A Novel Low-Profile Self-Expanding Biodegradable Percutaneous Heart Valve Frame That Grows with a Child

Mohamed Ibrahim 1, Kara X. Nghiem 2*, Kaitlin Chung 2, Moataz Elsisy 3, Uma J. Gosai 4, Seungil Kim 5,6*, Sangho Ye 5,6, William R. Wagner 2,5,6,7 and Youngjae Chun 1,2,5,*

1 Department of Industrial Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA
2 Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA 15261, USA
3 Department of Mechanical Design, Cairo University, Giza 12613, Egypt
4 Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA
5 McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA
6 Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA
7 Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA
* Correspondence: yjchun@pitt.edu

Abstract: According to rough estimates, one in every 125 newborns born in the United States has a congenital cardiac abnormality that must be repaired. With the recent development of new biomaterials and innovative treatment methods, percutaneous cardiac valve replacement has been considered as an alternative to surgical procedures. While percutaneous heart valve replacement is a relatively new procedure with a few commercially available devices, the devices are not sufficiently low-profile, and do not grow with the child. To address this issue, a novel low-profile growing percutaneous pediatric heart valve frame made of two types of unique metallic biomaterials (superelastic nitinol and biodegradable iron) has been developed through this study. The developed pediatric heart valve frame has an innovative mechanism that will expand its diameter by disconnecting biodegradable metals, enabling the growth of the device with the surrounding tissue in the cardiac space. The thermally treated iron wires show stable and gradual degradation characteristics, showing approximately 7.66% for both wires treated under 350 and 450 °C. Polymer-coated wires show a degradation range of 4.96 to 5.55% depending on the type of coating. Degradation test results show the predicted 9–23 months of degradation depending on the type of surface treatment (e.g., thermal treatment, polymer coating), which is a suitable range when compared with the theoretical arterial vessel remodeling process period in the human vascular system. Radial forces calculated by finite element analysis and measured by mechanical testing matched well, showing 5–6 N with a 20% diameter reduction considering the deployed valve frame in the heart. Biocompatibility study results demonstrated superior cell viability in thermally treated iron wires after 3 days of cell culture and showed rarely found platelets on the surface after 3-h blood exposure tests. Prototype devices were successfully fabricated using optimized advanced joining processes for dissimilar metallic materials such as nitinol and iron. This study represents the first demonstration of self-expanding and biodegradable percutaneous heart valve frames for pediatric patients that grow with a child.

Keywords: superelastic nitinol; biodegradable iron; percutaneous; pediatric heart valve

1. Introduction

Heart valve disease is a condition in which the valve between the main pumping chamber of the heart (left ventricle) and the main artery to the body (aorta) malfunctions. Heart valve disease sometimes may be a congenital condition. Defects in heart valves and associated structures for infants account for 25 to 30 percent of all cardiovascular malformations [1]. In adults, over 182,000 heart valve replacements are performed annually for the treatment of valvular heart disease, but it remains as a major cause of morbidity...
and mortality, with approximately 91,000 transcatheter valve replacements performed in the USA every year [2–4].

There are typically two types of prosthetic heart valves used for replacement—mechanical and bioprosthetic. Mechanical heart valves are made entirely of synthetic materials such as metals and polymers, while bioprosthetic heart valves are made of tissue from animals (e.g., bovine or porcine) or humans [5,6]. Mechanical heart valves are durable, lasting at least 20 to 30 years [7,8]. However, these valves have limited central flow due to their design, such as bileaflets, the ball in a cage, or a tilting disc [6,9]. In addition, a major drawback is that mechanical heart valves require daily anticoagulant treatment because of the increased risk of artificial material-induced thrombosis and thromboembolism [10–13].

On the contrary, bioprosthetic heart valves have improved central blood flow due to their bio-mimicking trileaflet design and do not require anticoagulant therapy. However, these bioprosthetic heart valves also have some drawbacks, including limited durability due to leaflet calcification, leaflet tearing, fatigue damage, and tissue failure [14–17]. Therefore, 10 to 20 percent of homograft bioprostheses and 30 percent of heterograft bioprostheses fail within 10 to 15 years of implantation and require replacement [18–20].

Furthermore, both mechanical and bioprosthetic heart valves are large and bulky and require open heart surgery, which has a severe risk factor for infants and young children who are too weak or ill to undergo major open surgery [5]. Recently, a less invasive therapy, percutaneous heart valve replacement, has drastically improved with the development of novel biomaterials and suggests innovative treatment strategies. While percutaneous heart valve replacement is an emerging technology with a few commercially available devices, the devices are still relatively bulky for infants or children and will not grow with the child, which may not be suitable for pediatric patients with congenital heart disease.

To address this issue, this study has demonstrated a novel concept of a pediatric heart valve frame that utilizes two types of metallic biomaterials, i.e., superelastic nitinol and biodegradable metals such as iron, as depicted in Figure 1. Biodegradation of surface-modified iron will enable the pediatric device to grow with the child, while superelastic nitinol can play an important role in the self-expanding mechanism. Both thermal treatment and polymer coating strategies were adapted to extend the degradation period for the purpose of the desired length of mechanical integrity. With the outcomes produced from the degradation study, prototypes have been designed and fabricated to demonstrate the growing pediatric valve frame. In addition, both the blood and cytocompatibility of the degradable metallic devices have been studied.

Figure 1. Schematic illustration of a growing pediatric percutaneous heart valve frame concept: (A) en face view of the frame that contains both superelastic nitinol and biodegradable metal, (B) original dimension of the device, showing the angle of leaflet, and (C) 200% increased dimension of the device with the leaflet angle change assuming the growth of the child.
2. Materials and Methods

2.1. Materials

Nitinol (Ni + Ti + Naval Ordinance Lab) was discovered in 1963 and has been used in a wide range of transcatheter devices due to its shape memory property [21]. The shape memory response is defined as mechanical deformation in a low-temperature state (i.e., martensite), with deformations fully recovered when the material is heated to body temperature (i.e., austenite). This shape memory behavior is critical for transcatheter devices because nitinol can easily be collapsed into a small-diameter catheter in its martensite phase. Upon exposure to blood temperature, it deploys spontaneously to its original shape (the austenite phase). Because the magnitude of its recoverable deformation is much greater than the elastic deformation of metals such as surgical steel, nitinol-based devices can be placed into remarkably smaller-diameter catheters for a wide range of catheter-based procedures [22–24].

An iron stent was first implanted in the rabbit model in 2001 [25]. Iron is one of the important biodegradable metallic biomaterials, with high radial strength compared with other biodegradable metals, e.g., magnesium. This attribute enables the iron-based stent to have thinner struts, permitting an endovascular low-profile device. There were no significant adverse events (e.g., thrombosis and excessive neointima hyperplasia) during a 6-18 month follow-up period with in vivo animal tests [25,26].

2.2. Surface Treatments

2.2.1. Thermal Treatments

A biodegradable material’s mechanical performance and biodegradation behavior are crucial for biodegradable implant applications. Thermal treatment, or annealing, has been proven to have a substantial impact on the mechanical performance of pure iron (99.85%, outer diameter of 250 µm, GoodFellow, Pittsburgh, PA, USA) [27]. However, only a few research articles have addressed the influence of thermal annealing on the biodegradation behavior of pure iron [28]. When pure iron samples are thermally treated, a newly formed iron oxide layer starts to cover the outer surface of the iron, which may affect the sample’s degradation rate. Furthermore, various treatment parameters, such as treatment temperatures and times, can significantly affect the growth of the iron oxide layer and its thickness [29]. At different treatment temperatures, Simmons et al. investigated the formation of iron oxide and its microstructure, showing that a distinct microstructure, a mixture of nonstoichiometric and stoichiometric magnetite and hematite, at 350 °C, was observed, while, at 450 °C, stoichiometric magnetite was the only oxide observed [30].

In this light, pure iron wire samples were prepared and subjected to multiple combinations of thermal treatments at different times to investigate the influence of these treatment parameters on the sample’s degradation. Iron wires were thermally treated at both 350 °C and 450 °C for 0.5, 1.5, and 4 h. Additional wires were prepared at 550 degrees but were deemed inappropriate for experimental use due to flaking of the outer oxide layer.

2.2.2. Ultra-Thin Polymer Coating

Iron (Fe) wires (length: 70 mm, outer diameter: 250 µm, GoodFellow, Pittsburgh, PA, USA) underwent phytic acid–metal conversion coating [31] and coating with poly(carbonate urethane) urea (PCUU, inherent viscosity: 0.80 ± 0.1) [32,33], in which each coating step was separately investigated using scanning electron microscopy (SEM), as illustrated in Figure 2. For the phytic acid–metal conversion coating, phytic acid (PA) solution in deionized (DI) water (10 µg/L) was mixed with the same volume of Zn(NO$_3$)$_2$ solution in DI water (5 mmol/L) and then the pH was adjusted to 6.0 by adding 1N NaOH solution. Iron wires were washed with DI water and then immersed in the mixed PA-Zn(NO$_3$)$_2$ solution for 10 min with gentle shaking. After the PA-Zn$^{2+}$ coating, the wires were washed with DI water three times and dried under a vacuum. In addition, PCUU was coated onto the PA-Zn$^{2+}$ coated wires by dip coating using 2% (w/v) PCUU solution in hexafluoro-2-propanol (HFIP). The dip coating was repeated ten times for each wire. For the spray-coated wires,
10 mL of 2% PCUU solution was sprayed onto each PA-Zn\(^{2+}\) and PCUU-dip-coated wire at a 15 cm distance using a customized airbrush.

Figure 2. Iron wire samples treated with (A) phytic acid–Zn, (B) phytic acid–Zn + PCUU dip coating, and (C) phytic acid–Zn + PCUU dip and spray coating.

2.3. Degradation Test

Directly after the surface treatments of the iron wires, the degradation performance is assessed by immersion testing in phosphate-buffered solution (PBS, Fisher Scientific, Waltham, MA, USA). PBS is a physiologic aqueous solution that imitates the ionic concentration, osmolarity, and pH value of human blood but does not contain larger particles such as proteins, lipids, or blood cells. The iron samples were placed at the middle of a 0.5-inch-diameter silicone elastomer tube (Thermo Scientific, Waltham, MA, USA) by fixing these wire samples at the inner walls of the tubes, as shown in Figure 3A. The PBS was designed to flow in the tubes with the help of a peristaltic pump (Harvard Apparatus, Holliston, MA, USA) at a flow rate of 147.961 mL/min, flowing with a 100 mm Hg flow pressure, to mimic the blood flow parameters inside the aortic artery of the human body. The samples were fully immersed in the flow of PBS to ensure constant solution circumstances, and the immersion testing setup was kept at a constant temperature of 37 °C.

Figure 3. In vitro test device performance test setups: (A) degradation test setup, and (B) radial force measurement test setup.

After weighing and before immersion testing, four wire samples with the same treatment parameter combination were prepared to be submerged in PBS for four weeks. During
Immersion testing, iron wires were formed into 0.25-mm-diameter and 10-mm-tall, exposed wires. In addition, wire samples were then regularly removed each week to check the effect of the immersion time on the degradation of the wires. Before weighing, all the prepared samples were cleaned in order with alcohol, acetone, and DI water and carefully dried. After sample removal, they were cleaned in acetone using an ultrasonic bath after immersion, and the leftover corrosion products were then removed with a small brush. Finally, the samples were washed with acetone once more before being weighed for the second time after the test.

2.4. Mechanical Testing

Radial force tests were performed using a force measurement system (FMS-500, Starrett, Athol, MA, USA) clipped to a Dacron strip, which was looped and tightened around the heart valve frame, as depicted in Figure 3B, to measure the required forces with the reduction of the diameter from 10 to 20% of its original diameter. To measure radial force, external circumferential pressure was applied on the outer surface of the valve while constraining the displacement of the lower surface of the valve. The pressure was multiplied by the surface area to calculate the radial force, and the change in diameter was used to calculate the diameter reduction %. The model was utilized to show the relationship between the valve diameter and the radial force. In addition, the model was used to predict the stress levels for the reduction ratio.

2.5. Computational Modeling

Finite element analysis (FEA) was utilized to predict the mechanical performance of the pediatric heart valve. The valve model was constructed as longitudinally repeated circumferential iron struts that were connected with nitinol connections. The 3D model of the valve was built using computer-aided design (SolidWorks, Waltham, MA, USA) and then imported into the Ansys software (Ansys, Canonsburg, PA, USA) for further computational analysis. A static structure module was employed to model and calculate the radial forces, stresses, and strains of the pediatric valve. The diameter of the valve was examined using 10, 12.5, and 15 mm while fixing the valve thickness to 0.2 mm. Figure 4A shows the structure of the pediatric valve, where the two materials were appropriately defined for the valve structure. In Figure 4B,C, the differences between connections made of nitinol and iron-based struts are, respectively, illustrated. The modeling of the nitinol behavior was conducted using the superelasticity built-in module in Ansys, where the material’s pseudoelasticity properties were adopted from Wu et al. The iron material model from the Ansys material library was exploited to model the struts [34].

2.6. Prototype Fabrication

Nitinol wires with different diameters were joined by a precision micro laser-welding system (LZR-100; Sunstone Engineering, Payson, UT, USA). Welding parameters were optimized to acquire the best material and mechanical properties of the structure for nitinol wires with various thicknesses. The laser process parameters were 1.4 KW power, 0.7 mm spot size, 1.2 ms time duration, 3Hz frequency, and rectangular wave. A machined aluminum mandrel based on the anatomy of the animal model was used to create the nitinol backbone with the desired cylindrical geometry, where the external diameter of the mandrel corresponded to the deployed device’s diameter. The mandrel diameter was oversized by 20% to produce the oversized stent backbone to achieve sufficient radial force for the device. The mandrel with the frame was heated up to 350–600 °C with a tube furnace (Lindberg/Blue M Moldatherm, Fisher Scientific, Pittsburgh, PA) for 30–40 min; then, the frame was rapidly cooled in water to 20 °C in 10 s (quenching). Thermal treatment was performed to set the final shape of the nitinol wires with the required superelastic properties, eliminating any potential local stress concentration caused by welding.
Figure 4. The 3D modeling of the pediatric heart valve: (A) valve’s struts linked with connections, (B) nitinol connections, and (C) iron-based struts.

2.7. Biocompatibility Studies

In vitro cell viability studies were designed and conducted using a typical cell culture method and MTS assay. Rat vascular smooth muscle cells (rSMCs) were cultured in Dulbecco’s modified Eagle medium (DMEM) with 10% heat-inactivated fetal bovine serum (HI-FBS) and 1% penicillin/streptomycin at 37 °C and 5% CO₂ [35]. Both the untreated and thermally treated iron wire samples were cultured for 3 days. Negative controls were also compared to determine the differences using the data normalization to the negative control including cultured cells in the medium. For the hemocompatibility studies, whole fresh ovine blood was collected and used under the approval of the Institutional Animal Care and Use Committee at the University of Pittsburgh. The collected blood was stored in a vacutainer tube (BD Vacutainer) and sterilized, and then incubated for 3 h at 37 °C in a hematology mixer (Fisher Scientific, Waltham, MA, USA) [36]. After 3 h, the samples were thoroughly rinsed with PBS solution 10 times, and then the deposited platelets on wires were qualitatively analyzed via scanning electron microscopy (SEM, JSM 6335F, JEOL, Tokyo, Japan).

3. Results

3.1. Degradation

Multiple wire samples were thermally treated at various combinations of treatment times and temperatures to investigate the effect of the iron oxide layer formation on the iron wires’ degradation. In addition, these samples were treated for three time periods to check the influence of the iron oxide layer thickness on the degradation rate of pure iron wires. All treated wires were typically compared with the original wire (i.e., with no treatment) with respect to the final diameter over several weeks of testing in PBS. When the samples were thermally treated at a temperature of 350 °C, as depicted in Figure 5A, the wire’s diameters increased with the increase in the treatment time before immersion testing due to the formation of an iron oxide layer. In this figure, at week zero, the wire diameter increased from 254 ± 1.23 μm for the untreated sample to 261 ± 0.89 μm after 4 h of heat treatment. The slope of the diameter reduction resulted in that of the 4 h treated samples being lower than that of the original one and the samples with a shorter treatment time, achieving a reasonable overall diameter of 241 ± 1.14 μm after 4 weeks of degradation testing.
3. Results

3.1. Degradation

Multiple wire samples were thermally treated at various combinations of treatment times and temperatures to investigate the effect of the iron oxide layer formation on the degradation rate of pure iron wires. As depicted in Figure 6A, the iron oxide layer with a bright glow only covers the right side of the wire, with a total diameter of 259.7 µm, while the dark iron wire with no oxide layer appears with a lower diameter of 253 µm on the left side of the image. Consistently, after two weeks of immersion testing, as shown in Figure 6B, the diameter over the wire’s length varied from 224.7 µm on the left to 249.6 µm on the right of the figure. Hence, the wire’s diameters collected from the SEM analysis were averaged for each sample due to the non-uniformity of the oxide layer over the length of the iron wires.

As in Figure 5B, the heat treatment temperature was increased to 450 °C, attaining a greater iron oxide layer thickness with a total wire diameter of 262 ± 1.04 µm for the 4 h heat-treated sample than the corresponding one under 350 °C heat treatment. The slope of the diameter reduction resulted in that of the 4 h treated sample being lower than that of the original one and the samples with a shorter treatment time, achieving a reasonable overall diameter of 242 ± 0.72 µm after 4 weeks of degradation testing. The lower slope of the diameter reduction indicates the superiority of heat treatment at different temperatures. Regarding the coated samples represented in Figure 5C, both dip and spray-dip-coated wires exhibited almost the same corrosion rate in terms of diameter reduction, but their slope of degradation was lower than the slope of thermally treated wires. In the fourth week, both coated samples showed a lower diameter reduction (diameter >250 µm), while all thermally treated wires were higher in corrosion with diameter (<250 µm).

As seen in Figure 6, when the wire samples were investigated using SEM, the diameter along the wire varied due to the non-regularity of the iron oxide layer along the wire length. As depicted in Figure 6A, the iron oxide layer with a bright glow only covers the right side of the wire, with a total diameter of 259.7 µm, while the dark iron wire with no oxide layer appears with a lower diameter of 253 µm on the left side of the image. Consistently, after two weeks of immersion testing, as shown in Figure 6B, the diameter over the wire’s length varied from 224.7 µm on the left to 249.6 µm on the right of the figure. Hence, the wire’s diameters collected from the SEM analysis were averaged for each sample due to the non-uniformity of the oxide layer over the length of the iron wires.

**Figure 5.** Iron wire diameter (µm) vs. the testing time (week): (A) heat-treated at 350 °C, (B) heat-treated at 450 °C, and (C) polymer-coated wire.

**Figure 6.** SEM imaging for the iron wire upon heat treatment at 450 °C: (A) for 4 h after the first week, and (B) for 3 h after the second week.
Since the wires were weighed before and after the immersion tests, another measure of degradation of body mass reduction was tracked and plotted, as in Figure 7. Both thermally treated samples at different temperatures showed the same corrosion trend as shown in Figure 7A,B. In both figures, the wire’s masses were increasing with the increase in the treatment time before the immersion test due to the formation of an iron oxide layer with no loss in corrosion products. Before testing, as in Figure 7A, the wire mass increased from 0.0161 ± 0.0075 g for untreated samples to 0.0186 ± 0.0037 g after 4 h of 350 °C heat treatment. The slope of the mass reduction resulted in that of the 4 h treated samples being lower than that of the original one and the samples with a shorter treatment time, achieving a final wire mass of 0.0136 ± 0.0054 g after 4 weeks of degradation testing. As seen in Figure 7B, the heat treatment temperature was increased to 450 °C, and the wires’ masses slightly increased compared to the values corresponding to the 350 °C heat treatment due to the greater iron oxide layer thickness. The wire mass increased to 0.0192 ± 0.0063 g for the 4 h heat-treated sample compared to the corresponding one under 350 °C heat treatment. The slope of the mass reduction resulted in that of the 4 h 450 °C thermally treated samples being lower than that of the original one and the samples with a shorter treatment time, achieving a reasonable overall mass of 0.0138 ± 0.0047 g after 4 weeks of degradation testing. The lower slope of the mass reduction indicates the superiority of heat treatment at different temperatures. Regarding the polymer-coated samples represented in Figure 7C, both dip and spray-dip-coated wires also exhibited very similar corrosion rates in terms of mass reduction to that in diameter reduction, but their slope of degradation was lower than the slope of thermally treated wires.

![Figure 7](image-url) The relationship between the iron wire mass (g) and the types of surface treatment over time (week): (A) heat-treated at 350 °C, (B) heat-treated at 450 °C, and (C) polymer-coated wire.

3.2. Biocompatibility Study Results

Figure 8 shows the biocompatibility study results on both the cytotoxicity (i.e., cell viability) and hemocompatibility of the thermally treated iron wires to assess basic biological interactions. The cell viability study was analyzed via methyltransferase (MTS) assays, as shown in Figure 8A, which demonstrated higher cell viability in the thermally treated iron wire compared to the untreated wire after 3 days of incubation in vitro. The thermally treated wires showed approximately 21% higher cell viability than the untreated wire samples. The representative SEM image shown in Figure 8B shows uniformly distributed cells on the surface of the iron wire. Another biocompatibility study to evaluate the implantable device focused on hemocompatibility. In this study, only a qualitative assessment was conducted to evaluate the surface to observe the thrombosis formation using SEM analysis.
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3.3. Prototype Fabrication

Figure 9A shows that the prototype pediatric valve frame consists of superelastic nitinol and biodegradable iron wires. The diameter is 15 mm and the length is 25 mm. Figure 1B shows three different segments of the nitinol–iron valve frame, which are the nitinol tube, iron wire, and “X”-shaped nitinol strut. This structure has been manufactured by (1) precision trimming of the “X”-shaped nitinol strut from a Neuroform stent (Stryker Corp., Fremont, CA, USA); (2) a superelastic thin-wall nitinol tube (0.006” inner diameter, Confluent Medical, Fremont, CA, USA) for joining two materials, and mechanical strengthening without creating severe deformation of the iron wire (125 µm thick, GoodFellow, Pittsburgh, PA, USA). A small amount of biocompatible polymer adhesive (Loctite 4902, Henkel Corp) was applied inside the nitinol tubes to tightly join both the nitinol strut and iron wire during the collapse and deployment procedure. An ultra-precision micro laser welding process was applied to create a solid joined structure via a localized metal melting process. Figure 9C shows the end section of the valve frame that required a “V”-shaped nitinol strut for the joining. A subsequent thermal annealing process was conducted under 350–600 °C for 30–40 min to release any potential stress concentration issue and to recover the superelasticity of the nitinol material. The fabricated frame was tested for radial strength exertion under varied diameter changes, which were compared with the computational modeling results to validate the device design.

3.4. Radial Strength Analysis and Experimental Validation

3.4.1. Computational Modeling Results of the Stress vs. Strain of the Valve Frame

The finite element model for the pediatric heart valve was built and utilized to estimate the stress caused at different sections of the valve. It was typically anticipated that the maximum stress in the proposed valve design would take place at the nitinol connections due to this being the location of the main deformation of the valve. As depicted in Figure 10A,B, the undeformed and the deformed shapes of the valve frames were observed, showing both the amount and shape of deformation that took place in the valve upon applying an external radial force. These figures show uniform valve deformation through the full length of the valve. The stresses caused in the structure of the valve after deformation were also calculated and are represented in Figure 10C, while the stresses inside the nitinol...
connections only are shown in Figure 10E. Figure 10D depicts that the maximum Von Mises stress occurred on the stent connections, with a maximum stress value equal to 552 MPa. In terms of strain values in the pediatric heart valve, Figure 10D,F show the Von Mises strain of the valve, whereas Figure 9E depicts the Von Mises strain in the whole valve, while Figure 10F depicts only the strain inside the nitinol connections. The maximum Von Mises strain inside the valve was 1.1%; however, the maximum Von Mises strain in nitinol was 0.9%.

Figure 9. Prototype valve frame and details: (A) entire valve frame, (B) the nitinol and iron wire integration using a thin-wall nitinol tube for the middle connection, and (C) the end section device details with “V”-shaped nitinol connection.

Figure 10. Stress and strain computational analysis of the pediatric valve: (A) undeformed valve shape, (B) deformed valve shape, (C) stress of the entire frame after deformation, (D) Von Mises strain in the frame after deformation, (E) stress of nitinol connection regions, and (F) Von Mises strain of nitinol connection regions.

3.4.2. Comparison of Computational Modeling and Experimental Results on Radial Strength

Upon solving the structural model of the heart valve, the radial forces were then computed with the advantage of the stress and strain results. The radial forces at multiple valve diameters of 10, 12.5, and 15 mm were solved to predict the effect of the designed
diameter on the radial force needed to deform the full structure. As shown in Figure 10A, the relationship between the radial force and diameter reduction % is composed of two segments: linear and non-linear segments. The first linear segment shows the reversible elastic deformation of the valve until it reaches a 10% diameter reduction, while the irreversible non-linear segment shows steady plastic deformation starting from 10% up to a +20% diameter reduction. In addition, the higher the valve diameter, the lower the radial forces that are required to crimp the valve to smaller diameters, and Figure 10A also depicts the radial force up to 30% diameter reduction. The maximum radial force for a 10 mm diameter is 6 N.

An experimental investigation was also performed to validate the computational simulation results for the radial forces required to collapse the valve up to various diameter reduction values (Figure 10B). Vertical forces were first collected at a sampling rate of 10 Hz, and then converted to circumferential averaged forces to plot the radial forces applied at various diameter reduction percentages. These depicted radial forces in Figure 11B also demonstrate the two successive linear and non-linear force–deformation segments, where the forces can be elastically reversible in the linear part and continue plastically after a 10% diameter reduction. The experimental test was performed up to a 20% diameter reduction to avoid the massive plastic deformation of the pediatric heart valve prototype, achieving 5 N as the maximum applied radial force.

![](https://example.com/figure11.png)

**Figure 11.** Computational (A) and experimental (B) results of the radial force (N) vs. diameter reduction (%) for the varied valve diameters.

### 4. Discussion

Despite the technological advancement in the area of endovascular devices, there are no appropriate heart valve devices available for pediatric patients who have congenital heart valve defects [37]. As the child grows, the implanted devices must be replaced often during growth. As a result, any percutaneous heart valve device technology that can avoid or eliminate repeated open surgery would provide a new therapeutic option for infants or children who have heart valve defects.

Vascular stents or percutaneous heart valves have offered an alternative to open surgical procedures including patients who are too weak or very young, who would be unsuitable for open operation [38]. In addition, a child will grow over time, so the endovascular device used in children must change its dimensions to accommodate the
anatomical size changes. A novel percutaneous heart valve frame studied here for pediatric patients allows partial biodegradation (>90%) for the device to change with the growth of the child. This new approach utilizes two novel metallic biomaterials, namely superelastic nitinol and biodegradable iron.

Iron degradation with surface treatments is one of the most important functions in the device. The iron materials used in our valve frame show an approximately 7%–10% diameter reduction per 4-week period in both thermally treated iron wires under two different temperature conditions, i.e., 350 and 450 °C (Figures 5–7). The polymer-coated iron wires showed slower degradation, with approximately 4% diameter reduction per 4 weeks. Therefore, 9–23 months are needed for the complete degradation of the wires. Considering a theoretical arterial vessel remodeling process period in the human vascular system of 6–12 months, the surface treatments shown in this study are valid and suitable for the required degradation period after the device’s implantation [39,40].

In addition to the iron degradation study, an in vitro biocompatibility study was conducted to assess the materials’ biological interaction, both quantitatively and qualitatively, using cell viability and hemocompatibility analyses. The thermally treated iron wire showed higher cell viability up to 21% compared to untreated samples, as shown Figure 8. This sample also shows qualitatively excellent hemocompatibility under an in vitro platelet adhesion study. There are limitations to the biocompatibility studies since only thermally treated wires were compared with untreated wire samples to assess cell viability, and only qualitative SEM-based analysis was used in the hemocompatibility evaluation. Although these study results show that the thermally treated iron wires are superior to untreated wires, a more detailed study including polymer-coated iron wires would be needed for diverse comparison studies in the future. In this work, the acute in vitro biocompatibility evaluation is important because any issues that may develop should be addressed prior to entering animal studies in the future.

The third fundamental study to develop a novel heart valve device is the design via computational modeling and subsequent mechanical testing [41,42]. Radial strength is one of the most important force values needed for self-expanding endovascular devices that contain superelastic nitinol [43]. Computational modeling and experimental test data, shown in Figures 9 and 10, have clearly demonstrated the optimized design and its validation through mechanical testing. The radial force exerted with 20% diameter reduction shows approximately 5 N both from computational and experimental results (Figure 10). It is challenging to compare the radial force of the newly developed nitinol–iron valve frame with commercial products, since there are no such devices available for pediatric patients. As a reference, commercial adult heart valve frames made of nitinol can be compared for validating the radial force produced in the experiment. Typical values of adult nitinol heart valve frames’ radial force are in a range between 9 and 54 N [44]. The Acurate neo S (ANS; Symetis, Switzerland) shows the smallest radial force, lower than 9N, but two other CoreValve devices (CV 23, CV26, Medtronic, Minneapolis, MN, USA) show higher forces with an increased deployed diameter [44]. This comparison study’s results show the relationship between the deployed diameter and radial force. The radial force is also dependent on the mesh geometry.

Once necessary fundamental studies were successfully conducted, a functional prototype was fabricated using various advanced manufacturing technologies, including a micro laser joining process [45–47]. As shown in Figure 9, a new joining process for constructing a heart valve frame was developed and optimized. Three typical endovascular device fabrication methods are (1) laser cutting of thin-wall metal tubes, (2) braiding thin metal wires, or (3) bending metal wires to the desired shape [48,49]. Since three different components were used to develop the new heart valve frame, none of these technologies could be used. Thus, a micro laser welding-based joining technique utilizing a thin-wall nitinol tube was selected as the best fabrication technique for the growing valve frame, minimizing the stress concentration and achieving durable connections for the three different materials.
5. Conclusions

In the present work, the development of a novel self-expanding biodegradable percutaneous heart valve frame for pediatric patients was conducted, which shows clinical significance. The new design of the heart valve frame employs two forms of metallic biomaterials, namely superelastic nitinol and biodegradable iron. The biodegradation of iron wires with varied surface treatment showed a gradual and stable diameter reduction of 7%–10% for 4-week blood-mimicking circulation tests. Polymer-coated wires show relatively slower degradation, showing approximately 4.69%–5.66% compared to the original wire diameter. The biodegradation of surface-modified iron struts allows the pediatric device to grow with the child with gradual degradation, and the superelastic nitinol connections offer a firm structure during delivery, deployment, and for the future tissue growth process. The device design was optimized both through computational modeling and experimental studies. The prototype valve frame has been successfully developed based on computational modeling, radial strength analysis, biodegradation, and acute in vitro biocompatibility studies. The radial force exerted with a 20% diameter reduction shows approximately 5 N both from computational and experimental results. The thermally treated iron wire showed higher cell viability up to 21% compared to untreated samples. This work has demonstrated the viability of employing nitinol–iron valve frames in children in vitro, showing potential as a new therapeutic option in children with congenital heart diseases.


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