, vagal withdrawal and an increase of the sympathetic/vagal balance

case report of cobalamin deficiency associated with orthostatic hypotension [11].

Of the cases of B12-deficiency, 75% are caused by gastric diseases, not only by antibodies against intrinsic factor but also by antibodies against parietal cells, as well as by helicobacter pylori-associated gastritis. The remaining 25 % of cases are due to a variety of conditions [20]: beside inadequate intake in vegetarians it may be due to chronic pancreatitis (which is commonly subclinical without steatorrhea and detectable only by enzyme measurements in stool specimens), to small bowel involvement as observed in celiac disease, to bacterial

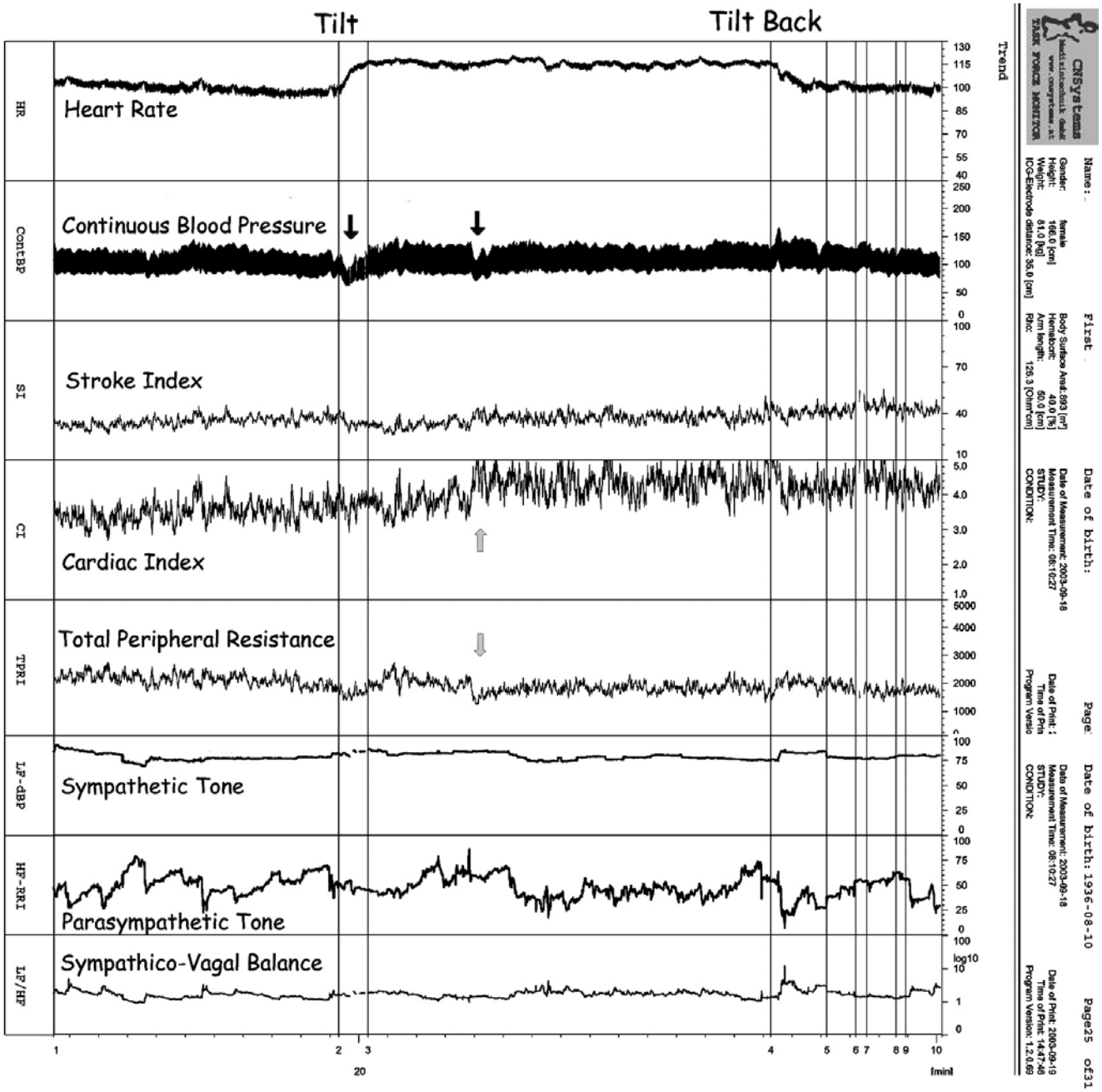

Fig. 2 The same recordings as in Fig. 1 in a patient with B12 deficiency. Although the heart rate response is still preserved, there is much less variation in the heart rate interval, stroke volume does not decrease and total peripheral resistance does not rise in response to HUT. During head-up tilt there is a further fall of total peripheral resistance (grey arrow) which must be compensated by a further rise of cardiac output (grey arrow) in order to prevent a fall of blood pressure. There is also no activation of sympathetic nervous system activity and no deactivation of the parasympathetic nervous system. Also seen are short-lived drops of blood pressure (black arrows), which are detected only by the beat-to-beat recording of blood pressure, but not by the simultaneous oscillometric blood pressure measurements. Since heart rate rises and since there are no long lived blood pressure falls detectable by conventional blood pressure measurement, this case of autonomic neuropathy due to cobalamin deficiency as so many others would have been overlooked if tilt testing would have been performed with the equipment used in the vast majority of hospitals worldwide, namely a conventional ECG tracing and oscillometric or auscultatory blood pressure measurements

overgrowth in the small bowel, to diverticula with stasis or to chronic inflammatory bowel disease.

In the elderly, atrophy of the gastric mucosa, small bowel mucosa and of the exocrine pancreas occurs even without a specific disease and this might be the reason that cobalamin deficiency occurs in up to 25 to 40 % of people between 75 and 80 years [20, 21].

At present, cobalamin determinations are usually not

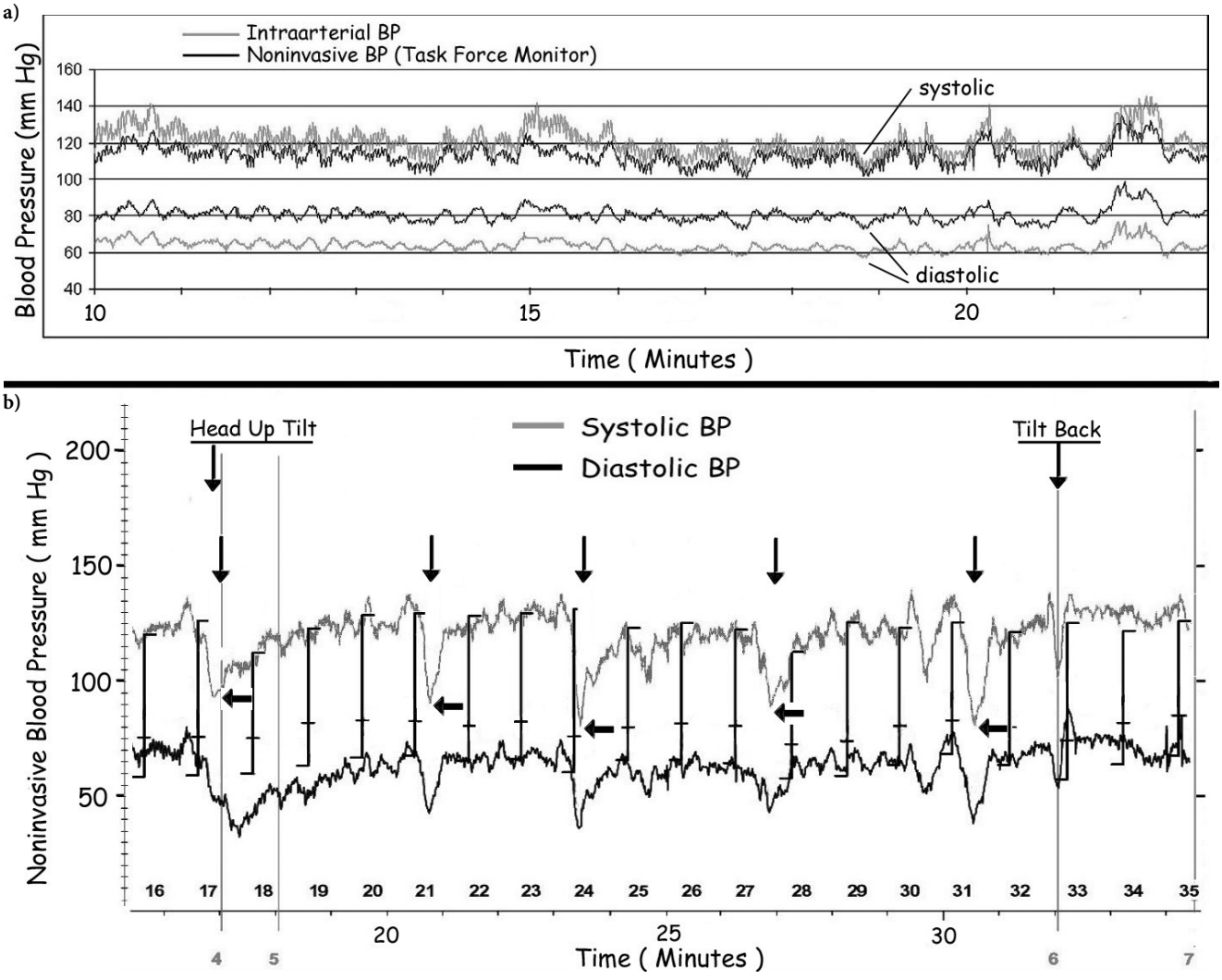

Fig. 3 **a** (Top) Comparison of systolic and diastolic intra-arterial and non-invasive beat to beat blood pressure (non-calibrated) in a patient at the intensive care unit. It is remarkable how all minute blood pressure changes detected by intraarterial recordings are tracked accurately by the non-invasive device over long periods of time. Absolute values of non-invasive systolic and diastolic blood pressure at the finger may or may not agree with intra-arterial blood pressure, therefore non-invasive blood pressure measurements need initial calibration e. g. with oscillometric blood pressure measured on the upper arm (see **b**).
b (Bottom) This figure shows the simultaneously derived oscillometric blood pressure values (vertical black bars) and beat to beat blood pressure derived non-invasively by the vascular unloading technique (continuous lines). The vertical lines (numbered 4 and 5) show the beginning of tilt in a subject with autonomic failure due to B12 deficiency. Five short falls of systolic blood pressure down to 70 mm Hg (black arrows) can be observed after head-up tilt, none of which are detected by the oscillometric blood pressure measurements even if performed every minute. This exemplifies that continuous non-invasive beat to beat blood measurement is mandatory for the evaluation of syncope

included in the routine laboratory screening of patients with syncope and falls. Therefore, the mean corpuscular volume (MCV) and the mean corpuscular haemoglobin concentration (MCHC) of erythrocytes have to be particularly scrutinised. Also, a careful neurological investigation not only by a neurologist but also by the practitioner and internist is in order. This should include a testing of the temperature- and position-sense and of the vibration threshold using a tuning fork. The quantitative vibration perception threshold using the Rydel-Seiffer graduated tuning fork or electronic devices are more sensitive than the standard tuning fork [22, 23]. B12 determinations should at least be ordered in borderline results of the above tests; we have certainly included this measurement in all elderly persons presenting with syncope and falls. Usually the patient himself can not differentiate as to whether the fall was caused by a short absence of consciousness or dizziness and usually explains his fall as the consequence of some external mishappening. Another problem is that even a cobalamin level in the so called "normal range" does not exclude cobalamin deficiency [6, 7]. Therefore it is sug-

gested that determinations of homocysteine [6] (and, if available, also of methyl malonic acid [24]) should also be included in the laboratory investigation of elderly patients with unexplained syncope. The serum level of these two substances increases significantly as no methyl groups can be transferred. Therefore, these tests would be more appropriate than cobalamin determinations. Given the low cost of therapeutic cobalamin (in the range of Euro 3 to 4/5000 µg), the ineffectiveness of cobalamin fortified food with impaired absorption and the high incidence of subclinical cobalamin deficiency (an incidence, which is close to that of vitamin-D deficiency in the elderly), it has also to be asked provocatively whether it would not be a wise investment to substitute cobalamin (e. g. 5000 µg twice per year intramuscularly) routinely in the elderly population. This could be done even without knowing their B12-status, similarly to the blind substitution of vitamin D in that age group. There could be even a synergistic effect of the blind substitution of vitamin D and cobalamin since vitamin D is also known to improve body sway and to prevent falls [25]. Given the high incidence of both cobalamin deficiency [21] and falls [26] (beside sensor neuropathy and mental impairment) in the old population and given the reported improvement of cobalamin therapy on the autonomic (and somatic) nervous system function as shown in the study of Moore et al. [17], this could be a pragmatic option, although a systematic population based study on the magnitude of the association of cobalamin deficiency and falls is lacking. In conclusion, modern technology including homocysteine and methyl malonic acid determinations in serum for the detection of cobalamin deficiency and non-invasive beat to beat blood pressure measurements and power spectral analysis of heart rate and blood pressure variability for the detection of autonomic failure are necessary to detect a common [20, 21], curable [17], and often life terminating disease of the old. Given the number of non-invasive beat to beat blood pressure measurement devices in use one can calculate that at least 95 % of hospitals whose daily bread is also the evaluation of falls and syncope use equipment unsuited for that purpose.

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References

1. Gullberg B, Johnell O, Kanis JA (1997) World-wide projections for hip fracture. Osteoporosis Int 7:407–413
2. Cummings SR, Rubin SM, Black D (1990) The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. Clin Orthopaedics and Related Res 252:163–166
3. Nyman JA, Krahn AD, Bland PC, Griffiths S, Manda V (1999) The costs of recurrent syncope of unknown origin in elderly patients. Pacing Clin Electrophysiol 22:1386–1394
4. Calkins H, Byrne M, El-Atassi R, Kalbfleisch S, Langberg JL, Morady F (1993) The economic burden of unrecognised vasodepressor syncope. Am J Med 95:473–479
5. Olshansky B (2004) Evaluation of the patient with syncope. UptoDate Online 11.3
6. Markle HV (1996) Cobalamin. Crit Rev Clin Laboratory Sci 33:247–356
7. Oh R, Brown DL (2003) Vitamin B12 deficiency. Am Family Physician 67: 979–986
8. Combe JS (1824) History of a case of anaemia. Transactions of the Medico-Chirurgical Society of Edinburgh 1:194–204
9. Addison T (1849) Anaemia-Disease of the supra-renal capsules. London Hospital Gazette 43:517–518
10. Biermer MA (1872) Eine eigenthümliche Form von progressiver perniciöser Anämie. Correspondenz-Blatt für Schweizer Aerzte, Basel, 2:15–18
11. Kalbfleish JM, Woods AH (1962) Orthostatic hypotension associated with pernicious anaemia: report of case with complete recovery following vitamin B12 therapy. JAMA 182:198–200
12. Toru S, Yokota T, Inaba A, et al. (1999) Autonomic dysfunction and orthostatic hypotension caused by vitamin B12 deficiency. J Neurol Neurosurg Psychiatry 66:804–805
13. Eisenhofer G, Lambie DG, Johnson RH, et al. (1982) Deficient catecholamine release as the basis of orthostatic hypotension in pernicious anaemia. J Neurol Neurosurg Psychiatry 45:1053–1055
14. Johnson GE (1987) Reversible orthostatic hypotension of pernicious anaemia. JAMA 257:1084–1086
15. Beitzke M, Pfister P, Fortin J, Skrabal F (2002) Autonomic dysfunction and haemodynamics in vitamin B12 deficiency. Auton Neurosci 97:45–54
16. Ewing DJ (1978) Cardiovascular reflexes and autonomic neuropathy. Clin Sci Mol Med 55:321–327
17. Moore A, Ryan J, Watts M, Pillay I, Clinch D, Lyons D (2004) Orthostatic tolerance in older patients with vitamin B12 deficiency before and after vitamin B12 replacement. Clin Auton Res 14(2):67–71
18. Heseltine D, Thomas T, Wilkinson R, James OF, Potter JF (1990) Potassium supplementation in the treatment of idiopathic postural hypotension. Age Ageing 19:409–414
19. Skrabal F, Auböck J, Hörtnagl H (1981) Low sodium/high potassium diet for prevention of hypertension: Probable mechanim of action. Lancet ii:895–890
20. Schrier StL (2004) Etiology and clinical manifestations of vitamin B12 and folic acid deficiency. UptoDate OnLine 11.3
21. Van Asselt DZ, de Groot LC, van Staveren WA, Bloom HJ, Wevers RA, Biemond I, Hoefnagels WH (1998) Role of cobalamin intake and atrophic gastritis in mild cobalamin deficiency in older Dutch subjects. Am J Clin Nutr 68:328–334
22. Coppini DV, Young PJ, Weng C, Macleod AF, Sönksen PH (1998) Outcome on diabetic foot complications in relation to clinical examination and quantitative sensory testing: a case-control study. Diabetic Med 15: 765–771
23. Martina IS, van Koningsveld R, Schmitz PI, van der Meché FG, van Doorn PA (1998) Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. J Neurol, Neurosurgery and Psychiatry 65:743–747

24. Stabler SP, Lindenbaum J, Allen RH (1996) The use of homocysteine and other metabolites in the specific diagnosis of vitamin B-12 deficiency. J Nutrition 126(Suppl 4):1266S–1272S

25. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C (2000) Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Min Res 15:1113–1118

26. Brennan nee Saunders J, Johansen A, Butler J, Stone M, Richmond P, Jones S, Lyons RA (2003) Place of residence and risk of fracture in older people: a population-based study of over 65-year-olds in Cardiff. Osteoporosis Int 14:515–519