Using Limiting Distribution of Transition Probability to Assess Coexisting Inflow and Outflow Stenosis in Experimental Stenotic Arteriovenous Grafts

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Abstract—This study proposes a screening model to assess coexisting inflow and outflow stenosis in an experimental arteriovenous graft (AVG). Early clots and thrombosis lead to stenosis progression and increase variations in inflow and outflow pressures, flow velocities, and flow resistances. A substitution rate matrix (SRM) is used to replace the pressure variations and derive a transition probability matrix (TPM). The limitation values of transition probabilities can be used to identify the normal conditions and flow instabilities using the Euclidean distance estimation method. The joint probability could then be specified as a critical threshold to identify the stenosis levels in the assessment of coexisting stenosis.

Index Terms— Arteriovenous Graft, Substitution Rate Matrix, Transition Probability Matrix.

1. Introduction

Cardiovascular diseases are major risk factors for morbidity and mortality in patients with both end-stage renal disease and diabetes. Dialysis patients who suffer from progressive atherosclerosis can develop stenosis in the lumen of the vascular wall at the arterial site or venous site. Thus, they can develop venous and arterial stenosis or vascular diseases, which can include complications such as hypertension, hyperlipidemia, dyslipidemia, and diabetes mellitus. In addition, an arteriovenous fistula (AVF) or an arteriovenous graft (AVG) is vital for delivering an adequate flow rate of >600 ml/min. Due to repeat puncturing in the vascular access or long-term use, early clots, thrombosis, and progression of atherosclerosis result in reduced blood flow. These complications could lead to venous (outflow) stenosis, arterial (inflow) stenosis, and ultimately progression of coexisting stenosis at the inflow and outflow sites, as shown by their structures in Figure 1. In clinical examinations, AVGs have a higher infection rate and a higher patency rate than AVFs in stenosis growth at the venous anastomosis site, leading to venous neointimal hyperplasia and thrombosis [1-2]. Therefore, an acute problem will affect the cardiovascular system and the dialysis circuit, including hemodynamic variations in blood

Figure 1. The structure of coexisting stenosis at inflow and outflow sites

flow, pressures, and flow velocities in the stenotic vicinity. Some studies [3-5] have proposed mathematical models or analytical solutions to analyze steady flow through a narrowed access or pulsatile flow in multiple stenotic accesses.

Numerical analyses have been performed to validate the correlation between *in-vivo* and *in-vitro* experiments. The Newtonian flow is through an elastic stenotic access, while the blood flow is characterized by the generalized power law model. Poiseuille's law [6-7] indicates a conversion from potential to kinetic energy. Thus, instability and turbulent flow in a stenotic route result in increases in pressure, pressure gradient, velocity, resistance, and wall stress. These increases can allow researchers to understand the important effects, impacts, and risks and then deal with real clinical problems. Dimensionless numbers, such as the Reynolds (Re) number, Womersley number, and Strouhal number [8-9], can also be used to characterize flow patterns, including steady laminar flow, transitional flow, and pulsatile flow. However, these analytical methods cannot be applied in the patient environment.

In real-time or online hemodynamic analysis, a narrowed access or higher degree of stenosis (DOS) limits the blood flow through the vascular access and increases access pressures in inflow sites, flow velocities, and flow resistances. Then, the pressure differences gradually increase between the inflow and outflow sites, while the hemodynamic condition has an outflow or coexisting stenosis at the inflow and outflow sites. The substitution rate matrix (SRM) method [10-13] was used for Euclidean

Figure 2. The circulation system in an experimental study

distance estimation and sequence analysis with pressure variations from the inflow to the outflow site. The Markov chain with two states of hemodynamic conditions expresses a matrix of substitution rates to replace the pressure variations. Then, the TPM can be derived. The SRM model screens the inflow and outflow pressure variations, while transition probabilities approach the same limitation value as the intra-hemodynamic stability over a finite timing interval. Different limitation values in the transition probabilities are used to separate normal conditions from flow instabilities under $\geq 50\%$ stenosis using the distance estimation method. These quantities can be specified as gross variations to assess stenosis progression in an experimental stenotic graft, particularly in coexisting inflow and outflow stenosis.

2. Experimental Setup

Figure 2 shows an experimental circulation system model representing the mock flow phenomena of a HD patient's circulation system. The experimental system consists of a roller pump as a pressure source regulator (Precision blood pump, COBE, Lakewood, CO, USA), a liquid tank, silicone tubes, and a stenotic tube (50–95% of tube diameter) (Figure 2). The roller pump (40–80 rpm) is used to drive the fluid mixture for an adult during HD condition with a flow rate of approximately 600 ml/min, including the heart rate (80–120 beats/min), blood pressure, blood flow, and pulsatile flow. The temperature in our experimental study is about 28°C (steady state). The mixed water–glycerin fluid, with a hematocrit ratio of 38–62%, kinematic viscosity of $3.2 \times 10^{-6} \text{ m}^2/\text{s}$, and density of 1090 kg/m^3 at 28°C, was used as a blood-mimicking fluid (BMF), similar to a normal adult. According to the practical HD condition, a blood flow of 600 ml/min and a rotor speed of 40–60 rpm were used in this study.

The inflow and outflow pressures were measured using

Figure 3. Inflow and outflow pressure measurements under 600 ml/min and rotor speed, 40–60rpm. (a) Inflow stenosis: 70% and Outflow stenosis: 0–95%, (b) Inflow stenosis: 0–95% and Outflow stenosis: 70%

venous needles, pressure transducers, and pressure sensors, as shown in Figure 2. Measurement data were transferred to a compatible PC or a tablet for further analysis using a data acquisition card (National Instruments Compact DAQ-9178 card, analog-to-digital converter, 8 channels, and 1 MHz sampling rate). The inflow and outflow pressure signals, P_{meas} , were extracted using the detrending process [14–15], as follows:

$$P_{meas}(t) = P_{org}(t) - \text{detrend}(P_{org}(t)) \quad (1)$$

where syntax $\text{detrend}(\bullet)$ is a function of the detrending process used to remove unwanted and unpredictable variations such as the influence of the roller pump (harmonics) and transverse vibration pressures [16–17]; $P_{meas}(t)$ is the determined pressure from the incoming pressure signal; $P_{org}(t)$ is measured via the pressure sensors; and t is the finite timing interval (sampling window length) represented by $t \in [0, T]$; $T = 10 \text{ s}$ in this study.

The pressures (mmHg) were measured at the inflow and outflow sites using pressure sensors that were continually monitored with pressure screening. We made 64 practical measurements at the inflow and outflow sites. For primary hemodynamic analysis, the inflow stenosis was 70% and the average inflow pressures steadily increased from the outflow stenosis from 50% to 95%, while the outflow pressures gradually decreased. In addition, the outflow stenosis was 70%, the inflow pressures steadily increased

Figure 4. Markov chain with two states

from the inflow stenosis from 70% to 95%, and the outflow pressure gradually decreased (Figure 3). It can be observed that the pressure differences, $\Delta P = |P_{I,mea} - P_{O,mea}|$, also gradually increased and reached about 40–72 mmHg, in terms of DOS from 0.0% to 95.0%. The DOS is defined as follows [18]:

$$DOS\% = [1 - (\frac{d_a}{D_a})^2] \times 100\% \quad (2)$$

where D_a is the diameter of the normal access or graft in the direction of the BMF flow and d_a is the diameter of the stenotic segment. Significant pressure variations were observed, while the inflow and outflow stenosis coexisted as the DOS increased. Therefore, we propose the substitution rate to derive the transition probabilistic model, and its limitation value can be used to identify stenosis progression with inflow and outflow pressure variations.

3. Transition Probability Matrix

The SRM-based mathematical model is a probabilistic method to describe variations between the inflow pressure, P_I , and outflow pressure, P_O , while an outflow stenosis or a coexisting inflow and outflow stenosis occurs. The vessel compliance is a pressure–volume relationship, which is the ratio of the difference of the systolic to diastolic amplitude of the diameter to the amplitude of the pressure. Thus, an increase in the pressure is accompanied by a decrease in vessel compliance. The inflow and outflow pressure variations can be defined as

$$\rho_I = \frac{P_{I,mea}}{P_{I,nor}} \quad \text{and} \quad \rho_O = \frac{P_{O,mea}}{P_{O,nor}} \quad (3)$$

where ρ_I and ρ_O are the inflow and outflow pressure ratios for pressure measurements; $P_{I,mea}$ and $P_{O,mea}$ are the pressures at the inflow (I) or outflow (O) site; and $P_{I,nor}$ and $P_{O,nor}$ are the pressures under the DOS% $\leq 50\%$.

With two states, the substitution rates for each pair of pressure ratios, ρ_I and ρ_O , are the parameters, λ_1 and λ_2 . The SRM can be defined as

$$Q = \begin{bmatrix} -\rho_I & \rho_I \\ \rho_O & -\rho_O \end{bmatrix} = U\Lambda U^{-1}, \quad -\rho_{ii} = \rho_{ij} \quad \text{for } i \neq j \quad (4)$$

The spectral decomposition of Q is [10]

$$\Rightarrow Q = U\Lambda U^{-1} = \begin{bmatrix} 1 & -\rho_I \\ 1 & \rho_O \end{bmatrix} \begin{bmatrix} 0 & 0 \\ 0 & -\rho_I - \rho_O \end{bmatrix} \begin{bmatrix} \frac{\rho_O}{\Delta} & \frac{\rho_I}{\Delta} \\ \frac{-1}{\Delta} & \frac{1}{\Delta} \end{bmatrix} \quad (5)$$

where $\Delta = (\rho_I + \rho_O)$. The TPM, $P(t)$, is derived for Markov chain with two states, and the general formulation is

Figure 5. The limiting distribution of transition probability for various flow rates and DOSs

$$P(t) = e^{Qt} = \begin{bmatrix} 1 & -\rho_I \\ 1 & \rho_O \end{bmatrix} \begin{bmatrix} e^{0 \times t} & 0 \\ 0 & e^{-\Delta \times t} \end{bmatrix} \begin{bmatrix} \frac{\rho_O}{\Delta} & \frac{\rho_I}{\Delta} \\ \frac{-1}{\Delta} & \frac{1}{\Delta} \end{bmatrix} \quad (6)$$

$$\Rightarrow P(t) = \frac{1}{\Delta} \begin{bmatrix} \rho_O + \rho_I e^{-\Delta t} & \rho_I - \rho_I e^{-\Delta t} \\ \rho_O - \rho_O e^{-\Delta t} & \rho_I + \rho_O e^{-\Delta t} \end{bmatrix} \quad (7)$$

$$\Rightarrow P(t) = \begin{bmatrix} p_{11}(t) & p_{12}(t) \\ p_{21}(t) & p_{22}(t) \end{bmatrix} \quad (8)$$

$$\text{subject to } 0 \leq p_{ij}(t) \leq 1, \quad \sum_{j=1}^2 p_{ij}(t) = 1, \quad i = 1, 2 \quad (9)$$

As shown by the Markov chain in Figure 4, the limiting distribution is the stationary distribution, $[\rho_O / \Delta, \rho_I / \Delta]$, as

$$\lim_{t \rightarrow \infty} p_{11}(t) = \lim_{t \rightarrow \infty} \frac{\rho_O}{\Delta} + \frac{\rho_I}{\Delta} e^{-\Delta t} = \frac{\rho_O}{\rho_I + \rho_O} \quad (10)$$

$$\lim_{t \rightarrow \infty} p_{22}(t) = \lim_{t \rightarrow \infty} \frac{\rho_I}{\Delta} + \frac{\rho_O}{\Delta} e^{-\Delta t} = \frac{\rho_I}{\rho_I + \rho_O} \quad (11)$$

For an ideal model, $\rho_I = \rho_O = 1.0$, when time t increases from 0 to ∞ , the diagonal elements, $p_{11}(t)$ and $p_{22}(t)$, decrease from 1.0 to 0.5, while the off-diagonal elements, $p_{12}(t)$ and $p_{21}(t)$, increase from 0.0 to 0.5. Hence, the limiting distributions are 0.5, 0.5, 0.5, and 0.5. The mean value, $\mu = 0.50$, can thus be obtained. Thus, the transition probabilities approach a value of 0.50 under the intra-hemodynamic stability (Figure 5). For coexisting stenosis, the pressure difference significantly increases and the limitation values of transition probabilities diverge from 0.50 for all inflow and outflow pressure ratios under different flow rates (40–60 rpm).

The distance estimation method is used to screen the similarity between the limitation value of transition probabilities, $p_{11}(t)$ and $p_{22}(t)$, as follows:

$$d_{11} = \sqrt{(\lim_{t \rightarrow \infty} p_{11}(t) - \mu_{11})^2}, \quad \mu_{11} = 0.50 \quad (12)$$

$$d_{22} = \sqrt{(\lim_{t \rightarrow \infty} p_{22}(t) - \mu_{22})^2}, \quad \mu_{22} = 0.50 \quad (13)$$

The joint probability, p_{IO} , accommodating the varying pressure ratios is given by the following formula:

Table 1. Experimental results, comparisons with the proposed screening model and hemodynamic analysis (60rpm)

DOS%		Pressure, mmHg		ΔP	Pressure Ratio		V_{est}	Re	Resistive Index, Res	Eigenvalue		Limitation		p_{10}
Inflow	Outflow	Inflow	Outflow	mmHg	ρ_i	ρ_o	, m/sec			λ_1	λ_2	p_{11}	p_{22}	
0.0	0.0	109.25	104.85	4.40	1.00	1.00	1.048	724.76	0.333	-2.00	0.00	0.50	0.50	1.0000
50.0	70.0	143.30	135.51	7.79	1.31	1.29	1.395	964.12	0.498	-2.60	0.00	0.49	0.50	0.9946
70.0		111.88	104.56	7.32	1.02	0.99	1.353	934.89	0.483	-2.01	0.00	0.49	0.51	0.9825
80.0		112.63	102.53	10.10	1.03	0.98	1.589	1097.99	0.559	-2.01	0.00	0.48	0.51	0.9326
85.0		117.34	102.45	14.89	1.07	0.98	1.929	1333.42	0.637	-1.98	0.00	0.48	0.52	0.8386
90.0		126.73	101.37	25.36	1.16	0.97	2.518	1740.09	0.722	-2.13	0.00	0.45	0.55	0.4381
92.5		129.79	92.43	37.36	1.19	0.88	3.056	2112.04	0.771	-2.07	0.00	0.43	0.57	0.1115
95.0		153.64	81.79	71.85	1.41	0.78	4.238	2928.73	0.835	-2.19	0.00	0.36	0.64	0.0003
70.0	50.0	113.84	106.90	6.94	1.04	1.02	1.317	910.23	0.468	-2.06	0.00	0.49	0.50	0.9882
	70.0	111.52	104.18	7.34	1.02	0.99	1.354	936.09	0.483	-2.01	0.00	0.49	0.50	0.9819
	80.0	110.95	100.86	10.09	1.01	0.96	1.588	1097.59	0.559	-1.97	0.00	0.48	0.51	0.9291
	85.0	115.05	100.29	14.76	1.05	0.96	1.921	1327.44	0.636	-2.04	0.00	0.48	0.52	0.7939
	90.0	121.67	97.35	24.32	1.11	0.93	2.466	1703.89	0.716	-2.07	0.00	0.45	0.54	0.4394
	92.5	129.68	92.88	36.80	1.19	0.88	3.033	2096.03	0.769	-2.07	0.00	0.43	0.57	0.1211
	95.0	152.15	80.07	72.08	1.39	0.76	4.245	2933.52	0.835	-2.15	0.00	0.35	0.65	0.0002

Note: (1) $V_{est} = \sqrt{\frac{(P_{I,mea} - P_{O,mea})}{4}} = \sqrt{\frac{\Delta P}{4}}$, $\Delta P = P_{I,mea} - P_{O,mea}$ is the pressure drop, (2) $Re_s = \frac{V_{est} - V_0}{V_{est}}$, where V_{est} is the estimated peak systolic velocity (m/sec), and $V_0 = 0.7$ m/sec is the peak systolic velocity under control conditions.

Figure 6. Stenotic segments in an experimental AVG

Figure 7. Original pressures and detrended pressures for coexisting stenosis (DOS% = 70% and 80%)

$$p_{10} = \exp\left(-\frac{1}{2}\left(\frac{d_{11}}{\sigma}\right)^2\right) \times \exp\left(-\frac{1}{2}\left(\frac{d_{22}}{\sigma}\right)^2\right) \quad (14)$$

where $\sigma = \mu \times 10\%$ is the standard deviation. The joint probability, $p_{10} > 0.81$, was used to find the same states or similarity states for each pair of screening pressure ratios as the intra hemodynamic stability in an experimental graft. Otherwise, this indicates flow instability, while joint probability, p_{10} , gradually approached zero. Thus, this index is calculated out to separate the normal condition (DOS% < 50%) from the coexisting inflow and outflow stenosis (DOS% $\geq$ 50%).

Figure 8. Joint probability versus DOS and pressure difference versus DOS

4. Simulation Results

An experimental model mimicking the human cardiovascular circulation system was set up in the laboratory. A computer-assisted tool was designed to process inflow and outflow pressure signals, and the screening model was implemented using LabVIEW programming software (National InstrumentsTM Corporation, Austin, TX, USA) and Matlab software (Mathwork, Natick, MA, USA). A flow rate of 60ml/min (roller pump, 40 – 60rpm) and a heartbeat of 75 beats/min were used to drive the BMF through different stenotic segments, as seen in Figure 6. Pressure signals were obtained via a data acquisition card connected to a tablet or a PC. Original inflow and outflow pressures in the time domain were measured using pressure sensors, as shown by the sampling data in Figure 7. Then, a detrending process was also used to remove unwanted influences and vibration pressures. For coexisting stenosis, the average inflow pressure was 110.95mmHg and the average outflow pressure was 100.86mmHg, while the inflow and outflow narrowed degrees were 70% and 80%,

respectively, in the vascular access. For example, given the average pressures, $P_{I,mea} = 110.95\text{mmHg}$ and $P_{O,mea} = 100.86\text{mmHg}$, the screening procedure was as follows:

- Step 1) compute the inflow and outflow pressure ratios, $\rho_I = 1.01$ and $\rho_O = 0.96$, using the equation (3),
- Step 2) compute the substitution rates, $\lambda_1 = -1.97$ and $\lambda_2 = 0.00$, using the equation (4),
- Step 3) computed the transition probabilities using the equations, (6) and (8), and then the limitation values of transition probabilities can be obtained using equations, (10) and (11),
- Step 4) compute the Euclidean distances with the equations, (12) and (13), and joint probability using the equation (14), the $p_{IO} = 0.9291$ can be obtained, as shown in Table 1.

The results indicate the average value, $p_{IO} = 0.9291$, used to identify the stenosis level. When the gross variations in the average probability dropped from 1.00 to < 0.81 , coexisting stenosis progression was confirmed, and when the gross variations reached < 0.64 , they represented a higher degree under various flow rates (40–60 rpm), as shown in Figure 8. The critical threshold, < 0.64 , suggests that transluminal angioplasty or surgical revision should be performed to enlarge the focal site using a balloon or to further to dilate the stenotic lesion. The experimental results are shown in Table 1. In addition, we also performed hemodynamic analysis to compute pressure differences, ΔP , between the inflow and outflow sites, injection velocities, V_{est} , across the vascular access, and the resistive (Res) indexes, as seen in Table 1. Pressure differences were caused by viscous losses in laminar flow, resulting in injection velocity increases through the stenotic segment and gradual increase in the average Re numbers; under a transition flow to pulsatile flow, the average Re number was greater than 1000, with $DOS > 70\%$. Pressure differences increased as the induced flow rate decreased, causing a resistance in the flow from 0.333 to 0.835. Comparing the proposed method with the hemodynamic analysis, the average joint probabilities showed inverse relationships (monotone decrease) with the increase in stenosis levels, providing a promising index for screening stenosis progression.

5. Conclusion

This experimental study has designed a measurement system and a screening model to assess stenosis progression in an *in-vitro* AVG. The pressure sensors were used to measure the inflow and outflow pressures. Pressure differences between the inflow and outflow sites were positively correlated with DOS from 0% to 95%. The SRM model replaced the pressure ratios and was used to screen for inflow and outflow pressure variations, and then the limitation values of transition probabilities were used to separate the normal conditions from the intra-hemodynamic instability. The joint probability can identify the stenosis levels in the assessment of coexisting stenosis. The results also indicate that the prototype system could be integrated

into a clinical hemodialysis machine, without any need for additional devices.

Acknowledge

This work is supported in part by the Ministry of Science and Technology, Taiwan, under contract number: **MOST 104-2221-E-244-010** and **MOST 105-2218-E-075B-001**, duration: August 1, 2015 ~ February 28, 2017, and is also supported in part by the research grant of Kaohsiung Veterans General Hospital, Tainan Branch, under contract number: **VHYK 105-15**, duration: January 1, 2016 ~ December 31, 2016.

Appendix

The proposed screening model was designed as a graphic user interface (GUI) using the LabVIEW graphical programming (National Instruments™ Corporation, Austin, Texas, U.S.) and Matlab software (Mathwork, Natick, Massachusetts, U.S.), as shown in Figure 9.

Figure 9. The proposed screening model was implemented in an embedded system and its graphic user interface (GUI)

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