Shear stress-mediated calcium signaling in cardiac myocytes

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During each contraction and hemodynamic disturbance, cardiac myocytes are subjected to fluid shear stress due to blood flow and the relative movement of sheets of myocytes. There are also intriguing clinical evidence that a regurgitant blood-jet during mitral valve incompetence causes atrial arrhythmia, and that a direct irritation due to a catheter whip on the intra-atrial wall elicits ectopic atrial tachycardia. However, atrial responses to shear stimulus remain poorly understood. A longitudinally propagating, regenerative Ca^{2+} wave is initiated in atrial myocytes under shear stress. We determined the cellular mechanism for this shear-induced Ca^{2+} wave using two-dimensional confocal Ca^{2+} imaging combined with pressurized fluid flow, and characterized shear stress-sensitive membrane current in atrial myocytes using the whole-cell patch clamp technique, combined with pressurized fluid flow, and pharmacological and genetic interventions of specific proteins. Our data suggest that shear stress triggers the Ca^{2+} wave through ryanodine receptors *via* $P2Y_1$ purinoceptor–phospholipase C-type 2 inositol 1,4,5-trisphosphate receptor signal transduction in atrial myocytes, and that this mechanotransduction is activated by gap junction hemichannel-mediated ATP release. Our patch clamp study further reveals that shear stress indirectly activates monovalent cation current carried by transient receptor potential melastatin subfamily 4 via type 2 inositol 1,4,5-trisphosphate receptor-mediated Ca^{2+} release in subsarcolemmal domains of atrial myocytes. Shear-specific mechanotransduction and the subsequent regenerative Ca^{2+} wave may be one way for atrial myocytes to assess mechanical stimuli directly and alter their Ca^{2+} signaling and excitability accordingly.