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Development of an In Vitro Model to Characterize the Effects of Transcatheter Aortic Valve on Coronary Artery Flow

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Abstract

Impairment of coronary artery flow, in either acute or chronic conditions, is a severe complication of transcatheter aortic valve (TAV) implantation, which can arise due to improper TAV positioning. However, little work has been done to quantify the effects of the TAV positioning on the coronary flow. In this study, a realistic in vitro model of coronary artery flow was developed and used to investigate the impact of TAV deployed orientations on coronary flow. The coronary hemodynamics was first replicated mathematically using a lumped parameter model with time-varying myocardial resistance. Based on the analytical model, two stepper motor controlled stopcock valves were integrated in a left heart simulator to represent the variable myocardial resistance in the experimental setup. The coronary flow and pressure waveforms obtained from the in vitro system were consistent with published data. With a TAV deployed in different orientations, the measured results demonstrated that TAV orientation does not have a significant impact on the coronary flow. The developed in vitro model can be further utilized to simulate coronary flow under various pathological conditions.

Keywords

Coronary flow; Coronary pressure; Transcatheter aortic valve; In vitro model; Lumped parameter model

Coronary artery disease (CAD) is the leading cause of death in the USA (1,2). CAD is characterized by an obstruction of blood flow in the coronary vessels that supply blood to the heart (3), which leads to myocardial or subendocardial infarction, decreased cardiac output, and in severe cases, fibrillation of the heart and death (4). CAD can stem from various disease conditions, such as atherosclerosis, diabetes, or insulin resistance (4). More recently, coronary artery stenosis or occlusion has also been identified as a severe, life-threatening complication of transcatheter aortic valve implantation (TAVI) procedures (5) with a reported incidence of 0.6–7% (6,7). Coronary obstruction can occur when the implanted trans-catheter aortic valve (TAV) displaces the native aortic valve leaflets toward the coronary ostia (5). Heavily calcified native leaflets, shallow sinuses of Valsalva, and

improper TAV positioning (8) increase a patient's risk of coronary obstruction. However, the precise impact of the TAV positioning on the coronary artery flow is largely unknown.

Coronary artery flow under physiological conditions has been studied extensively using mathematical models (9–11) and computational fluid dynamic (CFD) simulations (12–14). It is well accepted that the interaction or “cross-talk” between the cardiac muscle and the coronary vasculature is the mechanical determinant of coronary flow. The concept that distal vessels collapse due to compression of the surrounding myocardium gives rise to the waterfall model (10), that is, the flow is independent of the pressure gradient between the arterial and venous pressures when the pressure is below the waterfall pressure (threshold pressure). This simple model can describe the systolic decline in coronary flow; however, it cannot predict the experimentally observed inflow reversal or outflow augmentation (13). Spaan et al. (11) later introduced the intramyocardial pump model which considers intramyocardial volume variations and highlighted the importance of the vascular capacitance. Many subsequent models proposed in the literature have been based on the waterfall and intramyocardial pump mechanisms (15). Additionally, over recent years, there has been an increasing number of works utilizing CFD analysis to examine patient-specific flow characteristics in coronary arteries. For most of these works, neither flow nor pressure waveforms are known a priori; therefore, multiscale simulations have been applied by means of 3D CFD simulation coupled with reduced-order (1D or 0D) models at the boundaries, which represent the relationship between the pressure and flow rate at the upstream and/or downstream vasculature (12,14,16).

Compared with these computational studies, quantification of coronary artery flow using in vitro experiments has been very limited. A study by Geven et al. (17) detailed an in vitro model consisting of a synthetic aorta connected to a polyurethane coronary artery in which the coronary resistance was adjustable yet static throughout each flow cycle. A pressure-driven model was created by Gaillard et al. (18) that utilized a sealed chamber surrounding a segment of the coronary artery extension. This chamber was connected to the left ventricle such that the ventricular pressure drove the coronary artery resistance. However, the coronary flow waveform over time appeared to be inaccurately shifted out of phase compared with clinical data.

The objective of this study was to develop an in vitro experimental model that can be used to characterize coronary artery flow under different clinical conditions, particularly after TAVI procedures. Thus, we first developed a lumped parameter mathematical model of the coronary artery flow, which served as a guide for the in vitro experimental design. Then, we developed a methodology by which native aortic roots can be mounted into a left heart simulator (LHS) where they are subjected to physiological conditions to model normal human aortic flow and pressure values. An externally controlled coronary resistance device was developed to tune the in vitro coronary flow waveforms to match flow rate curves obtained from clinical data (19). Finally, we utilized the system to examine the effect of TAV deployment on the coronary artery flow. Currently, the rotation of the TAV device is difficult to control during clinical transfemoral implantation, and the impacts of this are unclear. Therefore, the effect of the orientation of the TAV commissures with respect to the native leaflet commissures was tested by implanting a TAV into a native ovine aortic root at two

different orientations: (i) with the commissures of the TAV aligned with the native root commissures; and (ii) with the TAV commissures rotated 60° with respect to the native root commissures.

METHODS

The lumped parameter model of coronary artery flow

Coronary velocity waveforms follow a very different pattern compared with aortic flow waveforms. Aortic flow is primarily pressure-driven flow, rising during the systolic phase of the heart, peaking, and then dropping down to very low values, in some cases negative, during diastole. Conversely, the coronary flow velocity remains low during systole, then immediately rises and peaks at the start of diastole (19,20). During the systolic phase, the myocardial muscle contracts and restricts flow to the coronary arteries (21). At the start of ventricular diastole, the myocardial muscle relaxation, combined with the increased back pressure on the aortic sinuses due to the closed aortic valve, induces a rapid spike in coronary flow velocity. To replicate this phenomenon experimentally, it is necessary to develop a method to model both the pressure-driven and resistance-driven aspects of coronary artery flow.

In this study, a lumped parameter model was used to describe these coronary flow characteristics. Although a lumped-parameter model has limited anatomical representation, it can describe the physiological basis of both the pressure and flow signals in the coronary circulation with a number of parameters. The model consisted of coronary arterial resistance R_a , coronary arterial compliance C_a , and a variable myocardial resistance $R_{ma}(t)$ dependent on the myocardial contraction (see Fig. 1a). This resistance $R_{ma}(t)$ is equivalent to a constant b in systole and a constant a in diastole (see Fig. 1b), respectively. To smooth the transition of this step function, a logistic function, as shown in Fig. 1b, was used. Thus, the myocardial resistance is larger in systole to mimic the impedance of coronary flow due to the myocardium contraction. The parameter values for the coronary model, i.e., $R_a = 10$ mm Hg s/mL, $C_a = 0.001$ mL/mm Hg, $a = 40$ mm Hg s/mL, $b = 120$ mmHg s/mL, were chosen based on physiological coronary flow and pressure waveforms in the literature (22). The total resistance can be estimated based on the mean flow rate and mean arterial pressure (i.e., $R_{tot} = \bar{P}/\bar{Q}$).

The lumped parameter modeling was performed by solving the following ordinary differential equation at a finite number of incremental time steps,

$$\frac{dP_c}{dt} = \frac{Q_c}{C_a} \left(1 + \frac{R_a}{R_{ma}} \right) - \frac{P_c}{R_{ma}C_a} + R_a \frac{dQ_c}{dt}, \quad (1)$$

which relates the coronary flow rate, Q_c , to the coronary artery pressure P_c . By tuning the values of the parameters, this model can replicate healthy or diseased coronary flow conditions observed in vivo.

LHS

An LHS was designed with the intention of providing physiological flow and pressure waveforms in the left atrium, left ventricle (LV), and ascending aorta, similar to commercially available devices such as the ViVitro LHS (ViVitro Labs, Victoria, Canada) but with additional specific functionalities, such as the ability to easily mount a native aortic root in position and the capability to characterize the coronary flow (Fig. 2a–d). The LHS consists of an atrial reservoir, a mitral valve, a ventricular chamber, an aortic valve mounting area, compliance chambers, and a peripheral resistance device. The ventricular chamber contains a ventricular drive diaphragm that is controlled by a pneumatic pump (Waldhausen Design, Annville, PA, USA) with adjustable heart rate, diastolic pressure, systolic pressure, and systolic duration. Peripheral resistance was achieved via a throttle valve which is located downstream of the aortic compliance chambers and connected to the atrial reservoir, completing the closed loop. Using the pneumatic pump controls along with the peripheral resistance device, various flow conditions, including those required by standard ISO-5840, appendix L (23,24) guidelines for valve testing were achieved. The aortic flow rate was measured immediately upstream from the aortic annulus using a square wave electromagnetic flow meter (Carolina Medical Electronics, East Bend, NC, USA) with an 88-mm circumference magnetic flow probe. When testing aortic valves, pressure transducers (World Precision Instruments, Sarasota, FL, USA) were connected approximately one valve diameter upstream and approximately three valve diameters downstream of the annulus of the aortic valve. Pressure and flow data were collected using Lab-Scribe2 data collection software (iWorx Systems, Inc., Dover, NH, USA).

Controls for coronary artery flow

To replicate the lumped parameter model (Eq. 1) in the in vitro system, a series of coronary flow controls were implemented. The first control was a two-way stopcock valve (SV_1) at the outlet of the coronary artery that could be adjusted to regulate the artery entryway size (R_a), thereby allowing the user to recreate conditions involving arteries of differing sizes. Adjustment of SV_1 restricts the initial flow into the coronary extension before the flow reaches the second control (SV_2). SV_2 was used to add resistance to the arterial extension during the systolic phase of the cardiac cycle and release that resistance during diastole (i.e., representing $R_{ma}(t)$ in the lumped parameter model). This control was adjustable to allow for varying degrees of resistance to be added to the coronary extensions, thus allowing the user to replicate a variety of diseased and healthy conditions.

The coronary arteries were cannulated with a 10- to 20-mm segment of 3-mm inner diameter tubing and connected to the first two-way stopcock valve (SV_1). The second two-way stopcock valve (SV_2) was connected by additional rubber tubing extending downstream from SV_1 . SV_2 was controlled by a stepper motor via a custom LabView (National Instruments, Austin, TX, USA) program that allowed the valve to oscillate between “open” and “closed” states. The “open” phase corresponds to the angular position of SV_2 during diastole (θ_0), and the “closed” phase corresponds to the angular position of SV_2 during systole (θ_1). The variable $d\theta$, which is equal to the difference between θ_0 and θ_1 , was adjustable via the LabView program. The stepper motor has 200 step increments, providing an incremental variation of 1.8° between steps. Each phase has a built-in timer in the

LabView program (T_0 and T_1 for “open” and “closed,” respectively) that can be adjusted to control how long each cycle lasts before switching. For a standard 70-BPM set up, T_0 was set to 0.350s and T_1 was set to 0.507s. The angular velocity and angular acceleration can also be controlled as the stopcock oscillates between positions 1 and 2 (Fig. 3). A small electromagnetic flow probe (10-mm circumference, Carolina Medical Electronics) was connected to the coronary artery tubing cannulation, immediately downstream of the LabView-controlled stopcock SV_2 .

SV_2 was synchronized with the pulsatile flow such that its “open” and “closed” phases coincided simultaneously with the LHS diastolic and systolic phases, respectively (19). To facilitate the synchronization, a pressure transducer was attached to the left ventricular chamber. This pressure transducer was used as a trigger mechanism in the LabView program to start the stepper motor. Once a threshold pressure was reached within the LV, a time delay (t) was initiated, after which the stopcock “closed” phase began. The LabView program allowed θ_0 , $d\theta$, and the length of the time delays T_0 and T_1 to be adjusted as needed in order to achieve waveform synchronization. The system was considered synchronized when the stopcock “closed” phase began concurrently with the sudden peak in flow rate as the aortic valve opened.

In vitro testing of coronary artery flow in native aortic roots

Native aortic roots with an annulus size of 19 mm were dissected from ovine hearts (Animal Technologies, Tyler, TX, USA) ($n = 3$). Each aortic root was dissected such that it extended from the annulus of the aortic root, just below the fibrous trigones, to the proximal portion of the aortic arch at the left subclavian artery with excess tissue removed. The aortic root was submerged into a 0.625% glutaraldehyde solution for at least 24 h prior to testing. The root was then mounted into the LHS and tested under physiological conditions. The standard testing conditions (STCs) were as follows: 5L/min cardiac output (CO), 70 BPM, and 100mmHg average aortic pressure (AP). The fluid used in the testing set up was 0.9% saline solution.

In vitro testing of coronary flow post-TAV deployment

The TAV used in this study was provided by Dura Biotech (Storrs, CT, USA). This TAV was a 23-mm bioprosthetic valve consisting of three main components: a nitinol stent, a cloth sewing skirt, and bovine pericardial leaflets. A single TAV was used for this study to allow for comparisons between different aortic roots without introducing variability between multiple TAV devices. First, the TAV was mounted into a 23-mm inner diameter molded silicone cylindrical tube holder and tested in the LHS under STC. Then, the TAV was deployed within an aortic root mounted in the LHS and retested. The effects of TAV deployment on coronary flow were tested for two scenarios: (i) TAV implantation with the commissures of the TAV aligned with the native root commissures, and (ii) TAV implantation with the TAV commissures rotated 60° with respect to the native root commissures.

RESULTS

Lumped parameter modeling of coronary artery flow

The aortic pressure measured from the experiments was used as the input (P_c) in the lumped parameter model to calculate coronary flow rate Q_c . As can be observed in Fig. 1c, the coronary artery flow rate obtained from the lumped parameter model closely resembled the true physiological waveform (18), which exhibited the systolic drop of coronary flow rate and the augment of diastolic coronary flow. The model also showed that the mean systolic flow was approximately half of the mean diastolic flow (17).

In vitro testing of native ovine aortic root

The average systolic transvalvular pressure across the native size 19-mm ovine aortic roots at STC was 10mmHg. The effective orifice area (EOA) was calculated to be 1.2 cm². The native valve closing volume and regurgitant volume was 5.46% of the stroke volume suggesting that the mounting process did not disrupt proper valve coaptation.

The total coronary flow volume was found to be approximately 3% of the total aortic flow volume. The coronary flow velocity measured in the left coronary artery from the experiment (Fig. 4) is compared with previously published in vivo coronary flow waveforms (19). It can be seen that our data are similar to the published data. By tuning the experimental parameters, this in vitro experiment setup can be used to mimic coronary flow for various pathological conditions. Figure 5a demonstrates the effect of the variable $d\theta$ on coronary flow. The maximum diastolic flow rate increased with increasing $d\theta$, but the systolic flow rate decreased. A change in the variable θ_0 will keep the general shape of the flow curve the same albeit shifting it along the y axis (Fig. 5b). As θ_0 increases, the total amount of flow allowed into the system is restricted. Therefore, an increase in θ_0 decreases both the mean systolic and diastolic flow rates.

In our experiments, three coronary flow rate curves corresponding to $d\theta=12.6^\circ$, $d\theta=10.8^\circ$, and $d\theta=9.0^\circ$ were generated, in Fig. 5a, which represented a range of stenotic conditions. In a study by de Bruyne et al. (25), the Doppler coronary velocity waveform of a 69-year-old patient with 62% diameter stenosis at the right coronary artery was given with a mean velocity of approximately 0.1 m/s during systole and a peak velocity of about 0.45 m/s during diastole (25). It can be seen that this patient's stenotic coronary waveform can be captured by the system.

TAV deployment

The TAV used in this study was tested at STC. We observed an EOA of 1.67 cm² which is in agreement with published results for similarly sized TAVs. EOAs of 1.61 ± 0.4 cm² (26) and 1.97 ± 0.11 cm² (27) have been reported for size 23- and 26-mm Edwards SAPIEN bioprostheses. The mean differential pressure of 7.5mmHg across the valve during forward flow was also consistent with published results for the Edwards SAPIEN bioprostheses (10 ± 4 mmHg) (26). The average stroke volume, closing volume, and regurgitant volume were calculated to be 76.89 mL, 2.70 mL, and 1.35 mL, respectively. This translated to a total back leakage of 5.26% per cycle. Note that ISO-5840 guidelines require the size of 23-mm

valves to function with a minimum EOA of 1 cm^2 and a maximum leakage of 10% per cycle (28,29).

Figure 6 shows the coronary flow waveform data for one of the roots tested at STC for the two TAV orientations aforementioned and one with native leaflets. Rotating the TAV commissures 60° with respect to the native commissures resulted in little to no change in the total coronary flow. All cases had very similar flow curves, and the average flow of the three scenarios was $190 \pm 13.5 \text{ mL/min}$.

DISCUSSION

In this study, we presented a method for measuring coronary flow using a custom-made LHS with the capability to mount native aortic roots and reproduce highly adjustable coronary flow waveforms. An externally controlled coronary resistance device was developed in conjunction with the LHS to produce coronary waveforms that resembled clinical data (Fig. 4). Previously, Gaillard et al. described an experimental protocol used to model coronary artery flow (18). In that study, Gaillard et al. also modeled coronary flow rates using a pulsatile flow loop but used a synthetic aortic root and utilized a pressure-driven coronary resistance device. One benefit of using a pressure-controlled system is that it may more closely mimic the in vivo conditions of the coronary arteries. This particular implementation may, however, have the drawback of introducing a phase shift into the coronary flow waveform. As shown in Fig. 5, there is a steep decline in the coronary artery flow rate at the beginning of systole (19,30). Because the coronary resistance is driven by the left ventricular chamber pressure alone, the flow restriction begins approximately one-tenth of a second prematurely (for a 70-BPM heart rate). Conversely, by controlling the coronary resistance with an externally driven motor, the exact starting point of coronary flow restriction can be adjusted to begin concurrently with the peak in aortic flow velocity associated with the start of systole.

The advantages of our design are the ability to create highly adjustable in vitro flow conditions that more closely replicate conditions seen in vivo, and the ability to allow the user to change parameters to replicate healthy or diseased coronary flow conditions. A practical use of the ability to modify the coronary flow is to model coronary diseases such as atherosclerosis. For instance, by adjusting the θ_0 and $d\theta$ variables, the coronary resistance can be adjusted in a manner that would severely restrict the coronary flow, effectively creating a hemodynamic representation of the effects of the disease. The mean systolic and diastolic flow rates and heart rate can also be easily adjusted in the system by changing the θ_0 (Fig. 5b) and time delay variables (T_0 and T_1) respectively, which is suitable for studying coronary artery flow under various conditions.

As an initial study, the system was used to determine the impact of TAV rotation on coronary artery flow. The implantation of TAV changes the hemodynamics; however, the responses of coronary vascular beds (i.e., intrinsic resistance and compliance of coronary arterial trees) are assumed to be the same for the post-TAVI condition. Therefore, our in vitro experiments can be used to determine the flow waveforms affected by the TAV. The results showed that variations in the TAV alignment between 0° and 60° rotation with respect to the native valve

commissures, representing the extremes, have a minimal impact on the coronary artery flow. This result suggests that the TAV rotation does not increase the risk of coronary obstruction. In the future, our in vitro model may be used to further explore the effects of other deployment variables such as the TAV height with respect to the annulus or implantation within an existing bioprosthesis as in the valve-in-valve configuration (7). These studies will be critical for identifying optimal deployment strategies, especially given the repositioning mechanisms available in many second generation TAV devices (31).

Limitations

Animal (ovine) aortic roots were used in this study rather than stenotic human aortic roots. However, because human and ovine aortic roots are similar in anatomic shape and size (32), and the distance between the coronary arteries and the annulus in the ovine roots was 12 mm, which is considered at risk for coronary obstruction (33,34), the use of ovine roots in this study may be acceptable. The extension of the coronary artery is constructed from rubber tubing in the system, which does not follow the exact coronary geometry. However, the use of the rubber tubing allows standardization between tests, and as the objective of this study is to design an in vitro system, it is not possible to include the entire coronary arterial tree. A simplified mathematical model of coronary flow is used in the current study. The multiscale model, integrating the coronary artery, left ventricle, and aorta may be more accurate to capture the characteristics of coronary blood flow, and will be considered in the future.

CONCLUSIONS

In this study, we developed a lumped parameter mathematical model which served as the basis for the development of a novel in vitro experimental coronary circulation system coupled with a left heart simulator. Mathematical model was used to accurately mimic clinically obtained patient-specific coronary artery flow waveforms and further investigate how experimental settings may be modified in order to model various pathological conditions. The in vitro system was then used to measure aortic flow and coronary artery flow and pressure in ovine aortic roots pre- and post-transcatheter aortic valve deployment. Our experimental results demonstrate that the alignment of the TAV commissures with respect to the native commissures has a minimal impact on the coronary flow in a healthy ovine model. The results also showed that our system can reproduce hemodynamic conditions comparable with commercially available LHS systems, and the TAV used in this study performs similarly to clinically available valves. Thus, the lumped parameter and experimental models presented here may be used in the future to explore more complex TAV deployment scenarios or pathological coronary artery flow conditions.

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FIG. 1.

(a) Schematic representation of the lumped parameter model. (b) The prescribed change of myocardial resistance in a cardiac cycle (BPM = 70). (c) Aortic pressure from the experiment (solid line) used as model input, and the corresponding coronary flow rate calculated from the lumped parameter model (dashed line) is compared with the coronary flow waveform from (18) (dotted line).

FIG. 2.

(a) Overview of the LHS system in the experimental setup during coronary flow testing. (b) A top-down view of the ventricular chamber without the compliance. Viewports were machined into the acrylic block to allow viewing of the aortic and mitral valves from the ventricular chamber. (c) View of a native ovine aortic root mounted in the LHS. (d) Image of the bladder compliance used in the ascending aorta portion of the LHS.

FIG. 3.

A diagram representing stopcock (SV₂) orientation with respect to the adjustable parameters: $d\theta$ and θ_0 . $\theta_0 = 0$ corresponds to the condition where the stopcock is fully open, providing no resistance to the coronary artery flow. As the value of θ increases, the coronary flow will experience more resistance.

FIG. 4.

A comparison of our experimental and previously published in vivo coronary velocity data and aortic flow data.

FIG. 5.

(a) Experimental coronary flow velocities at three different values of $d\theta$ with fixed $\theta_0 = 1.8^\circ$, and the stenotic coronary flow velocity from de Bruyne et al. (25). (b) Experimental coronary flow velocities at three different values of θ_0 .

FIG. 6.
Experimental coronary flow velocities during different TAV deployments.