IBMS BoneKEy. 2010 July;7(7):259-262
http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/7/259
doi: 10.1138/20100456

MEETING REPORTS

The Interface Between Nerves, Muscles and Bone: Meeting Report from the 7th International Workshop on Musculoskeletal and Neuronal Interactions

May 20-23, 2010 in Cologne, Germany

Jörn Rittweger[1] and Frank Rauch[2]

[1]Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany
[2]Shriners Hospital for Children, Montreal, Canada

The 7th International Workshop on Musculoskeletal and Neuronal Interactions is hosted bi-annually by the International Society for Musculoskeletal and Neuronal Interactions (ISMNI). ISMNI meetings and the journal issued by this society (http://www.ismni.org/jmni/) are a forum for multidisciplinary research on the interface between nerves, muscles and bone. This *Meeting Report* summarizes some highlights of the 2010 meeting.

The Muscle and Bone Response to Mechanical Challenges

Mechanotransduction is of central interest for researchers in the field of musculoskeletal interactions, as this is how the mechanical signal from the muscle is converted into a biological signal in bone. Alexander Robling (Indiana University, Indianapolis, Indiana) was invited as a Keynote Speaker to address this topic. He showed that signaling through LRP5 plays an important role in mechanotransduction. LRP5 is in part controlled by sclerostin, which is produced by osteocytes and which is downregulated when bone is stimulated mechanically. He presented a series of elegant experiments to prove that LRP5 is indeed acting as a local regulator of bone formation through direct action in osteoblasts. The sclerostin/LRP5 pathway thus seems to be a key component of the mechanotransduction machinery.

Wilhelm Bloch (German Sports University, Cologne, Germany) gave an overview of mechanical adaptation of skeletal muscle. He briefly dealt with the ‘usual suspects’ – focal adhesion kinase and tenascins – as mediators of mechanical strain, and with the intracellular signals that transfer mechanical information, but then focused on an understudied area: molecules that can be released from the extracellular matrix into the bloodstream. Particularly exciting results were presented on endostatin and matrix-metalloproteinases 2 and 9 (1;2). Potentially, this field of research may allow an understanding of how vascular and muscular adaptive processes are co-ordinated.

Muscle Function in Mighty and in Clumsy Mice

The importance of myostatin as a negative regulator of muscle size is well-known, as seen in the murine myostatin knock-out results in the ‘mighty mouse’. Mighty though the mouse appears, the maximal isometric tetanic force of its muscles is similar to that of normal mice, suggesting that the force-generating capacity per unit muscle mass, specific tension, is decreased. Hans Degens (Manchester Metropolitan University, Manchester, UK) examined the force-generating capacity in single skinned muscle fibers of mighty mice to investigate whether this apparent deficit is reflected at the single cell level. Surprisingly, the studies showed that the contractile function of individual muscle fibers is not diminished in mighty mice. The relative force deficit observed in these mice, therefore, must be due to other factors, such as neuromuscular transmission failure or alterations in muscle architecture.

Vitamin D receptors are expressed in nerves, muscles and bones, which makes vitamin D a key study topic for researchers interested in neuro-musculo-skeletal interactions. Linda Ma (Lilly Research Laboratories, Indianapolis, Indiana, USA) investigated the role of vitamin D in muscle function. Vitamin D-deficient mice had impaired neuromuscular coordination and reduced maximal tetanic muscle force. Treatment with either 1,25-dihydroxyvitamin D_3 or a vitamin D receptor ligand normalized these deficits.

Mechanography

Although force plates have been available in specialized human performance laboratories for a long time, they are now becoming more widely used in clinical studies under the banner of 'mechanography'. One session of the meeting was dedicated to this topic. Frank Rauch (Shriners Hospital, Montreal, Canada) reviewed how the results of jumping mechanography and the results of peripheral quantitative computed tomography (pQCT) at the tibia can be combined to assess mechanosensitivity. The approach is based on the mechanostat theory and assumes that the bone adapts to the largest forces that the muscles can produce. It can be shown, for example, that a simple exercise such as hopping on the forefoot of one leg generates forces on the tibia that are about 12 times higher than body weight. When relating this result to cortical cross-sectional area, it becomes possible to calculate the stress that this force is creating in the bone. When mechanosensitivity is higher, the maximal stress in the bones should be lower. This approach should be useful for testing the effect of environmental and genetic factors on mechanosensitivity.

Jörn Rittweger (German Aerospace Center, Cologne, Germany) explained how, by integrating force measurements over time, it is possible to derive additional mechanical parameters, such as the power, speed and height of a jump. He showed that the maximal power achieved during a two-legged jump is a very reproducible measure that in adults follows an inexorable downward trend from 30 years onward. This decrease in jumping power is unlikely to be due to a more sedentary lifestyle in later years, as it was also observed in top athletes over the age of 35 years.

Oliver Fricke (Children's Hospital, University of Cologne, Germany) highlighted the importance of being precise when reporting muscle performance. For example, performance of a two-legged jump can be expressed as maximal force, maximal power or jumping height. All of these parameters might be classified as indicators of 'muscle strength', when in fact there is very little relationship between these measures.

New Uses of pQCT

Using pQCT often yields new insights into disease-induced skeletal changes. Prisca Eser (Inselspital Bern, Bern, Switzerland) presented a new method to assess metacarpal bones by pQCT. In a group of patients with rheumatoid arthritis, she found that metacarpal trabecular bone mineral density (BMD) was low, cortices were thin and the marrow cavity was expanded. Thinner cortices, according to Hans-Georg Zmierczak (Ghent University Hospital, Ghent, Belgium) are predictive of fractures in young, healthy men. In his study on 677 men aged 25 to 45 years, trabecular BMD also seemed to have some predictive power, whereas cortical BMD was not associated with fractures. This latter observation is apparently in contradiction to a report in dialysis patients (3).

José Luis Ferretti (National University of Rosario, Rosario, Argentina) provided a profound overview of the possibilities offered by pQCT. Expanding on his recent publication on the subject (4) he explained the principal design of the human tibia, as structurally assessed by pQCT: mainly compression in its distal part, doubling of the effective joint size from the ankle to the knee joint, as the latter has to bear varus and valgus stresses, and increasing bending moments towards the proximal end of the tibia. Increased mechanical usage, *e.g.*, in runners, does not affect effective joint size, but compressive strength in the distal part and bending strength in the proximal part of the tibia. Disuse, such as in spinal cord injury, however, does not yield a picture that is symmetrically opposed to increased usage.

Spinal cord injury is usually followed by rapid bone loss. According to the mechanostat theory, this decline should follow an exponential time course and reach a new steady state after a certain number of years. Cross-sectional studies support this view (5). However, a presentation given by Sylvie Coupaud (Department of Mechanical Engineering, University of Glasgow, Glasgow, UK) challenged this view. Her longitudinal pQCT data in patients with recent spinal cord injury suggest that, at least during the first 12 months, bone loss does not at all follow an exponential time course. A larger patient population will be needed to determine the predictors of the variable bone loss trajectories.

Lisa Micklesfield (Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa) reported on skeletal differences between ethnic groups in her country. Overall, these differences are rather mild, but black children had a wider bone cross-section and a thinner cortex than white children.

An exciting novel approach to study bone on the microscopic level was presented by Marita Kratz (University of Marburg, Marburg, Germany). The new technique is called 'optical coherence tomography'. It already offers better spatial resolution than micro-CT, and it can also provide insight into the lamellar structure of bone. This seems to be a very promising technique that should find wider use in the hopefully not-too-distant future.

Whole Body Vibration (WBV)

WBV is receiving increasing attention as an exercise modality, and also as a therapeutic strategy. Accordingly, one session of this meeting was dedicated to WBV. The physical principles of WBV were outlined by Harri Sievänen (UKK Institute, Tampere, Finland). He stressed the necessity to report findings from vibration studies in appropriate terms, namely frequency, peak-to-peak displacement and peak acceleration for sinusoidal vibration (6). Not all devices maintain their vibration settings constant when loaded, so that it may be left to clinical researchers to verify these settings in a given study. Side-alternating devices need to be distinguished from synchronous vibration (7). Moreover, he gave an introduction to the phenomenon of resonance, which might in theory amplify the forces created by WBV – although in practice it rarely, if ever, occurs.

Jörn Rittweger (German Aerospace Center, Cologne, Germany) then discussed what is known about the acute physiological effects of WBV. Acute WBV leads to an increase in energy turnover, as measurable by oxygen uptake (8). From a mechanical point of view, WBV causes cyclical muscle stretches and shortening (9) and thus elicits concentric and eccentric work. Tissue perfusion seems to be sufficient for the metabolic demand imposed by that work, or even in excess of it, as a recent study has shown (10). Evidence suggests that part of the mechanical energy during the stretch phase may be dissipated and transformed into heat (11).

The muscle stretch during each WBV cycle evokes stretch reflexes, as was pointed out by Albert Gollhofer (University of Freiburg Institute of Sport and Sport Science, Freiburg, Germany). There is an inhibition of the H-reflexes during and shortly after exposure to WBV. Nevertheless, one has to assume that stretch reflexes play an important role in the mediation of WBV, and that they are responsible for phase-linked electromyographic activity (12).

Finally, Marco Toigo (University of Zurich, Zurich, Switzerland) reported a recent training study in which WBV was combined with squatting exercise and arterial occlusion. Results suggest that this regimen can combine effects of strength and resistance training, which normally exclude each other, and that it can enhance the mechanical efficiency of the musculoskeletal system, at least on a bicycle ergometer.

Posters

Finally, there were a couple of excellent posters presented at the meeting. Elwyn Firth (Massey University, Palmerston North, New Zealand) studied the effect of voluntary exercise during pregnancy in a rat model that did lead to an increase in stress hormone levels. Twenty-one days of exercise resulted in bone modeling as assessed by pQCT. This model will be useful for future studies of the effects of exercise during pregnancy on offspring.

Jenna Stevens-Smith (Department of Human Metabolism, Medical School, University of Sheffield, Sheffield, UK) demonstrated deterioration of the trabecular network by diet-induced obesity in a rat model. These results are interesting as they are in contrast to what is widely believed to occur in humans.

Conflict of Interest: None reported.

References

1. Suhr F, Brixius K, Bloch W. Angiogenic and vascular modulation by extracellular matrix cleavage products. *Curr Pharm Des*. 2009;15(4):389-410.

2. Suhr F, Rosenwick C, Vassiliadis A, Bloch W, Brixius K. Regulation of extracellular matrix compounds involved in angiogenic processes in short- and long-track elite runners. *Scand J Med Sci Sports*. 2009 Jun 23. [Epub ahead of print]

3. Jamal SA, Gilbert J, Gordon C, Bauer DC. Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res*. 2006 Apr;21(4):543-8.

4. Capozza RF, Feldman S, Mortarino P, Reina PS, Schiessl H, Rittweger J, Ferretti JL, Cointry GR. Structural analysis of the human tibia by tomographic (pQCT) serial scans. *J Anat*. 2010 Apr;216(4):470-81.

5. Eser P, Frotzler A, Zehnder Y, Wick L, Knecht H, Denoth J, Schiessl H. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. *Bone*. 2004 May;34(5):869-80.

6. Kiiski J, Heinonen A, Järvinen TL, Kannus P, Sievänen H. Transmission of vertical whole body vibration to the human body. *J Bone Miner Res*. 2008 Aug;23(8):1318-25.

7. Rittweger J. Vibration as an exercise modality: how it may work, and what its potential might be. *Eur J Appl Physiol*. 2010 Mar;108(5):877-904.

8. Rittweger J, Ehrig J, Just K, Mutschelknauss M, Kirsch KA, Felsenberg D. Oxygen uptake in whole-body vibration exercise: influence of vibration frequency, amplitude, and external load. *Int J Sports Med*. 2002 Aug;23(6):428-32.

9. Cochrane DJ, Loram ID, Stannard SR, Rittweger J. Changes in joint angle, muscle-tendon complex length, muscle contractile tissue displacement, and modulation of EMG activity during acute whole-body vibration. *Muscle Nerve*. 2009 Sep;40(3):420-9.

10. Rittweger J, Moss AD, Colier W, Stewart C, Degens H. Muscle tissue oxygenation and VEGF in VO-matched vibration and squatting exercise. *Clin Physiol Funct Imaging*. 2010 May 23. [Epub ahead of print]

11. Cochrane DJ, Stannard SR, Sargeant AJ, Rittweger J. The rate of muscle temperature increase during acute whole-body vibration exercise. *Eur J Appl Physiol*. 2008 Jul;103(4):441-8.

12. Ritzmann R, Kramer A, Gruber M, Gollhofer A, Taube W. EMG activity during whole body vibration: motion artifacts or stretch reflexes? *Eur J Appl Physiol*. 2010 Apr 24. [Epub ahead of print]