Contractile force generation by 3D hiPSC-derived cardiac tissues is enhanced by rapid establishment of cellular interconnection in matrix with muscle-mimicking stiffness.

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Public Summary:
Engineering 3D human cardiac tissues is of great importance for therapeutic and pharmaceutical applications. As cardiac tissue substitutes, extracellular matrix-derived hydrogels have been widely explored. However, they exhibit premature degradation and their stiffness is often orders of magnitude lower than that of native cardiac tissue. There are no reports on establishing interconnected cardiomyocytes in 3D hydrogels at physiologically-relevant cell density and matrix stiffness. Here we bioengineer human cardiac microtissues by encapsulating human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) in chemically-crosslinked gelatin hydrogels (1.25 x 108/mL) with tunable stiffness and degradation. In comparison to the cells in high stiffness (16 kPa)/slow degrading hydrogels, hiPSC-CMs in low stiffness (2 kPa)/fast degrading and intermediate stiffness (9 kPa)/intermediate degrading hydrogels exhibit increased intercellular network formation, alpha-actinin and connexin-43 expression, and contraction velocity. Only the 9 kPa microtissues exhibit organized sarcomeric structure and significantly increased contractile stress. This demonstrates that muscle-mimicking stiffness together with robust cellular interconnection contributes to enhancement in sarcomeric organization and contractile function of the engineered cardiac tissue. This study highlights the importance of intercellular connectivity, physiologically-relevant cell density, and matrix stiffness to best support 3D cardiac tissue engineering.

Scientific Abstract:
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