The development of complex physiological loading profiles for the study of the intervertebral disc

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INTRODUCTION:

The integration of complex physiological loading in bioreactors represents a step forward by improving the resemblance of the in-vivo environment in intervertebral disc (IVD) whole organ culture models. The use of simplified uniaxial cyclic loading protocols with fixed diurnal patterns has been successfully applied using bioreactors [1-3], and the coupling of axial compression with other degrees of freedom such as torsion [4] and bending [5] has been applied in a limited number of studies using simplified loading regimes, which has demonstrated that different loading conditions affect the cellular response within the IVD. However, the integration of complex loading protocols that reflect real life activities remains unexplored. This study aims to develop a methodology for the creation of population specific activity loading profile for the study of the IVD using a unique six-axis bioreactor system. The generation of varying loading protocols will provide a unique opportunity to investigate the coupling of mechanical and biological environments of the intervertebral disc, and how they relate to the development of disc degeneration and the evaluation of regenerative treatments.

METHODS:

The Harmonised European Time Use Surveys (HETUS) database was used to determine the time spent in a variety of activities by the UK population during a period of 24h using the information reported in 2010. The activity profiles used in this study were created using the data corresponding to both sexes and the 25-44 year-old age group. This group was selected to represent the UK working population and the age group with the higher incidence of low back pain reported by the Nation Health Service [6]. Loads experienced by telemeterized vertebral body replacements (VBR) when carrying out a series of activities *in vivo* were accessed using the Orthoload database [7]. The reported loads were recorded on five patients performing a series of activities with an accuracy of 2% for force and 5% for moment components. Different activities replicated and recorded in the Orthoload database were selected to represent the main activities carried in the UK, according to the HETUS categorization. A time series was developed using the survey data, and a Python script was used to process and create transitions between activities. The range of activities reported in the Orthoload database might not allow an exact replication of the specific activity category but instead provided a proxy for the activity level and load profile for that particular activity.

RESULTS:

A 24h baseline loading protocol has been successfully created for a UK specific population (Figure 1). A day duration has been distributed among the following main categories: personal care, employment and study, household and family care, leisure, social and associative life and travel. These categories are composed of 40 subcategories as described by the HETUS database resulting in a 24h activity profile comprising a total of 805 individual activities taken from the Orthoload database. Using the average time spent by the population in the selected category, a balance between working and household related activities has been identified. Based on the reported participation times, the UK participants between the 24-44 year old group spent most of the time engaging in light intensity activities according to the metabolic equivalents (METs) for each activity. This profile provides a baseline protocol from which to investigate more active and sedentary behaviors.

DISCUSSION:

IVD studies using whole organ cultures should prioritize the application of loads whose match human activities, preferably integrating loads in six-axis. The protocols developed have taken available HETUS and Orthoload data to compile a physiological six-axis load profile for a 24 hour period. This baseline protocol is currently being implemented using a six-axis bioreactor system to provide an initial understanding of how complex loading in the disc affects the cell viability and disc composition. The integration of physiological loads matching values presented during human activities in all six-axis could provide relevant data to understand the mechanical behavior of the human IVD and evaluate the biochemical changes under specific conditions. The use of truly representative physiological loading profiles in IVD research could result on a more comprehensive evaluation of regenerative therapies at earlier stages, and better evidence-based recommendation for rehabilitation, surgery recovery and pain management. Evaluation of human-like parameters is necessary to translate the findings of *in vitro* studies into animal testing and clinical settings. The methodology for the physiological loading protocols could be applied to account for different levels of activity, lifestyles, populations (e.g. countries, age groups, sex, occupations, etc.) using available survey data such as the American Time Use, Australia's Time Use Survey and HETUS. The Orthoload database offers a vast source for activities, however, not every common daily activity has been executed and reported and the activities used to illustrate those cases might not be fully representative of such actions. To overcome the database limitations, the integration of biomechanical modeling, simulation and validated *in-silico* models could offer an alternative to obtain information on additional activities to improve the accuracy of the profiles.

SIGNIFICANCE:

The combination of physiological loading protocols and six-axis test systems will pave the way for investigations of disc nutrition, degenerative mechanisms, and regenerative therapies under complex loading, which are not currently possible. The implementation of these protocols will provide valuable capabilities in investigating complex loading in the spine to study the properties of the IVD, and the efficacy of orthopedic devices such as total disc replacements and nucleus replacements.

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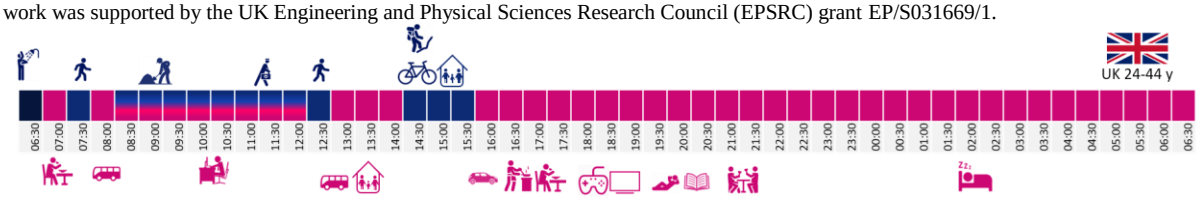

Figure 1. Activity distribution in a 24h period for a UK population in the 24-44 year old group. The upper activities (blue) represent more active action while the bottom activities (magenta) are representative of light intensity activities