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## Unilateral lower limb suspension can cause deep venous thrombosis

*To the Editor:* We would like to bring to your attention and to the attention of the scientific community that unilateral lower limb suspension (ULLS), a model for physical inactivity and simulating microgravity unloading in humans, is associated with an increased risk of deep venous thrombosis (DVT). In the ULLS model, which was originally developed by Berg et al. (2), subjects use crutches for support while one leg is unloaded from weight bearing. The ULLS model has been used extensively to study neuromuscular adaptations to unloading and microgravity. Recently Deschenes et al. (5) published a study in this journal, in which they used a modified version of the ULLS model.

When we started our studies, we were unaware of any serious side effects associated with the ULLS model and adopted this model to study vascular adaptations to physical inactivity. However, one of the eight subjects who participated in our 28-day ULLS study developed, after 10 days of ULLS, a proximal DVT of the suspended leg, extending 10 cm proximal of the popliteal fossa. A PubMed search for “lower limb suspension” and “venous thrombosis” did not reveal any previous cases of thrombosis using this model. However, after carefully rereading all the published articles using this model, we identified two prior cases of venous thrombosis in male subjects: one case of DVT and one case of superficial thrombosis (3, 6). Since these side effects were only described briefly in the method sections of both articles, they can easily be overlooked. To our knowledge, 110 subjects so far participated in studies using the ULLS model, and three of those subjects developed venous thrombosis. Although these numbers are too small to accurately identify the risk of thrombosis during ULLS, this risk may be as high as 2.7%, which is substantially higher than in the general population [incidence of DVT 0.01–0.03% per year (9)].

The ULLS model has evolved to several versions and the risk of developing DVT may be different among these versions. We used a model very similar to the original description by Berg et al. (2). The leg was suspended by attachment of a sling to a nonrigid ankle brace and to a harness on the upper body. The knee was slightly flexed at an angle of ~130 degrees, and the ankle was at a resting position (5–15 degrees plantar flexion) and fully mobile. Both previous cases of thrombosis occurred in subjects using a similar model, with the addition of 5-cm elevation of the contralateral sole. In another version of ULLS, the contralateral foot is 10 cm elevated without ankle suspension and the knee is not flexed. Because in most studies there are variations in the ULLS model and in the additional precautionary measures, the number of subjects exposed to each specific version is small. Consequently, it is not possible to make a reliable assessment of the risk of the development of DVT for each version.

To our knowledge, no cases of DVT have been reported during a bed rest study or during spaceflight. The number of people exposed to microgravity is too limited to make a reliable assessment of the risk of DVT. However, the incidence of DVT seems to be greater during ULLS than during spaceflight and bed rest. This may be in part due to a stricter screening and subject selection and/or to higher calf muscle activity in spaceflight and bed rest studies.

Furthermore, in contrast to microgravity, during ULLS, gravity will lead to pooling of blood in the legs and this may affect DVT susceptibility. If during ULLS vascular complications occur more often than during microgravity, this may indicate that the simulation of vascular effects of microgravity, in particular in the venous system, is not completely accurate. However, the ULLS model has been shown to cause neuromuscular changes very similar to those observed during spaceflight and bed rest (12). Furthermore, this does not decrease the validity of ULLS as a model for vascular adaptations to physical inactivity, because physical inactivity is a well-known risk factor for deep venous thrombosis. For instance in the Sirius study the odds ratio for the development of venous thrombosis due to confinement to bed or to bed and arm chair was 5.61 (95% confidence interval: 2.30–13.67) (10).

The subject who developed DVT in our study was a 27-year-old female. She has been treated with oral anticoagulation for 3 mo and has been prescribed elastic compression stockings. She has improved markedly but, 6 mo after the event, she is still not completely free of symptoms. To prevent DVT in future studies, we have implemented several precautions. The affected subject used a third-generation oral contraceptive and, therefore, had a higher risk of developing thrombosis. She did not have inherited risk factors for thrombosis. We now exclude subjects with an inherited or acquired increased risk for venous thrombosis from our studies. Subjects have to wear elastic compression stockings on the suspended leg during ULLS, because there is evidence that compression stockings prevent DVT (1). Subjects are recommended to engage in passive, range of motion, non-weight-bearing exercises of the ankle and knee twice a day, similar exercises have been used in previous studies (5, 11). Furthermore, we measure D-dimer plasma concentrations serially to detect thrombosis in an early, sub-clinical phase. If D-dimer is positive or symptoms arise, venous compression ultrasound is performed. D-dimer plasma concentrations, measured with a quantitative latex method (Tinaquant), have a high sensitivity of 99–100% for the detection of thrombosis (7, 13). Screening for subclinical DVT with plasma D-dimer concentrations is not common clinical practice, but there is evidence that it may be beneficial (8). Although anticoagulants such as low-molecular-weight heparin or warfarin were used as a preventive measure in other studies (3, 6), we do not use anticoagulants in our study because of the substantial risk of bleeding complications, i.e., 3% major bleeding complications per year in low-risk subjects (4).

We conclude that during ULLS precautionary measures should be taken to prevent venous thromboembolism.

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