von Willebrand factor, exercise, and ischaemia/reperfusion injury

Sir: Farrell *et al*¹ suggest that exercise induced release of von Willebrand factor (vWF) is evidence for hypoxic reperfusion microvascular injury in rheumatoid arthritis (RA). They found that increases of plasma vWF in patients with RA were greater than those in age matched controls without RA who performed the comparable exercise. One interpretation for this greater increase is excess release from synovial endothelial cells as a result of ischaemia/reperfusion injury. However, Farrell *et al* may have overlooked another possible mechanism. One would presume that blood pressure and pulse rate would be increased in both patients and controls owing to the exercise. Increased systolic and diastolic blood pressure is associated with increased vWF,² and a short (10 minute) acute venous occlusion stress to the lower arm will also increase vWF.³ It may be, therefore, that some of the increased vWF in the patients with RA might have been due to release from more fragile endothelial cells in response to haemodynamic forces, even if the exercise was apparently within the patient's capacity.

Nevertheless, we have been using a similar exercise regimen (where haemodynamic forces are controlled) to study the effects of ischaemia-reperfusion in patients with intermittent claudication but without evidence of connective tissue disease.⁴ Our experience is that five minutes of treadmill exercise leads to a burst of thromboxane, peaking five minutes after exercise has stopped, and a peak in vWF an hour after the cessation of exercise, only in patients. Our interpretation includes the possibility that vWF release from the lower limb endothelium is due to ischaemia-reperfusion. Thus both our data²⁻⁴ and those of Farrell *et al*¹ support the growing hypothesis that increased vWF reflects endothelial injury. The remaining debate seems to be of which cells, and by what mechanism.

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Elusive 'α-δ' sleep in fibromyalgia and osteoarthritis

Sir: Association between disturbed sleep and primary fibromyalgia syndrome (PFS) is well

Patient characteristics. Mean (range) is shown

	PFS* (n=10)	OA* (n=10)
Female:male	10:0	10:0
Mean age (years)	47 (35-62)	53 (40-61)
Mean symptom duration (months)	18 (8-36)	38 (16-48)

*PFS=primary fibromyalgia syndrome; OA=osteoarthritis.

recognised.^{1,2} Moldofsky and colleagues³⁻⁵ report frequent occurrence in PFS of an abnormality of deep, non-rapid eye movement (NREM) sleep in which α-like waves superimpose upon more usual δ waves – so called 'α-δ' sleep, first characterised by Hauri and Hawkins.⁶ Furthermore, experimental interruption of NREM, but not REM, sleep can reproduce features of PFS in normal subjects,⁷ suggesting a causal role for NREM sleep abnormality in PFS. Moldofsky *et al* also suggest that non-restorative sleep may influence pain reporting and morning symptom exacerbation in patients with osteoarthritis (OA)⁸ and rheumatoid arthritis.⁹ We were interested in using sleeping electroencephalogram (EEG) abnormalities in intervention studies in PFS and OA and therefore undertook the following pilot study.

Ten patients with PFS and 10 with OA were studied (table). All complained of pain and interrupted sleep. The patients with PFS had had typical symptoms for more than three months¹ and had more than 12 hyperalgesic tender sites (axial and peripheral, affecting arms and legs^{1,10}), negative control sites,¹⁰ and no OA or disease that may cause widespread symptoms.¹ Patients with OA had symptomatic hip or knee OA (non-nodal), or both, but no tender sites or widespread symptoms of PFS. For all subjects the results of screening investigations were normal, including blood count, erythrocyte sedimentation rate, antinuclear factor, calcium, thyroid function, and creatine kinase. Sleeping EEGs were performed at home without acclimatisation using an Oxford Medilog 4 channel recorder: EEG (C4:A1 and C3:A2), electro-oculogram (outer canthus:supraorbital), and electromyogram (submental). All patients completed a sleep diary. Tapes were replayed through an Oxford deck and displayed on Gould electrostatic tapes for visual assessment and recording. The C4:A1 EEG channel was also played through analogue active Butterworth filters (Barr and Stroud EF 5-02, attenuation rate 48 dB/octave) to give pass bands from 7 to 10 Hz and from 0.5 to 2 Hz (3 dB points), corresponding to frequencies constituting the α-δ pattern.⁶ Filter outputs were displayed in parallel on a Gould electrostatic writer (paper speed 1 mm/s). As tape replay speed was 20 times the recorded speed the write out corresponded to 0.05 mm/s. If the 0.5 Hz band amplitude approached or exceeded 75 μV that segment was rewritten at 250 mm/s (corresponding to 12.5 mm/s) and the amplitude of the 7-10 Hz band was measured. If this simultaneously exceeded 50% of the unfiltered signal amplitude it was termed α-δ sleep.

All patients experienced disturbed sleep with reported episodes of waking and often prolonged sleep latency. Sleeping EEGs in addition often showed frequent episodes of

unreported mini-arousal. No period of α-δ sleep⁶ was identified in any patient. No qualitative differences in recordings between groups were noted.

Our failure to detect α-δ intrusion in NREM sleep by visual and automated assessments most likely reflects differences in EEG interpretation rather than patient selection or technical differences. We used the strict criteria of Hauri and Hawkins who coined this term in a study of sleep disturbance in a heterogeneous, predominantly psychiatric, patient group.⁶ We commonly detected α waves, but mainly in relation to light (not NREM) sleep and frequent arousal. Poor sleep and frequent arousal alone could account for reports of α-δ sleep in PFS when only two EEG channels were used³ without additional EEG channels to facilitate recognition of arousal. This could also explain non-specific α-δ sleep in patients without PFS^{8,9} and indeed normal subjects⁶ with poor sleep.

Similarity of sleeping EEGs in PFS and OA suggests that factors other than poor sleep alone are important for development of PFS. Although our study questions the assertion that a characteristic non-restorative sleep pattern is central to development of PFS,^{2,3,7} the importance of sleep to symptoms and disability in subjects with locomotor pain is not necessarily undermined. We suggest that further studies are required in this difficult area, and that full multiple EEG channel recording is necessary to allow adequate assessment and interpretation of electrophysiological findings.

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