Abstract  We previously reported the development of a new hybrid medical material comprising bio-based materials with high biocompatibility and artificial materials with characteristics of excellent strength and processability. This material shows sufficient biocompatibility and excellent stability in vivo. Moreover, when applied to the surface of an implantable sensor, the biological reaction on the sensor function surface can be well controlled. For commercialization and widespread use of hybrid materials with such superior properties, sterilization and storage are critical considerations, given that hybrid materials must be processed outside the body prior to application as medical materials in vivo, thus posing a risk of contamination despite best efforts. Therefore, the aim of the present study was to establish an optimal sterilization method that will not impair the biocompatibility of the hybrid material. Toward this end, we tested six sterilization methods for the hybrid material: autoclave (121°C, 20 min), dry heat (160°C, 120 min), ethylene oxide gas (37°C, 120 min), hydrogen peroxide plasma (45°C, 45 min), and gamma ray (25 kGy) with and without lyophilization. After sterilization, the material was cultured with vascular endothelial cells to evaluate the engraftment rate, and was observed with light and scanning electron microscopy to determine shape and structure changes. The results demonstrated that gamma sterilization without lyophilization was the best sterilization method for this material, which preserved the collagen network and showed no change in number of adhered vascular endothelial cells compared to the pre-sterilized material. These findings are useful to promote the commercialization of this hybrid material with combined advantages of synthetic and bio-based materials for widespread clinical application in the engineering of artificial organs.

Keywords: biocompatible material, artificial heart, sterilization, antithrombotic, inflammation.

1. Introduction
The main materials currently used for artificial organs are synthetic materials and biomaterials. Synthetic mate-
with artificial materials as scaffolds. A core, serving as a scaffold, is inserted into an external form or mold to effectively control the shape. The external mold and cores are then implanted subcutaneously, and are removed once the living tissue is induced. The core organized in the scaffold is removed from the body and decellularized to obtain the final material.

This integrated approach for the scaffold makes it possible to obtain biomaterials with good strength and durability (Fig. 1). In addition, we previously demonstrated that these hybrid materials exhibit excellent stability in vivo, and superior ability to control biological reactions when applied to the surface of an implantable sensor [14–17]. To further promote and market these hybrid materials with superior properties, it is necessary to consider critical aspects of their sterilization and storage. Currently, these hybrid materials have to be processed first outside the body for application as medical materials in vivo. Although all of these processes are operated under aseptic conditions, a completely aseptic environment cannot be achieved in practice. Thus, establishing a sterilization process is an essential requirement for commercial distribution of a medical material. Therefore, in the present study, we sought to establish an optimal sterilization method that will not impair the biocompatibility of the hybrid material.

2. Materials and Methods

2.1 Production of hybrid materials

The core scaffold was a polyester raised fiber that is used for the creation of artificial blood vessels, as reported previously [9, 10, 14]. The scaffold was processed into a circle with a diameter of 15 mm and thickness of 1 mm, which was used as the sample for sterilization (Fig. 2A). The scaffold has two surfaces: a surface with raised fibers and an unprocessed surface. One side of the surface of the scaffold is raised and has a high porosity. To control the shape of the living tissue emerging on the scaffold, an acrylic outer mold was prepared, and the scaffold was inserted into the mold. The outer mold was composed of an upper and a lower part with a thickness of 2 mm, length of 35 mm, and width of 35 mm. With this design, it is possible to incorporate four scaffolds into a single outer mold. Pores were made in the outer mold to allow cell induction, with five pores on each side of the scaffold (Fig. 2B). The prepared core was embedded subcutaneously in an adult goat (Japanese-Saanen goat, female, age 4 years, body weight 45 kg), and was left for 3 months to induce living tissue (Fig. 2C). The

![Fig. 1](image1.png)  
**Fig. 1** Design concept of the hybrid material.  
A: Polyester fabric scaffold, B: Acrylic outer mold, C: Implantation on the muscle, D: Removed core from the body, E: Decellularized core, F: Sterilization and storage, G: Clinical use and non-clinical study.

![Fig. 2](image2.png)  
**Fig. 2** Artificial material as a core of the hybrid material.  
A1: Scaffold made of polyester velor (raised functional surface (front side), A2: Woven back side, B1: External mold to determine the shape of the induced tissue, B2: Outer mold lid with tissue guiding hole, C: Implanted on the muscle (latissimus dorsi).
Ethics Committee of the University of Tokyo approved the animal experiments (P12-156).

Since the hybrid materials are intended for use in xenotransplantation and allotransplantation, when applied to a recipient, the material was decellularized to prevent immune rejection. Tissue-derived cores were exposed for 6 h in a 1.0% aqueous sodium dodecyl sulfate solution at 37°C. In addition, the cores were washed with saline for 3 days to complete preparation of the hybrid material for in vivo application (Fig. 3C). Figure 3B and D shows HE stained images of vertically sliced sections of the material. These images were observed near the front side of the material. The surface of the material has a high clearance rate of the scaffold material and a large proportion of the regenerated tissue. This material is intended for use with the surface in contact with blood or bio-tissue.

2.2 Sterilization methods
Since no sterilization method has yet been established for these novel hybrid materials, we tested several common sterilization methods to determine the most suitable method for this material.

The hybrid material was freeze-dried since the sample must be in a dry state for practical application of most sterilization methods. For this purpose, lyophilization was performed because it is desirable to maintain a stable long-term sterile condition while the sample is maintained in a dry state. The sample was cut into quarters, and each section was flash-frozen in liquid nitrogen and then lyophilized for 24 h using a lyophilizer (FDU-1200, EYELA, Japan). The lyophilized samples were then sterilized by five methods: autoclave, dry heat, ethylene oxide gas, hydrogen peroxide gas plasma, and gamma ray. In addition, another sample was prepared by gamma-ray sterilization of the material in physiological saline without freeze-drying. Thus, a total of six types of samples were produced. Each sterilization method was performed using the standard protocol, and the conditions are summarized in Table 1.

2.2.1 Verification of sterilization
To verify the effects of various methods of sterilization, the samples were checked by viable count methods [18]. Sterilized samples were homogenized in sterilized water, diluted 10-fold, and applied to an agar medium. The number of colonies was counted after culturing in an in-

| Method                        | Abbreviation | Mechanism | Conditions     | Equipment                          |
|-------------------------------|--------------|-----------|----------------|------------------------------------|
| Autoclave                     | AC           | High-pressure steam | 121°C, 20 min | TA33E, TOHO, Japan                 |
| Dry heat                      | DH           | Heat      | 160°C, 120 min | SH62, Yamato Scientific, Japan     |
| Ethylene oxide gas            | EO           | Chemical  | 37°C, 11 h     | SA-N540, Canon, Japan              |
| Hydrogen peroxide gas plasma  | GP           | Chemical  | 45°C, 45 min   | STERRAD50, APS Japan, Japan        |
| Gamma ray with freeze-drying  | GD           | Ionizing radiation | 25 kGy       | Koga isotope (Outsourcing)         |
| Gamma ray without freeze-drying | GW         | Ionizing radiation | 25 kGy, Saline| Koga isotope (Outsourcing)         |

Fig. 3 Removed core and decellularized material.
A: Enriched blood vessels and tissues were induced into the scaffold, B: Tissue image of the core with many nuclei (HE staining), C: Completed hybrid material after decellularization, D: Hybrid material with only collagen and remaining scaffold (HE staining).
2.3 Evaluation of the negative effects of sterilization
To compare the effects of the various sterilization methods, we assessed the adverse effects of sterilization in terms of changes in shape, structure, and cell adhesion of the hybrid material before and after sterilization.

2.3.1 Evaluation of structural changes by light and electron microscopy
The sterilized samples were observed with a light stereo-microscope (SZ61, Olympus, Japan) and scanning electron microscope (SEM; S-2250N, Hitachi, Japan). The sample was coated with platinum Pt (Pt + Pd) using ion sputtering for SEM observation at an acceleration voltage of 20 kV and a current of 120 μA.

2.3.2 Adhesion of vascular endothelial cells
When a hybrid material is applied to the blood contact surface, it is recellularized by recipient cells and exhibits high antithrombotic properties. Therefore, the cell viability of the material was assessed by culturing with bovine-derived vascular endothelial cells (BAE-1) to assess the effects of sterilization on cell adhesion. After sterilization, 150 μL of a cell suspension (2.5 × 10^6 cells/mL) was added to the sample and placed in a 5% CO₂ incubator (BNA-11, ESPEC, Japan) at 37°C for 5 days. After culture, tissue staining was performed to count the number of adhering cells.

2.4 Histological evaluation
To confirm the cell adhesion ability, hematoxylin and eosin (HE) staining was performed to observe the process of cellularization and decellularization. The samples were fixed in 10% buffered formalin solution for 24 h. Fluorescent staining was performed to visualize the living cells. For this purpose, we added 1 μL of 4',6-diamidino-2-phenylindole dihydrochloride (DAPI) solution (Dojin Chemical, Japan) to 2 mL of 0.3% Triton™ X-100 (Sigma-Aldrich, Japan) solution. The samples were infiltrated with this solution for 5 min. The samples were then observed with a fluorescence microscope (BZ-9000, KEYENCE, Japan), and the numbers of viable cells were counted.

2.5 Statistical analysis
Differences in number of cells among the seven samples were assessed using one-way analysis of variance (ANOVA) and Tukey’s multiple comparisons (p < 0.01). All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (the R Foundation for Statistical Computing) [19].

3. Results

3.1 Verification of sterilization
The results of verification of sterilization are shown in Fig. 5. Many colonies were found in the non-sterile hybrid material used as a control sample. No colonies were found in all samples sterilized by the six methods.

3.2 Effects of sterilization on structural changes
The changes in shape of the materials after sterilization are shown in Fig. 4. With autoclaving, the material surface turned brown and shrank. In particular, extensive contraction was observed on the raised surface side, where many living tissues are present. SEM images showed some portions with a clear network structure, and the collagen fiber diameter of the tissue increased markedly. After dry heat sterilization, the sample surface turned slightly brown. SEM observation demonstrated a network structure and a uniform surface structure without gaps. Moreover, the fiber diameter of the pores was essentially maintained. Ethylene oxide gas sterilization did not result in any discoloration or deformation of the sample, and SEM observation showed a network structure with the same thin fiber diameter as that observed before sterilization. After hydrogen peroxide gas plasma sterilization, the raised surface with many biological tissues became rounded and shrunk, and the raised surface side was very fragile. SEM observation showed only a few portions in which the network structure could be confirmed, and the fiber diameter increased. No discoloration or deformation was observed after gamma sterilization with freeze-drying and without freeze-drying. Moreover, SEM observation showed a network structure with the same fine fiber diameter as that before gamma sterilization with freeze-drying.

Fig. 5 Verification of sterilization.
Control, No sterilization; AC, autoclave sterilization; DH, dry heat sterilization; EO, ethylene oxide gas sterilization; GP, hydrogen peroxide gas plasma sterilization; GD, gamma-ray sterilization with freeze-drying; GW, gamma-ray sterilization without freeze-drying.
Figure 6 shows the results of culturing vascular endothelial cells on the samples after sterilization. The HE-stained vertical sections in the left column show the structural changes of the samples. Compared to Control and GW, the other samples were stained with eosin that binds to positively charged proteins. In particular, AC had a thick eosin area and was stained strongly, showing strong protein aggregation. In DH, the result of HE staining (Fig. 6) and SEM (Fig. 4) showed a greatly enlarged spaces, and the structure changed to an unstable state. GP changed to a rough surface with a fuzzy collagen surface. When GD and GW were compared, GD had larger pores and larger fiber diameter. GW showed no significant difference from Control.

3.3 Cell adhesion test by culture of vascular endothelial cells

The results after culturing the cells for 5 days on the materials after sterilization are shown in Fig. 6. The left column shows HE-stained vertical sections of the samples, with the nuclei of the cultured cells stained deep purple. The right column shows the DAPI-stain viable cells (white dots) observed under fluorescence microscopy. The number of cells per unit area is shown in Fig. 7.

In both the control (non-sterilized hybrid material) and gamma ray-sterilized samples, cells were found on the entire surface of the material, with no significant difference in cell numbers (p > 0.9). For all other sterilization methods, the cells were sparsely distributed and almost no nuclei were observed in the vertical sections (Figs. 6, 7). There was a significant difference in cell numbers among AC, DH, EO, GP, GD (methods with lyophilization) and GW (gamma-ray without lyophilization) groups (ANOVA, p < 0.01). There was no significant difference among AC, DH, EO, GP, and GD groups (p > 0.01).

4. Discussion

This exploratory study demonstrated the most suitable method for sterilizing hybrid materials (composed of bio-based and synthetic materials) for ultimate application as artificial organs, by comparing several commonly used sterilization methods. Since many of these conventional methods were originally developed for sterilizing metal-based medical instruments, adverse effects of protein denaturation were observed in the hybrid materials after sterilization. In particular, deformation of the autoclaved and dry heat-sterilized samples was caused by the effects of pressure and heat. This occurred because most of the hybrid materials are composed of collagen proteins that readily deform upon heating [20].

In this study, the samples were lyophilized as a pre-treatment for sterilization. When protein is in a dry state, the energy is relatively thermodynamically low, and heat would have less effect compared with a saline-based material [21–24]. Since the extent of denaturation of a protein in the dry state is unclear for these hybrid materials, heating was carried out at 120°C in an autoclave and at 160°C in dry heat sterilization. As a result, the sample shrank and deformation of the collagen network was observed. Light microscope and SEM observations showed that the autoclaved sample was more deformed than the
This result is considered to reflect the effect of high pressure.

In ethylene oxide gas sterilization, an irreversible reaction is caused by substituting the hydrogen atoms of amino groups (-NH₂), hydroxyl groups (-OH), and thiol groups (-SH) in microorganisms with alkyl groups. Since the hybrid material is also considered to contain a hydroxyl group, it is likely that the structure would be changed by performing ethylene oxide gas sterilization [25–27]. Although we did not perform chemical analysis, no apparent structural destruction or change was observed when comparing the pre- and post-sterilized samples, at least by SEM observation.

The structural change of the sample subjected to hydrogen oxide gas plasma sterilization is probably due to the action of free radicals. Hydrogen peroxide low-temperature plasma sterilization has a combined bactericidal effect from the vaporized hydrogen peroxide itself along with a killing effect from the various active free radical substances that are generated by bringing the hydrogen peroxide into a plasma state at low temperature. Indeed, this is a common sterilization method that kills microorganisms. By irradiating with high-frequency energy, hydrogen peroxide is plasmainized, and the released electrons produce hydroxyl and hydroperoxyl radicals, which are highly reactive free radicals and oxidizing agents; the former react with all biological substances such as carbohydrates, proteins, and lipids. Consequently, DNA and
RNA of microorganisms are damaged to achieve a sterilized state [28–30]. However, almost 50% of the composition of the hybrid materials are proteins that will also be damaged as part of the mechanism of microbial sterilization, which explains why the sample shrank and became very fragile. In addition, the hybrid material had a porous structure, facilitating adsorption of hydrogen peroxide that penetrated the material. Collectively, these phenomena resulted in a change in shape of the material following sterilization.

By contrast, gamma-ray sterilization breaks the chemical bonds in a molecule by the ionizing energy generated from applying radiation to a substance. The active species generated outside the cell then invade the cell and combine with the active species generated inside the cell. By damaging the DNA molecules, they stop the cell proliferation, leading to cell death [31–33]. While damaging the bacteria on the hybrid material, it is possible that the gamma rays also cause a change in the structure of the hybrid material itself. Despite the lack of chemical analysis, no such apparent structural destruction or change was observed in the pre- and post-sterilized samples, at least by SEM observation.

Overall, for long-term storage, it is more desirable to store hybrid materials in a dry state than using storage methods that require liquids such as saline. However, comparing the results of gamma ray sterilization with and without lyophilization, we found that lyophilization should be avoided when sterilizing this material.

This paper focuses on the biocompatibility of hybrid materials by sterilization, but the changes in mechanical strength of the hybrid materials by sterilization are not clear. Gamma sterilization (25 kGy) has been reported not to change the structure of polyester [34]. Hara et al. [35] and Bessho et al. [36] reported that the degradation and cross-linking of collagen and gelatin occurred simultaneously by irradiation with gamma rays. They also reported that collagen was degraded when heat treatment was performed before gamma irradiation [35, 37]. Depending on the pH of the liquid to be stored, cross-linking of collagen changes after gamma sterilization [38]. The effect of sterilization on polyester fabric is considered to be sufficiently small compared to living tissue [39]. On the other hand, heat and gas produced by general sterilization methods have an effect on polymer materials [40]. Sterilization obviously affects macromolecules and living tissues, but the magnitude of negative effects depends on conditions such as dose, temperature, and pH. Therefore, the change in mechanical strength by sterilization requires further study. In addition, to determine specific sterilization conditions, it is necessary to evaluate effectiveness by animal experiments.

None of the sterilized samples showed culture growth on an agar medium, demonstrating the overall success of each of the sterilization methods tested.

5. Conclusion

We explored the optimal sterilization method that does not compromise the biocompatibility of a hybrid material by investigating morphological changes and cell adhesion. Although lyophilization is generally considered to be effective for sterilization and storage, this treatment negatively affected cell adhesion to the hybrid material. Based on these results, gamma sterilization without lyophilization appears to be the most suitable sterilization method for hybrid materials, which can promote their clinical application and marketability.

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