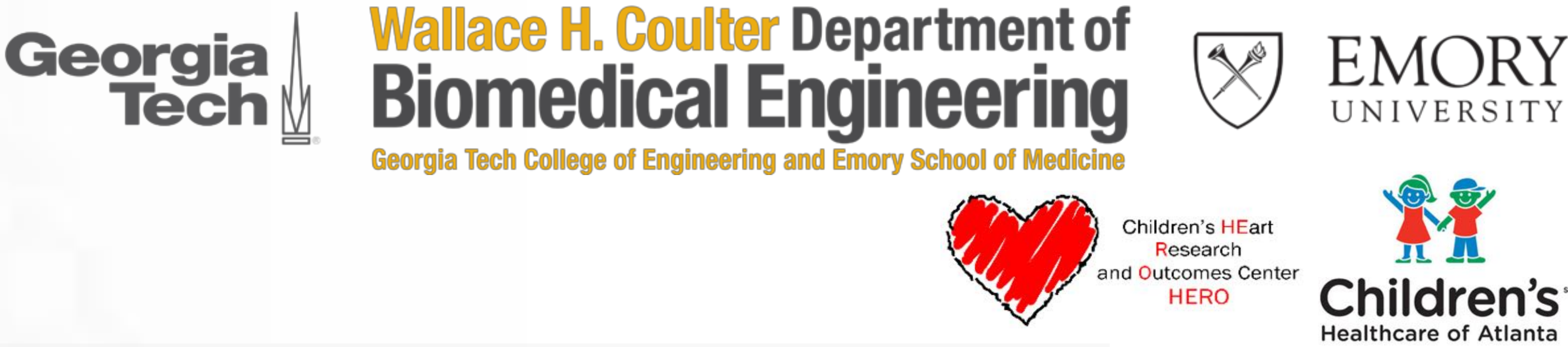


3D Bioprinted Hemodynamic Flow Models of the Developing Heart to Study Congenital Heart Disease

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Abstract

Congenital heart diseases (CHDs), such as hypoplastic left heart syndrome (HLHS), are characterized by a variety of underdeveloped heart structures, including the atria, ventricles, aortic and pulmonic outflow tracts, and mitral valve. We ***hypothesize*** that impaired hemodynamic flow and heightened wall shear stress correlate with this underdevelopment of the heart and the onset of CHDs. In this project, we model an idealized and anatomical human heart at Carnegie Stage 10 (21-23 days). 3D images of fetal hearts reconstructed from segmented immunohistochemistry stains were computer animated design (CAD) processed to reconstruct, smooth, and append flow conduits. Physical reconstructions of these 3D models were 3D printed with clear photoresists (rigid and elastic) and 3D bioprinted using pluronic hydrogels. With an anatomical flow model, experimental and theoretical flow metrics of velocity and shear stress at the wall can be analyzed. Additionally, the proof-of-concept 3D bioprinted models demonstrate the feasibility and accuracy of our constructs for cell seeding. Overall, this developing heart model platform paves the way for simulating the effects of normal and disturbed blood flows to study cardiac cells.

Introduction

- Although HLHS is prevalent in less than 4% of all heart related birth defects, it accounts for a disproportionate, 20-25%, of congenital heart defect related mortalities. This translates to about 2000 infants every year.
- HLHS comes in spectrum of severity, and there is much variability in cases. Currently, there is no known cause. Literature points to a multifactorial etiology, including maternal infection, genetics, or a reduction in left ventricular inflow or outflow.
- The primary method of treating patients with HLHS is a three stage surgical procedure. The purpose is to circumnavigate the left ventricle and have the right ventricle perform the functions of both pulmonary and systemic circulation. These surgeries have significant morbidity, and no single approach works for all HLHS patients, so there is much to gain in uncovering more of the etiology and possible treatment options of HLHS before birth.

Methods

- 3D images of fetal hearts reconstructed from segmented immunohistochemistry stains were tuned using CAD processing programs, including MeshMixer and Autodesk Fusion 360.
- The lumen is the innermost layer of the heart and was chosen to model because it contains the cells that are most directly affected by the pulsatile flows of the heart, and are likely to contribute to the maladaptive growth of the fetal heart with CHDs.
- Carnegie stage 10 (CS 10) lumen was chosen as complex twisting of the forming heart begins.
- This 3D model was 3D printed using clear photoresist resin (rigid and elastic) with a Form 2 Labs 3D printer, and 3D bio-printed using pluronic hydrogels on the CELLINK BIOX printer.

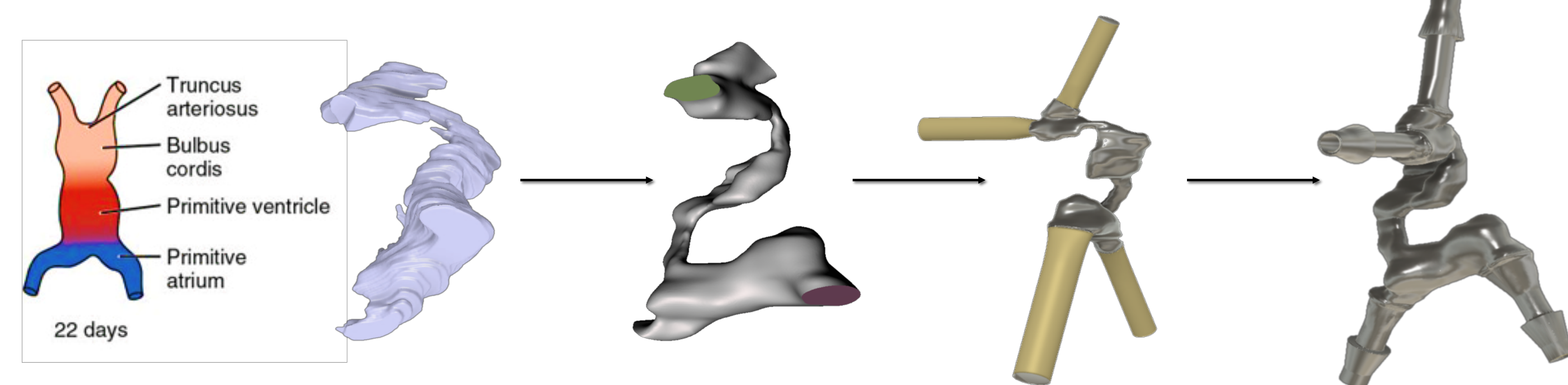


Fig 1. Carnegie Stage 10 heart model manipulations. Image cross-sections are smoothed. Inlets and outlets are extended as flow conduits for flow simulations.

Results

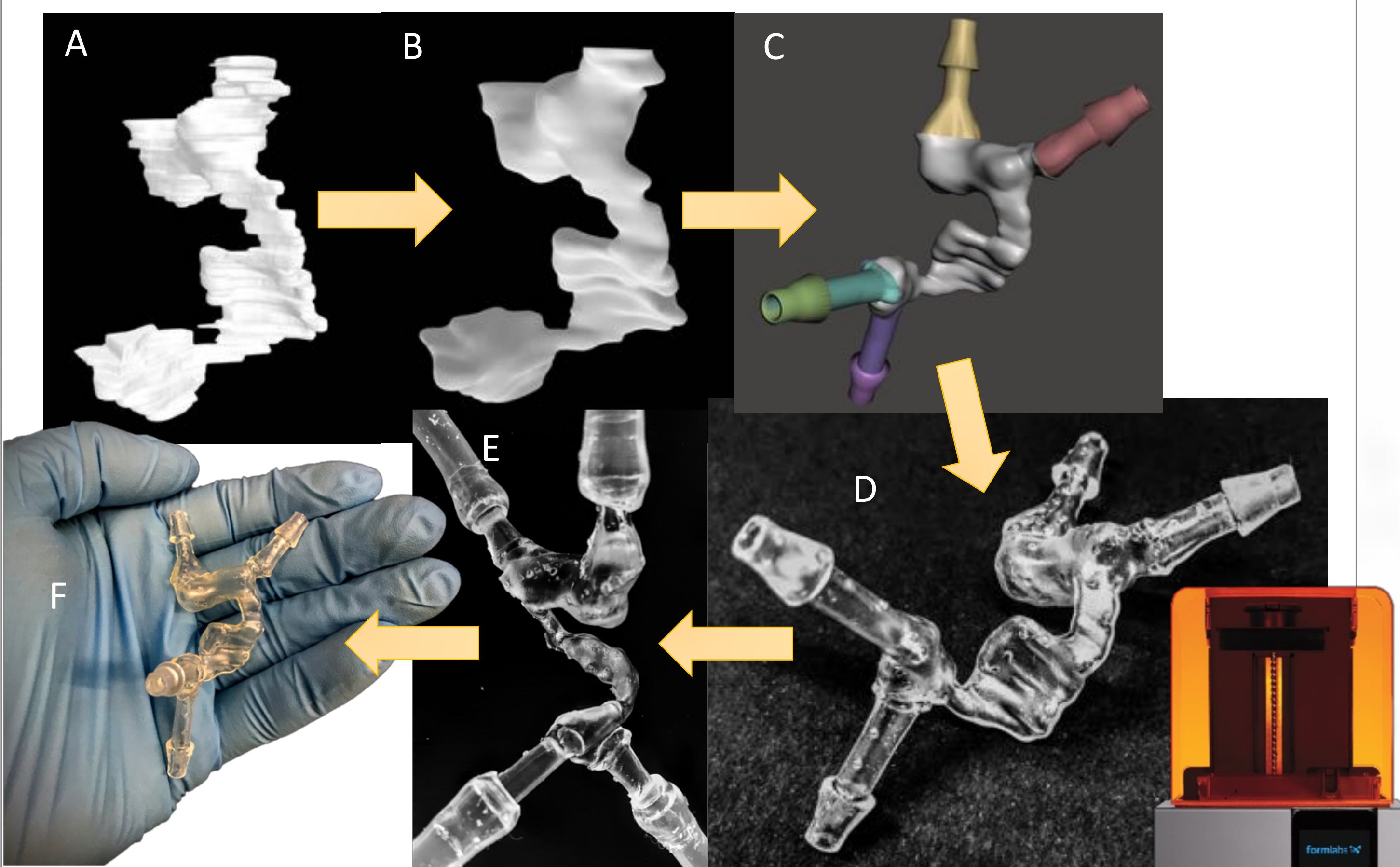


Fig 2. Carnegie stage 10 cardiac lumen .stl model to physical flow model. (A) Original segmented model reconstruction. (B) Smoothed model. (C) Cardiac lumen model showing custom barb connections to heart model (Meshmixer). (D) 3D printed clear, rigid photoresist resin (Form 2 Labs 3D Printer). (E) Sample flow of model with Tygon tubing connections. (F) Physical model in hand, scaled 50x.

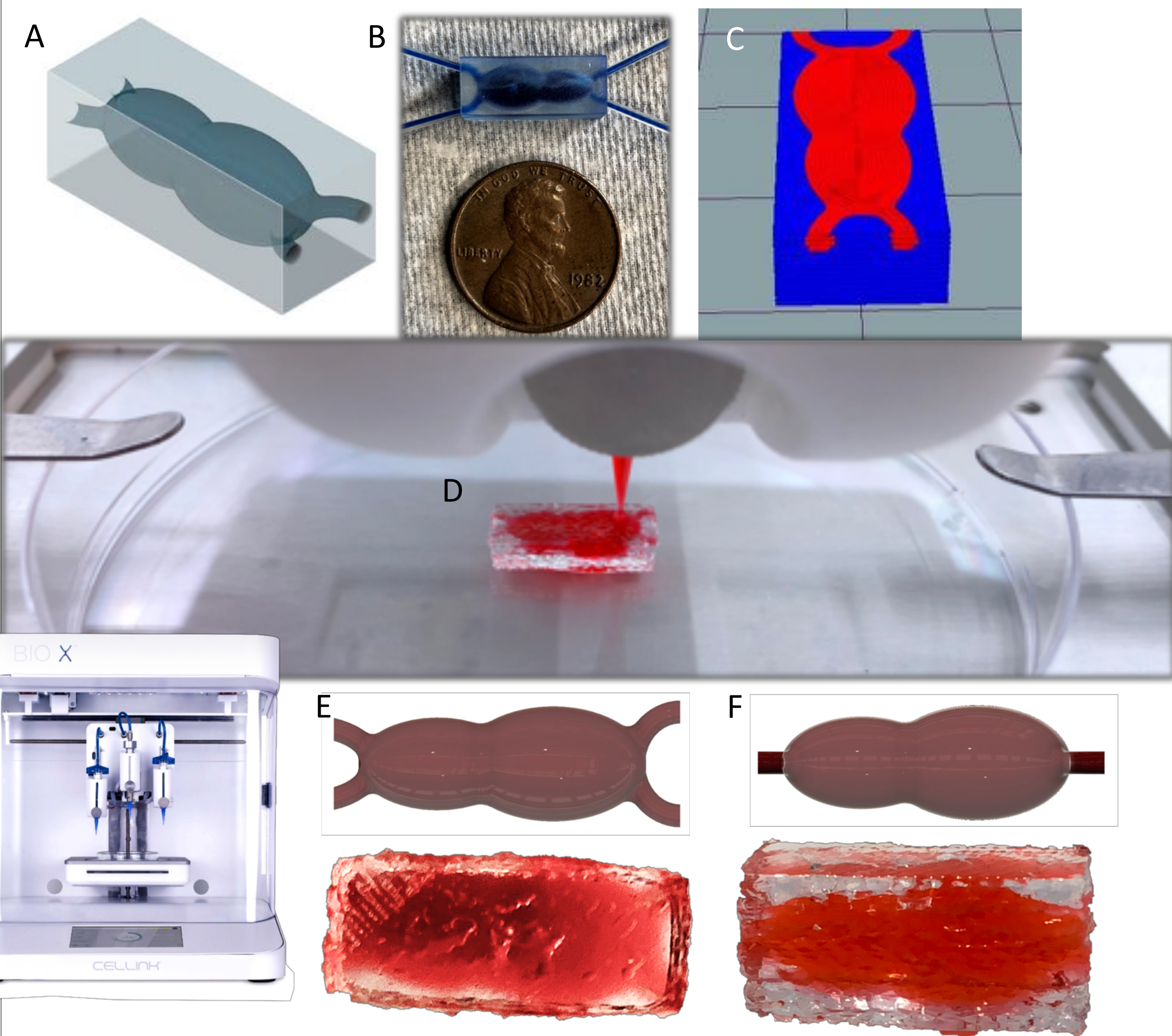


Fig 3. Idealized CS 10 heart tube lumen model created using Autodesk Fusion 360. (A) Positive and negative models. (B) Physical clear resin. (C) Generating gcode of dual extruded positive and negative model (Repetier-Host). (D) Bioprinting with pluronic (CELLINK BIOX). (E) Top and (F) side views comparison of CAD and bioprinted lumens.

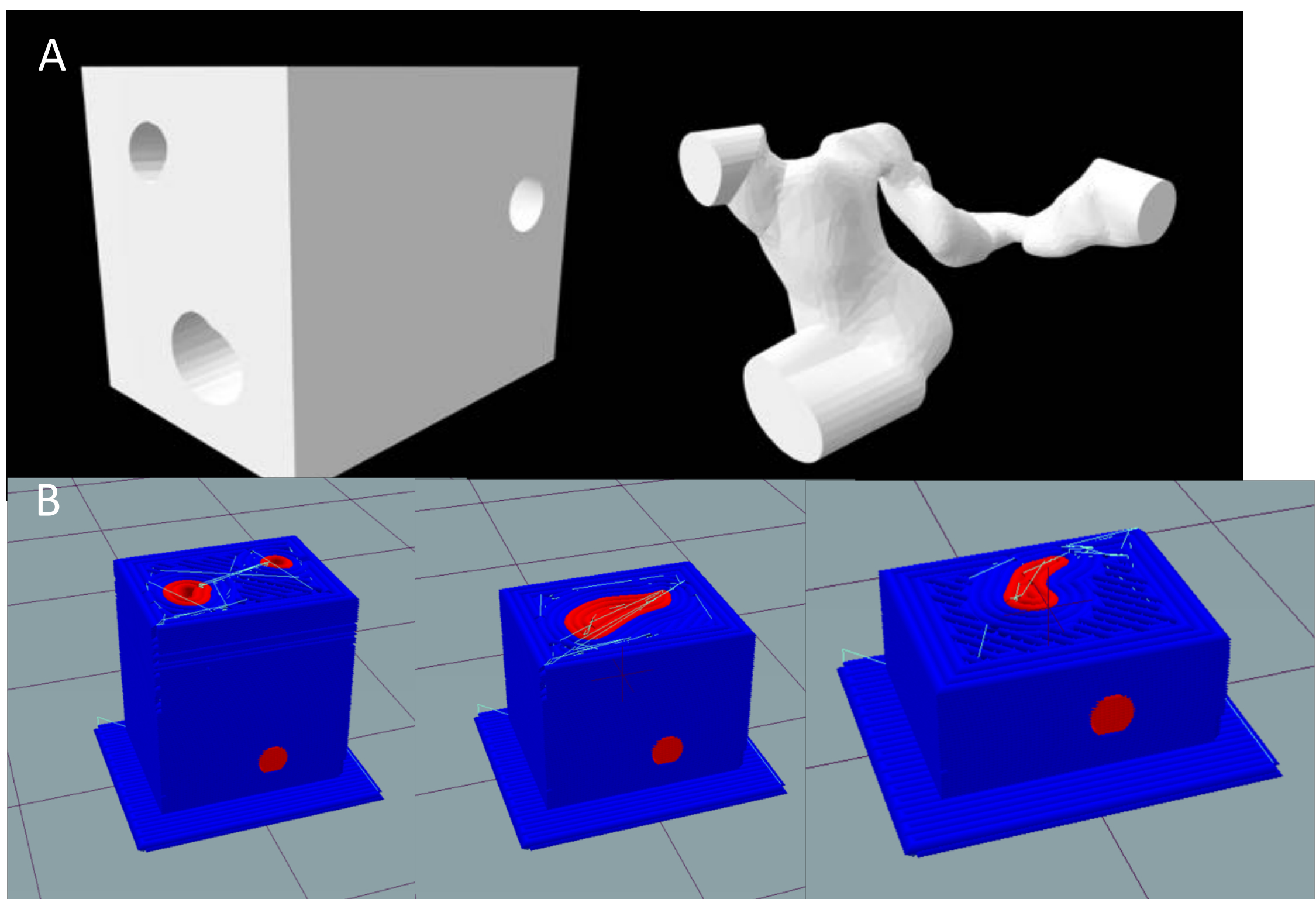


Fig 4. Bioprinting anatomical heart lumen model. (A) Negative and positive models. (B) Lumen models compiled for cross sections shown.

Discussion

- We demonstrated the possibility of generating a developing heart model accurately scaled in three dimensions for 3D printing and bioprinting. Flow visualization can now be used to investigate relationships between mechanical hemodynamic stresses and CHDs.
- Future versions of these 3D models will be lined with HUVECs and perfused with laminar and pulsatile flow patterns. We suspect variations in cellular proliferation and morphology of the mimicked cardiac endothelium under impaired hemodynamics, unveiling a potential factors in CHD onset.
- This model enables us to study the heart during an inaccessible time frame that modern imaging cannot resolve.
- This model framework can also be applied for different heart layers, heart stages, and other organs to leverage tissue engineering approaches for the study of organ (mal)formation.

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