Construction of arteriovenous circulation system to gain of the close feeling to insert a catheter into human vessel

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Abstract We first developed a model of the normal human left heart and simulated blood and clarified the relationship between catheter insertion load and temperature in the coronary artery. The close feeling to insert a catheter into human vessels could be reproduced for medical staff. We also developed an arteriovenous circulation simulator (AVCS), simulating the normal heart and blood vessels, reproduced hemodynamics and simulated angiography and catheterization procedures. Using an auxiliary artificial heart, simulated blood was circulated through AVCS and blood pressure was set to 120/72 mmHg of peripheral vascular resistance by a pressure gradient regulator. Because the increase in contrast agent volume in the circulation fluid of AVCS affects X-ray fluoroscopy, we also developed methods for neutralization and removal of ionic contrast agents. The developed AVCS enabled to simulate following procedures: Guiding catheterization; directional coronary atherectomy (DCA); balloon catheterization; and stent delivery system introduction.

Keywords simulator, catheterization, coronary artery, training, frictional resistance, simulated blood

1. Introduction

Various devices have been developed for the endovascular treatment of lesions in the whole body, such as the heart, arms, neck, chest, abdomen, and femur. Spread of such devices requires off-the-job training of medical staff to cultivate their knowledge and operational feeling of the device. Device developing companies also need a simulator for the assessment of performance of devices by medical staff and developers.

Partly due to stagnant development of lesion models and circulation model simulators for reproducing the human body, many studies reported on the evaluation and simulation of endovascular treatment in animals such as pigs and rabbits [1–7]. It is also urgent to develop human circulation model simulators that do not need animal from the bioethical viewpoint. Recently, studies on virtual reality simulation have been reported [8–10], but it cannot reproduce the catheter insertion feeling or the sense of insertion length. Past studies on simulators have reported vascular models simulating the coronary artery, arteriovenous circulation in the arm, or a coronary circulation simulator for children [11–15]. Although these models reproduced blood circulation and hemodynamics in the arm or heart, they did not function for the practice of endovascular catheterization by medical staff or for the evaluation of an endovascular therapeutic device. In fact, there is a problem of large frictional resistance when inserting a catheter into the plastic model of the heart/blood vessels and is no heart-beating. Furthermore, there have been no research reports that simulator enables medical staff and developers to gain of the close feeling to insert a catheter into human vessels.

The objective of this study is thus to develop simulated blood for reducing the frictional resistance and an arteriovenous circulation system driven by an auxiliary artificial heart [16] that enables medical staff and developers to gain of the close feeling to insert a catheter into human vessels and that enables medical staff to simulate catheterization and evaluate endovascular treatment device.
2. Materials and Methods

2.1 Preparation of a model of the left main heart and simulated blood, and measurement of catheter insertion load into the heart model

First, we prepared a test model (Nipro-Goodman) of the left main heart to clarify the relationship between temperature and load at catheter insertion into the coronary artery. There was a problem of large frictional resistance when inserting a catheter into the plastic model of the heart. We developed simulated blood to add catheter slipperiness and viscosity which enabled us to simulate catheterization. The simulated blood contained 0.05 mM trimethylstearyl ammonium chloride (TAC) (Wako Pure Chemical Industries, Ltd), 0.05 mM tetradeyl dimethyl(3-sulfopropyl)-ammonium hydroxide inner salt (TDS) (Tokyo Chemical Industry, Co Ltd), 0.05 mM polyoxyethyl sorbitan monolaurate (T20) (Tween 20, Yoneyama Yakuhin Kogyo Co., Ltd), and 0.61% (W/W) magnesium chloride hexahydrate (MgCl₂, Wako Pure Chemical Industries, Ltd) as active components. Glycerol (Yoneyama Yakuhin Kogyo Co., Ltd) was added at the concentration of 20% (w/w) to adjust the viscosity to that of actual blood as described at a Japanese Patent Gazette (Tokkai 2013-235094, 20 wt% glycerol: 1.047 g/m³). The viscosity at each temperature (15–37°C) of simulated blood was measured by MARS III Rheometer (Thermo Fisher Scientific) with a temperature controller, and insertion load of a balloon catheter was measured at each temperature by load measurement equipment (Machine Solutions Company). A guiding catheter (Profit-plus, JL-7Fr, Goodman) was engaged at the left coronary artery ostium via a femoral approach. The balloon catheter was then inserted into the artery, and the insertion load measured when the catheter reached at the site of 7 cm distant from the ostium. The insertion depth was set to 7 cm because the distance from the ostium to the end of the artery was 14.7 cm, and the diameter decreased toward the end up to 1 mm.

2.2 Arteriovenous circulation system construction, hemodynamics reproduction and coronary artery angiography simulation

An arteriovenous circulation system (AVCS) that allowed catheter-based endovascular treatment via femoral, radial and brachial approaches was prepared. The system comprised a heart model (Nipro-Goodman), an arteriovenous model (Nipro-Goodman), a peripheral vascular resistance regulator with a simulated blood reservoir (Nipro), a circulation pump (VAD, Nipro) and a blood flow regulation program (Nipro).

In AVCS, hemodynamics was reproduced by circulating the simulated blood (0.05 mM TAC, 0.05 mM TDS, 0.05 mM T20, 0.61% (W/W) MgCl₂ and 20% (W/W) glycerol) with similar viscosity to that of actual blood. The pressure gradient in peripheral vessels was reproduced by distributing the pressure of the blood pumped to the arteries using the peripheral vascular resistance regulator. Simulated blood pressure was measured at a pulse rate of 60 bpm using a sphygmomanometer (Bedside Monitor BSR-6000, Japan Photoelectric) and a blood pressure transducer (pressure monitoring tube set, 51-001 Logical MX9604J, Nipro).

Then, the simulated blood was circulated at a pressure of 120/80 mmHg to perform the simulation of angiography. An introducer sheath (7Fr, Goodman) was inserted into the femoral artery. Then, using a guide wire (0.035 inch, Goodman) and a guiding catheter (7Fr, Profit-JL/-JR, Goodman), Profit-JL/-JR was fixed at the ostium of the left or right coronary artery. After installing a Y connector (Goodman) to Profit, angiography of the left and right coronary arteries was conducted using an ionic contrast agent (Hexabrix, serial No 15HJ031, Guerbet LLC).

2.3 Derivation of neutralization condition of contrast agent

Diluted solutions (×1, ×5 and ×10) of the ionic contrast agent were prepared, and the radiopaque of each solution was examined. After the simulation of angiography in AVCS mentioned above, the contrast agent could be neutralized and removed from the simulated blood by adding acid (ex. hydrochloric acid) at 1:1 molar ratio at room temperature to precipitate the contrast agent as white precipitate and by filtering it through a filter paper. The radiopaque of the filtrate was checked.

2.4 Simulation of catheterization in AVCS

In simulated catheterization, catheterization feeling was evaluated by the sensation in the hand of an operator. First, the reproducibility of hand sensation was assessed in 8 developers who performed the insertion into artery of AVCS through femoral/radial approach using guidewire (0.014/0.035 inch) and guiding catheter (5/6/7 Fr). Subsequently, sensory evaluation of catheterization in artery of AVCS was performed by a cardiovascular physician to bring the feeling closer to that in the human artery.

Catheter operability in AVCS was examined by inserting guiding catheters (7Fr/8Fr, Profit/Roadmaster, Goodman), DCA catheters (ϕ3.5–3.9 mm, Nipro) and balloon catheters (NSE alpha, ϕ3.00 × 13 mm, Goodman) [17,18] and stent delivery system (Vival stent, ϕ3.50 × 15 mm, Goodman) into the left coronary artery. We used guidewires (0.014/0.035 inch),
Y connectors and inflation devices manufactured by Goodman.

3. Results

3.1 Preparation of a left main heart model and simulated blood, and measurement of catheter insertion load into the heart model

The left main heart model prepared is shown in Fig. 1. Catheter insertion was found difficult due to large friction resistance between the base of the arteriovenous model and catheter. To reduce friction resistance, aqueous solutions containing various reagents were prepared and tested the increase of catheter slipperiness. As the results, the simulated blood (0.05 mM TAC, 0.05 mM TDS, 0.05 mM T20, 0.61% (W/W) MgCl₂ and 20% (W/W) glycerol) mentioned above (2.1 of Materials and Methods) could be developed.

The heart model prepared was immersed in the simulated blood, the fluid temperature was changed to 15, 20, 22, 25, 30, 35, and 37°C, and the insertion load of a balloon catheter into the left main coronary artery was measured at each temperature by developer (n = 3). The plot between insertion load and temperature showed lowest mean insertion loads at fluid temperatures of 25–37°C (Fig. 2).

Measured values of viscosity (Pa·s) of the aqueous lubricating solutions were 0.009, 0.01 and 0.009 at 25, 30, and 37°C, respectively, and 0.012 and 0.013 at 15 and 22°C, respectively (n = 2). The relationships between temperature of the simulated blood, viscosity and mean catheter insertion load are shown in Fig. 3.

3.2 Arteriovenous circulation system construction, hemodynamics reproduction and coronary artery angiography simulation

We constructed an AVCS which enabled us to simulate coronary angiography and various catheter approaches and to reproduce arteriovenous circulation hemodynamics (Fig. 4A). Simulated blood circuit and catheter approach sites are shown in Fig. 4B.

Under conditions at room temperature where catheter insertion load was lowest, blood pressure was reproduced, and coronary angiography and catheter insertion were simulated (Fig. 5).

By setting pulse rate of the axillary artificial heart at 60 bpm, simulated blood pressure could be controlled at 120/72 mmHg (Fig. 5A: typical example).

To simulate angiography in AVCS, the simulated blood was circulated at the pressure of 120/80 mmHg. After engaging a guiding catheter at the ostium of the left coronary artery, angiography was carried out with an ionic contrast agent (Fig. 5B: typical example). Then, right coronary angiography was carried out after engaging another guiding catheter.
catheter at the ostium of the artery with the ionic contrast agent. As shown in Fig. 5B, blood vessel area in the heart was clearly visualized in the simulated angiography by cardiovascular physician.

3.3 Derivation of neutralization condition of contrast agent

To investigate the neutralization condition of the ionic contrast agent, its diluted solutions (∗1, ∗5 and ∗10) were prepared, and the radiopaque of each solution was examined (Fig. 6A).

Fig. 2 Catheter insertion load into the left main coronary artery and temperature of simulated blood. Fig. 2 shows typical example of insertion load of a balloon catheter (NSE alpha, ϕ2.25 × 13 mm, Goodman) into the coronary artery of the left main heart model (Fig. 1D) immersed in simulated blood at 15, 20, 22, 25, 30, 35, and 37°C (n = 3).

Fig. 3 Measurements of viscosity of simulated blood and relationships between mean load and viscosity at each temperature. Fig. 3 shows the mean values of mean load with a standard deviation (n = 3) and those of viscosity of simulated blood (n = 2). The viscosity of simulated blood was measured through MARS III Rheometer (Thermo Fisher Scientific) with a temperature control chamber including Liquid N₂. The rheological properties measurement parameters are following; measuring mode (rotating), plate gap (1.000 mm), plate rotating velocity (γ = 0.03491 (1/s) to 1,571 (1/s) increasing at 30 steps to the end).
Fig. 4 Construction of an AVCS. A, Entire view of AVCS, B: Heart model (Nipro-Goodman), C: Peripheral vascular resistance regulator with simulated blood reservoir (Nipro), D: Circulation pump (Nipro), E: Pump control program (Nipro), and F: Simulated blood circuit and catheter approach sites.
Fig. 5 Blood pressure reproduction and coronary angiography in AVCS. A: Picture showing the control blood pressure at 120/72 mmHg, B: Pictures showing angiography of the left (left) and right (right) coronary arteries. The contrast agent was mixed with water at 1:1.

Fig. 6 Development of method for neutralization and removal method of contrast agent. A: Radioscopic images of diluted solutions (×1 (undiluted), ×5 and ×10) of ionic contrast agent (Hexabrix, Guerbet), B: White precipitation of the agent by hydrochloric acid addition, C: Filtration and removal of the precipitate, D: Radioscopic image of the filtrate after neutralization and removal of the contrast agent.
After the simulation of angiography in the AVCS, hydrochloric acid was added to precipitate the contrast agent and remove it (Fig. 6B). After that, the contrast agent could be removed by filtering the precipitate (Fig. 5C) from the simulated blood (Fig. 6D).

### 3.4 Simulation of catheterization in AVCS

To assess the influence of a side hole of a guiding catheter on radiopaque, angiography was conducted by fixing a guiding catheter with or without a hole at the ostium of the left coronary artery and injecting contrast agent. The result demonstrated that side hole improved radiopaque of a spherical part of coronary artery (Fig. 7A).

In plaque excision using DCA, the housing (where cutter is housed) of DCA should be pressed (via inflation of the balloon) to the plaque. Training is required for the operation.

In AVCS, a guiding catheter was engaged to the ostium of the left coronary artery, a DCA was inserted into the artery, and the deliverability was checked by cardiovascular physician (Fig. 7B). Then, the position was confirmed by X-ray fluoroscopy to adjust the direction of the housing.

The deliverability and extractability of a balloon catheter at the insertion site were examined by cardiovascular physician (Fig. 7C). No big trouble was found in delivery and removal of NSE alpha.

A stent delivery system was inserted into the left coronary artery to examine its deliverability and to simulate stent placement (Fig. 7D), and confirmed the absence of any big trouble in system delivery or stent implantation by cardiovascular physician.

Ischemic lesions in the coronary artery include vasoconstriction and thromboembolism, for example. Balloon catheters and stents mentioned above are used for the treatment of vasoconstriction.

### 4. Discussion

**Preparation of simulated blood to reduce friction at catheter insertion and quantification of catheter insertion load**

It was necessary to reduce friction resistance between catheter and the base of the arteriovenous model to simulate catheterization in the AVCS. It was also considered necessary to prevent bacterial growth because it was concerned in the circulating fluid.

Therefore, we examined various surfactants that were likely to add lubricity. Resultingly, we prepared the simulated blood consisting of trimethyl stearyl ammonium chloride (a cationic surfactant), tetradecyl dimethyl-(3-sulfopropyl)-ammonium hydroxide inner salt (an amphoteric surfactant), and polyoxyethyl sorbitan monolaurate (Tween) (a nonionic surfactant) as principal ingredients. The three components provided lubricity even in aqueous solution undergoing pH changes. We confirmed no bacterial growth in the simulated blood at room temperature over one year (in house data). In catheterization in AVCS, the simulated blood prepared markedly reduced the friction resistance between catheter and the base of the arteriovenous model, so that we are able to realize smooth catheter insertion feeling.

A document in Japanese Patent Gazette (Tokkai 2013-235094) reported the use of water-soluble polyhydric alcohol for adjusting the viscosity of simulated blood for flow phantom of diagnostic ultrasound equipment, and mentioned that the viscosity of glycerol solution approached to that of blood at 25°C. Therefore, we adjusted the viscosity of the simulated blood developed to the actual blood viscosity by adding water-soluble polyhydric alcohol (ex. glycerol) and measured its viscosity. The Newtonian fluid viscosity (in Pa*s) of the simulated blood was 0.009, 0.01 and 0.009 at 25, 30, and 37°C, respectively, and 0.012 and 0.013 at 15 and 22°C, respectively. Finally, the feeling of catheter insertion was evaluated by medical staff and was found to be like that of catheterization into human blood vessels. Further study is needed to repeat the number of trials regarding measurements of viscosity of the simulated blood and mean load of a catheter insertion (ex. Fig. 3).

As shown in Fig. 2 and Fig. 3, catheter insertion load was found to change by the temperature of filling fluid, suggesting its relationship to the change in viscosity of the fluid. Further investigation is needed to quantify the catheter insertion feeling of medical staff, which will serve as evaluation standards for research and development of endovascular treatment devices.

**Derivation of neutralization condition of contrast agent**

Adsorptive removal of nonionic contrast agents using a domestic dialyzer has been published in its package insert. However, no study has been reported on neutralization and removal of contrast agents.

We focused on the fact that the ionic contrast agent (Hexabrix) [19] was alkaline and hypothesized that it could be neutralized by adding acidic solution. As predicted, addition of acidic solution to the ionic contrast agent formed white precipitates. We showed that the agent can be filtered and removed (Fig. 6). Methods of neutralizing and removing ionic contrast agents have not been reported. A neutralization and removal system can be constructed by applying our method in, for example, circulatory simulators that use a large amount of contrast agent. We will further continue study.

**Simulating catheterization in AVCS**

The AVCS constructed in this study enabled the simulation of catheterization including insertion of sheath and wire, operation of guiding, DCA, balloon catheters and introduc-
Fig. 7 Assessment of effect of a side hole on guiding catheter and operability simulation of DCA, balloon and stent delivery system. A: Left coronary angiography using Profit (JL, 7Fr) with or without side hole (−)/(+). The contrast agent was mixed with water at 1:1. B: Simulation of DCA catheter (ϕ3.5–3.9 mm, Nipro) insertion after engaging Roadmaster (8Fr, Goodman) to the left coronary artery. C: Insertion of NSE alpha balloon (ϕ3.00 × 13 mm, Goodman) into the left coronary artery and balloon inflation (6 atm) and deflation. D: Insertion of Vival stent (ϕ3.50 × 15 mm, Goodman) into the left coronary artery and balloon inflation (10 atm) and deflation (stent implantation).
tion of stent delivery system. However, the simulator was modeled based on CT data of the normal human heart and blood vessels. Therefore, construction of a system corresponding to diverse lesion models such as abnormal vessel alignment, stenosis and calcified lesion is a future issue.

5. Conclusion

We firstly constructed left main heart model and developed simulated blood to evaluate relationship between load value of catheter insertion and viscosity of simulated blood at each temperature. The simulated blood developed markedly reduced the friction resistance between catheter and the base of the arteriovenous model enabling simulation of catheterization and endovascular treatment device evaluation.

Furthermore, we constructed AVCS that gave the catheter insertion feeling like that of human blood vessel and reproduced human hemodynamics. Finally, cardiovascular physician confirmed the close feeling to insert a catheter into human vessel using simulated blood and AVCS.

On the other hand, we found the neutralization condition of ionic contrast agents and developed the method for neutralizing and removing contrast agents in circulation fluid. Its uses in AVCSs by medical staff and developers in catheterization simulation and as a device evaluation system are expected.

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References

1. Waksman R, Lipinski MJ, Acampado E, Cheng Q, Adams L, Torii S, Gai J, Torguson R, Hellingsa DM, Westmany PC, Joner M, Zumstein P, Kolodgie FD, Virmani R. Comparison of acute thrombogenicity for metallic and polymeric bioabsorbable scaffolds: magmaris versus absorb in a porcine arteriovenous shunt model. Circ Cardiovasc Interv 2017. 10(8), pii: e004762.
2. Waksman R, Zumstein P, Pritsch M, Wittchow E, Haude M, Lapointe-Corriveau C, Leclerc G, Joner M. Second-generation magnesium scaffold Magmaris: device design and preclinical evaluation in a porcine coronary artery model. EuroIntervention. 2017; 13(4): 440–9.
3. Cheng Y, Shibuya M, McGregor J, Conditt GB, Yi GH, Kaluza GL, Gray W, Doshi M, Sojitra P, Granada JF. Biological effect on restenosis and vascular healing of encapsulated paclitaxel nanocrystals delivered via coated balloon technology in the familial hypercholesterolaemic swine model of in-stent restenosis. EuroIntervention. 2016; 12(9): 1164–73.
4. Nakazawa G, Torii S, Iijichi T, Nagamatsu H, Ohno Y, Kurata F, Yoshikawa A, Nakano M, Shinozaki N, Yoshimachi F, Ikari Y. Comparison of vascular responses following new-generation biodegradable and durable polymer-based drug-eluting stent implantation in an atherosclerotic rabbit iliac artery model. J Am Heart Assoc. 2016; 5(10): pii: e003803.
5. Nakazawa G, Shinke T, Iijichi T, Matsumoto D, Otake H, Torii S, Hiranuma N, Ohsume T, Otsuka F, Shite J, Hirata K, Ikari Y. Comparison of vascular response between durable and biodegradable polymer-based drug-eluting stents in a porcine coronary artery model. EuroIntervention. 2014; 10(6): 717–23.
6. Kinoshita Y, Kashima Y, Suzuki T. Directional coronary atherectomy—experimental use of single-blade cutting balloon. J Invasive Cardiol. 2006; 18(9): 428–31.
7. Ruitter MS, Doornbos A, de Waard V, Attevet NJ, Steendam R, de Vries CJ. Long-term effect of stents eluting 6-mercaptopurine in porcine coronary arteries. J Negat Results Biomed. 2016; 15(1): 20.
8. Przemyslaw K, Ruth JW, Fernando B. VCSSim3: VR simulator for cardiovascular interventions. Int J CARS 2017. doi10.1007/s11548-017-1679-1.
9. Saratzi A, Calderbank T, Siodoff D, Bown MJ, Davies RS. Role of simulation in endovascular aneurysm repair (EVAR) training: a preliminary study. Eur J Vasc Endovasc Surg. 2017; 53(2): 193–8.
10. Shiliote KE, Ganesan P, Salmin AJ, Cherry EM, Pertsov AM, Ghoraanii A. Catheter simulator software tool to generate electrograms of any multi-polar diagnostic catheter from 3D atrial tissue. Conf Proc IEEE Eng Med Biol Soc; 2016. p. 2741–4.
11. Fresiello L, Ferrari G, Di Molfetta A, Zielinski K, Tzallas A, Jacobs S, Darowski M, Kozarski M, Meyns B, Katertsisid NS, Karvounis EC, Tsipouras MG, Trivolla MG. A cardiovascular simulator tailored for training and clinical uses. J Biomed Informatics. 2015; 57: 100–12.
12. Nicole V, Steven D, Daniel P, Doran M, Karl S, Karl A, Ankur C. In vitro hemodynamic model of the arm arteriovenous circulation to study hemodynamics of native arteriovenous fistula and the distal revascularization and interval ligation procedure. J Vascular Surgery. 2014; 59: 1410–7.
13. Nakano T, Itoyama T, Yoshida K, Sawada Y, Ikeda S, Fukuta T, Matsuda T, Negoro M, Arai F. Multiscale fabrication of a transparent circulation type blood vessel simulator. Biomicrofluidics. 2010; 4: 046505.