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Piezo1 in migraine in older adults: a mechanobiological link between arterial stiffness and trigeminovascular nociception

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Introduction
Migraine in older adults may be influenced by age-related vascular remodeling and increased arterial stiffness. Chronic hypertension, lipohyalinosis, and reduced arterial compliance can impair pulse-wave damping, allowing excessive pulsatile energy to reach cerebral and meningeal microvessels. Within the mechanically constrained cranial environment, altered pulsatile strain may act as an endogenous mechanical stressor. Piezo1, a mechanosensitive ion channel expressed in trigeminal and endothelial compartments in preclinical models, is a plausible mediator capable of converting abnormal vascular forces into nociceptive signaling.

Objective
To propose a mechanoneurobiological model linking arterial stiffness to migraine persistence or chronification in older adults through Piezo1-dependent trigeminovascular activation.

Methods
A theoretical mechanistic modeling study was conducted by integrating three evidence domains: clinical studies associating migraine with arterial stiffness in older populations, hemodynamic principles of pulse-wave transmission and vascular damping, and preclinical evidence of Piezo1-mediated trigeminovascular mechanotransduction. The model was designed to generate a plausible pathway and testable predictions in the absence of direct human studies evaluating Piezo1 in older adults with migraine.

Results
The model predicts that reduced arterial compliance may increase pulsatile mechanical strain in meningeal and cerebral microvascular beds. Vascular remodeling and impaired Windkessel buffering could facilitate deformation of perivascular trigeminal afferents and endothelial structures, lowering the threshold for Piezo1-dependent activation. Piezo1 opening may promote calcium influx and contribute to ATP and calcitonin gene-related peptide release, favoring pulsatile nociceptive transmission. Repeated mechanotransduction may amplify neurogenic inflammation through endothelial activation, immune-cell recruitment, and mast-cell degranulation, increasing local levels of histamine, serotonin, cytokines, prostaglandins, leukotrienes, and nitric oxide. In a low-compliance vascular system, inflammation-related edema and vascular distension may further increase mechanical stress, creating a positive feedback loop between pulsatile strain, Piezo1 activation, and trigeminovascular sensitization. Persistent activation of this pathway may contribute to central sensitization and help explain refractory or chronic migraine phenotypes in older adults.

Conclusion
Arterial stiffness may provide a mechanical substrate for sustained trigeminovascular activation in older adults with migraine. By linking impaired vascular damping, meningeal mechanical stress, Piezo1-dependent calcium signaling, and neuroinflammation, this model offers a plausible mechanobiological explanation for migraine persistence in aging. Piezo1 should be considered a potential target for future experimental and translational studies.

Keywords:
Migraine
Piezo1
Arterial stiffness
Trigeminovascular system
Mechanotransduction

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