Unbiased Heart Rate Variability Profiling Reveals Three Stress Phenotypes in Late-Stage Osteoarthritis

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INTRODUCTION: We recently reported that patients with late-stage osteoarthritis (OA) display sympathetic predominance indicated by significantly reduced heart rate variability (HRV), with a heterogeneous pattern[1]. Here, we aimed to delineate distinct stress-response phenotypes through unbiased profiling of autonomic, endocrine, and inflammatory markers.

METHODS: We evaluated data from 298 late-OA patients pre- and post-operatively (females:males - 54%:46%). Various HRV parameters were assessed to evaluate sympathetic (low-frequency [LF] power) and parasympathetic (high-frequency [HF] power, pNN50[%], RMSSD [ms], SDRR [ms], CVRR [%]) activity. Chronic stress levels were measured using questionnaires (Perceived Stress Questionnaire (PSQ). Additionally, serum catecholamines were quantified by LC–MS/MS and the serum ratio of the stress hormones cortisol and dehydroepiandrosterone sulfate (DHEAS) as well as cytokines was determined using ELISA. Continuous and categorical features were log‐transformed if highly skewed and imputed with Random Forests (missForest). A mixed‐data Gaussian mixture model (VarSelLCM) and model‐based clustering (Mclust) were used. Cluster profiling was performed using Kruskal‐Wallis and χ^2 tests, followed by Benjamini‐Hochberg‐adjusted pairwise Wilcoxon or χ^2 post‐hoc comparisons. Pre‐ versus post‐operative responses within clusters were assessed by paired Wilcoxon tests (BH-adjustment).

RESULTS SECTION: Using 35 selected relevant variables, we identified three distinct patient clusters. Cluster1 (n=141, "Intermediate Stress") exhibited lower adrenal parameters (particularly adrenaline) than Cluster3 ($p<1\times10^{-6}$). Parasympathetic measures (CVRR, HF, $p<1\times10^{-7}$ vs. 2 and 3) as well as albumin and DHEA-S were intermediate in this Cluster 1 ($p>0.6$ vs. 2; $p<1\times10^{-3}$ vs. 3). Cluster2 (n = 86, "High Resilience") exhibited the highest parasympathetic indices ($p<1\times10^{-6}$), lower serum cortisol:DHEA-S ratio and cortisol than Cluster1 ($p=0.015, 0.03$), and elevated synovial fluid noradrenaline and dopamine concentrations ($p=2\times10^{-7}$). Cluster3 (n=71, "High Stress/Inflammatory") showed elevated sympathetic markers (synovial fluid adrenaline, serum aldosterone and albumin; $p<0.01$), the lowest parasympathetic activity (HF, CVRR; $p<1\times10^{-7}$), high LF/HF ($p<1\times10^{-7}$), and significantly increased serum IL-6 ($p<0.01$).

DISCUSSION: The three late-stage osteoarthritis phenotypes we identified exhibit distinct patterns in autonomic regulation, hypothalamic-pituitary-adrenal (HPA) axis activity, and systemic inflammatory burden. Despite the relatively limited cohort size, the observed differences reached high statistical significance. Future investigations with larger patient populations and additional outcome measures, including joint pain, will be essential to further elucidate the relationship between autonomic dysregulation and osteoarthritis symptomatology.

SIGNIFICANCE/CLINICAL RELEVANCE: Identification of these phenotypic profiles in routine clinical practice could facilitate the development of personalized perioperative management and targeted therapeutic strategies, potentially improving patient outcomes.

REFERENCES:

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