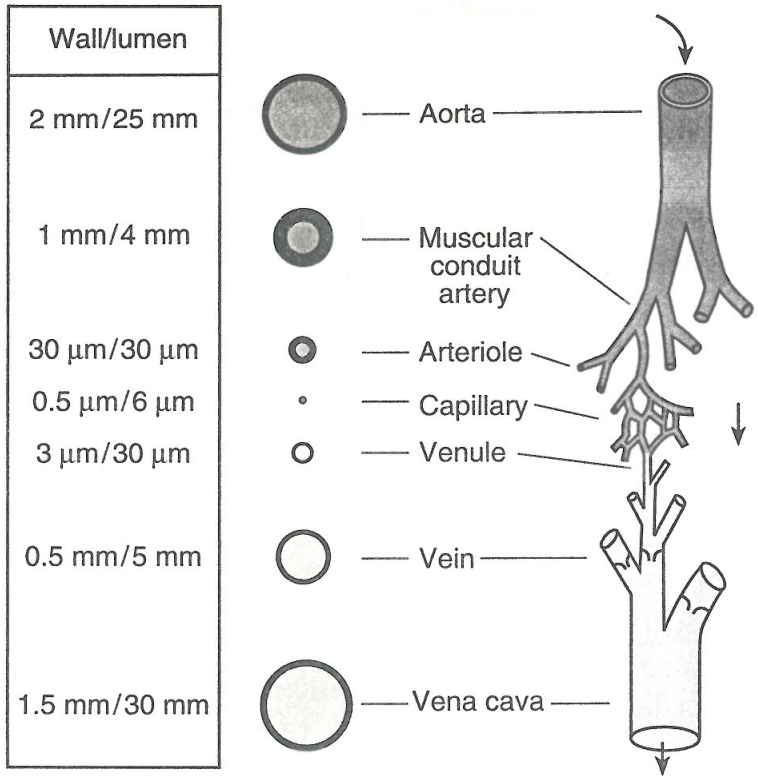
Introduction to Mathematical Modeling of the Circulatory System

2023. 12. 11.

이완호 (산업수학연구본부 수리모델링연구팀)

Circulatory System Model

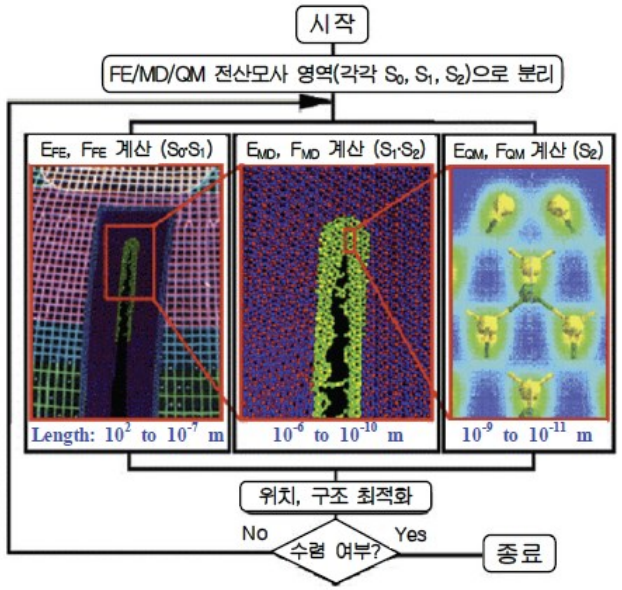
- Thickness of the wall relative to the diameter of the lumen in different blood vessels.

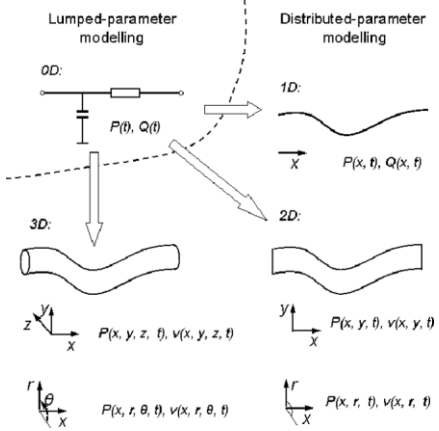


- Echocardiography results for a normal human left ventricle

Wall or septum thickness	0.7~1.1 cm
End-diastolic internal diameter	3.5 ~ 5.6 cm
End-systolic internal diameter	1.9 ~ 4.0 cm
Aortic valve orifice	1.6 ~ 2.6 cm

- Schematic Graph of the Multiscale Model

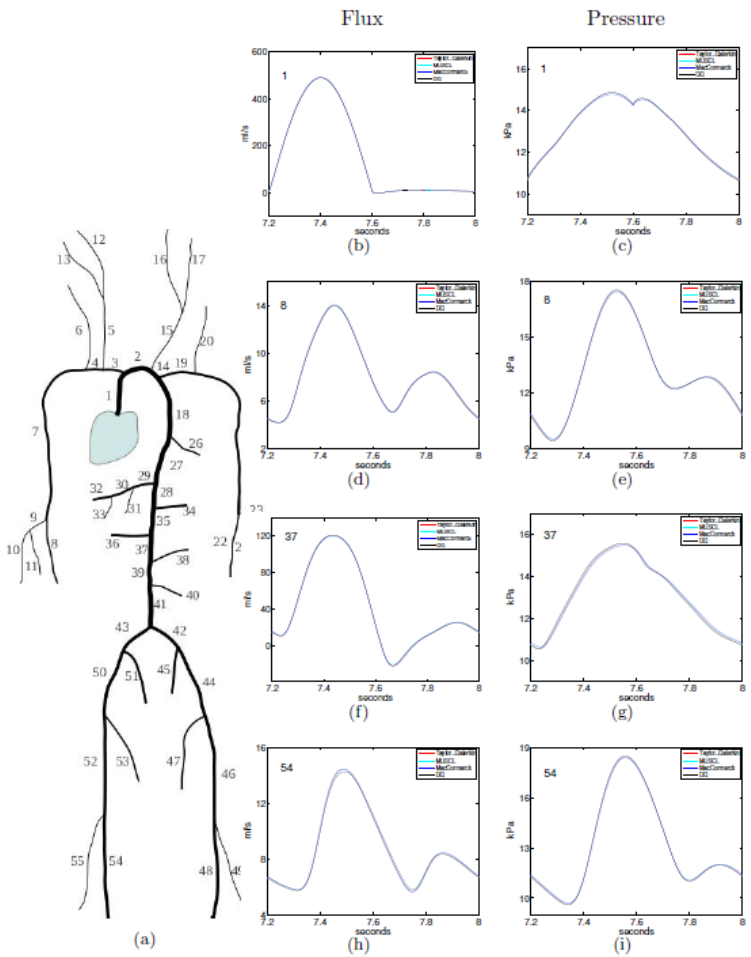




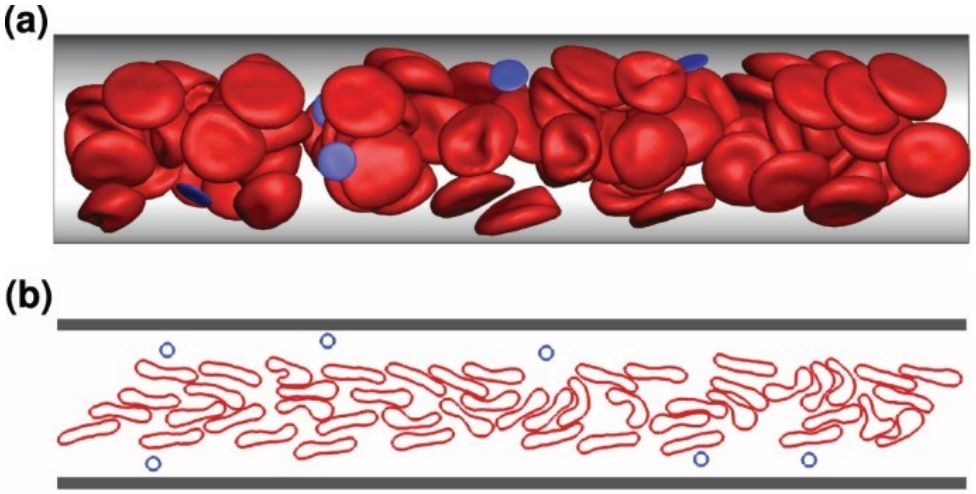
- Comparison of modelling techniques for cardiovascular dynamics studies

Method of Study		Suitable Research Target
Lumped Parameter model	0D	Global cardiovascular dynamics in the whole circulation system; General pressure and flow-rate changes in a local circulation loop; possible to provide boundary conditions for local 3D models
Distributed Parameter Modeling	1D	Pulse wave transmission; improved boundary conditions for 3D local models, capable of capturing systemic wave reflection effects
	2D	Local flow field study in axisymmetric domains; further improvement of boundary conditions for local 3D models, but limited applicability
	3D	Local flow field study in full 3D domains

Blood Vessel Simulation



Wang, Xiaofei. *1D modeling of blood flow in networks: Numerical computing and applications*. Diss. Université Pierre et Marie Curie-Paris VI, 2014.

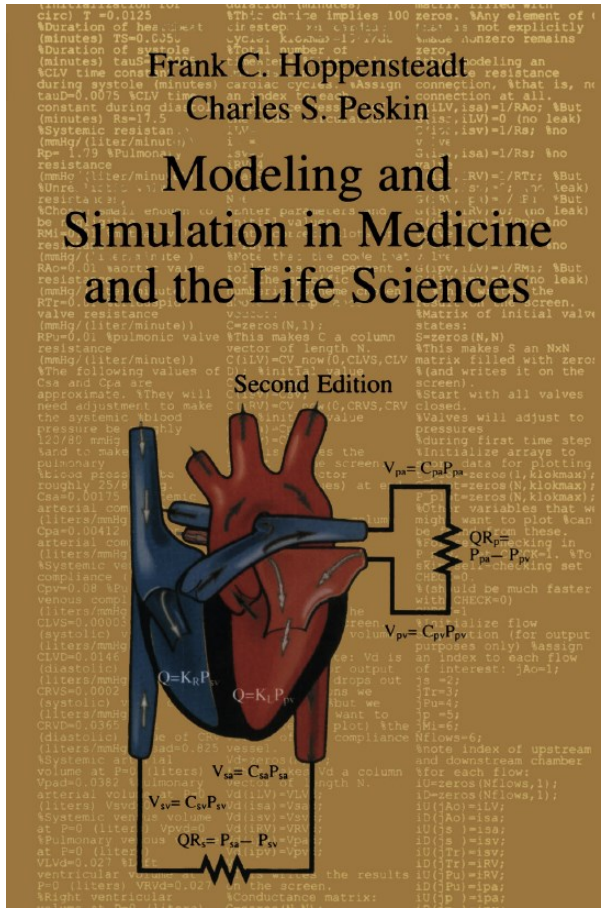


Müller, Kathrin, Dmitry A. Fedosov, and Gerhard Gompper. "Margination of micro-and nano-particles in blood flow and its effect on drug delivery." *Scientific reports* 4.1 (2014): 1-8.

Heart Flow simulation

HeartFlow®

References (0D model)



Contents

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www.JBiomech.com

Transition from fetal to neonatal circulation: Modeling the effect of umbilical cord clamping

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ABSTRACT

Hemodynamics of the fetal to neonatal transition are orchestrated through complex physiological changes and results in cardiovascular adaptation to the adult biventricular circulation. Clinical practice during this critical period can influence vital organ physiology for and congenital heart defect patients. Particularly, the timing of the (ICC) *vs.* delayed cord clamping (DCC), is hypothesized to be an ir *hemodynamics.* The clinical need for a quantitative understandi development of a lumped parameter model (LPM) of the fetal ca late-gestation to neonatal period. The LPM was validated with i predict the effects of cord clamping procedures on hemodynamics a resistance functions to simulate the vascular changes were intro (31.3 ml) increased neonatal blood volume by 11.7%. This increased b in preload pressures by ~20% compared to ICC, which in turn inc (CO_{ICC}=993 ml/min; CO_{DCC}=1197 ml/min). Our model accurately pr DCC was shown to maintain oxygenation if the onset of pulmonary r the other hand, a significant 25% decrease in oxygen saturations was same physiological conditions. We conclude that DCC has a significa mainly because of the improved blood volume and the sustained pl

J. Korean Math. Soc. **43** (2006), No. 4, pp. 885–897

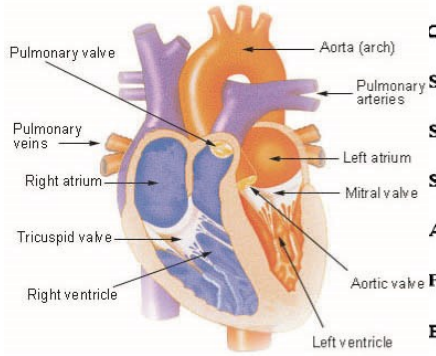
LUMPED PARAMETER MODELS OF CARDIOVASCULAR CIRCULATION IN NORMAL AND ARRHYTHMIA CASES

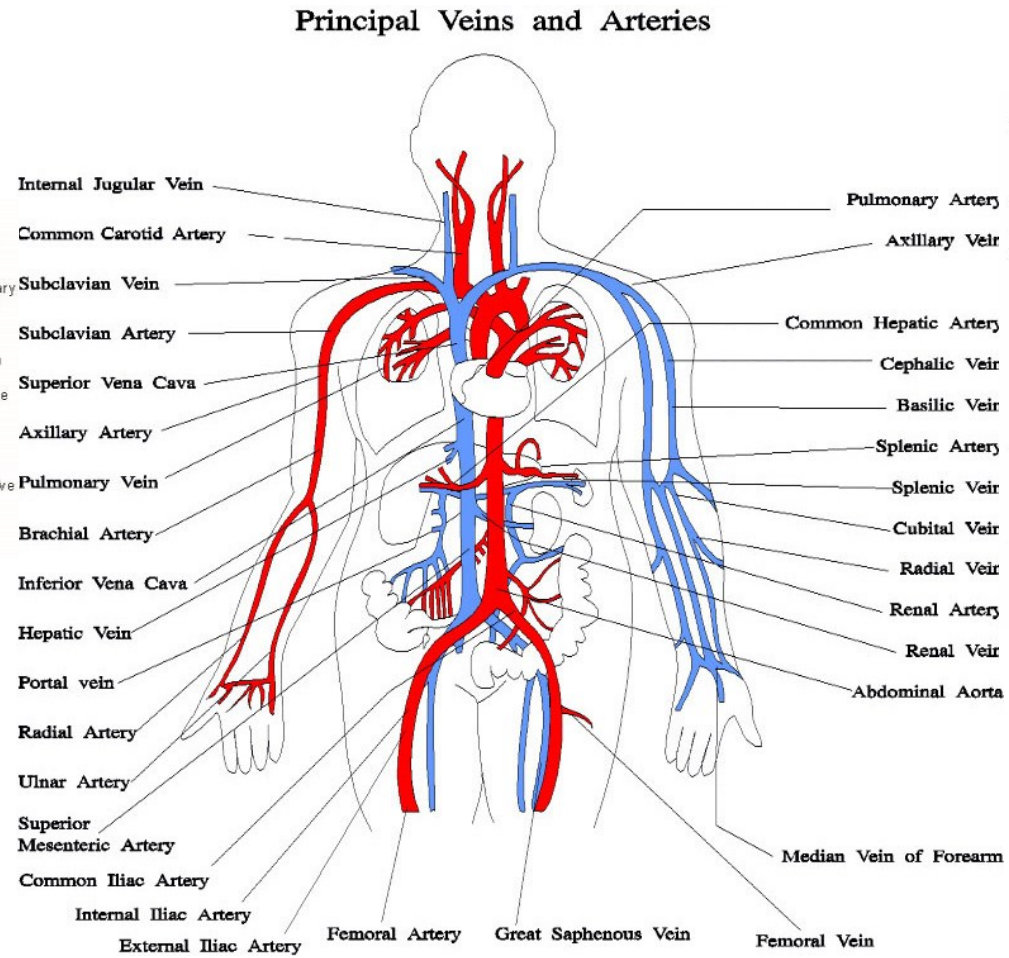
EUNOK JUNG AND WANHO LEE

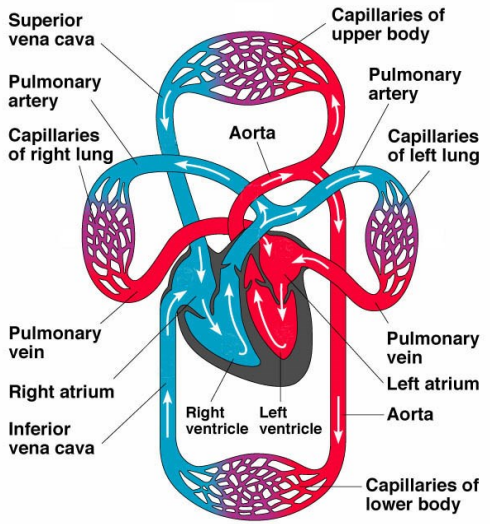
ABSTRACT. A new mathematical model of pumping heart coupled to lumped compartments of blood circulation is presented. This lumped pulsatile cardiovascular model consists of eight compartments of the body that include pumping heart, the systemic circulation, and the pulmonary circulation. The governing equations for the pressure and volume in each vascular compartment are derived from the following equations: Ohm's law, conservation of volume, and the definition of compliances. The pumping heart is modeled by the time-dependent linear curves of compliances in the heart. We show that the numerical results in normal case are in agreement with corresponding data found in the literature. We extend the developed lumped model of circulation in normal case into a specific model for arrhythmia. These models provide valuable tools in examining and understanding cardiovascular diseases.

https://www.math.nyu.edu/~peskin/

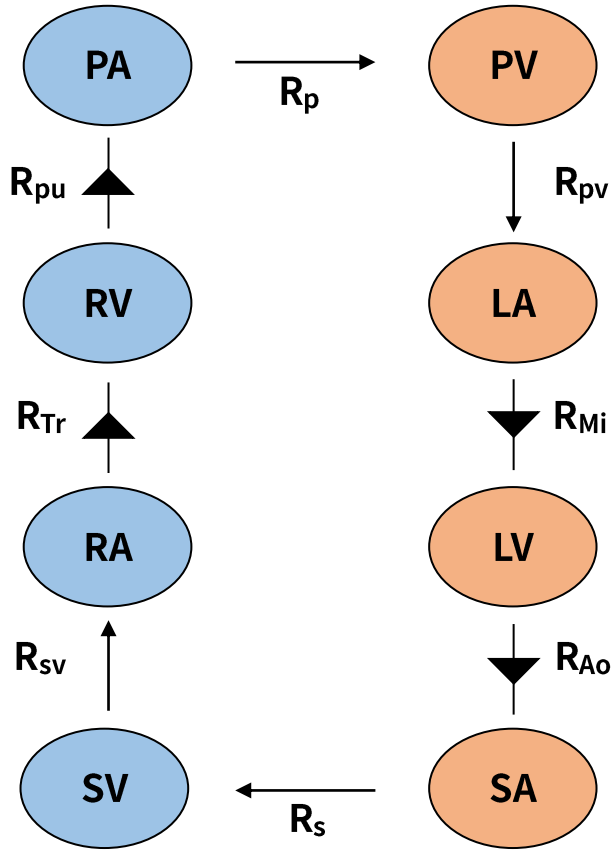
Blood Circulation



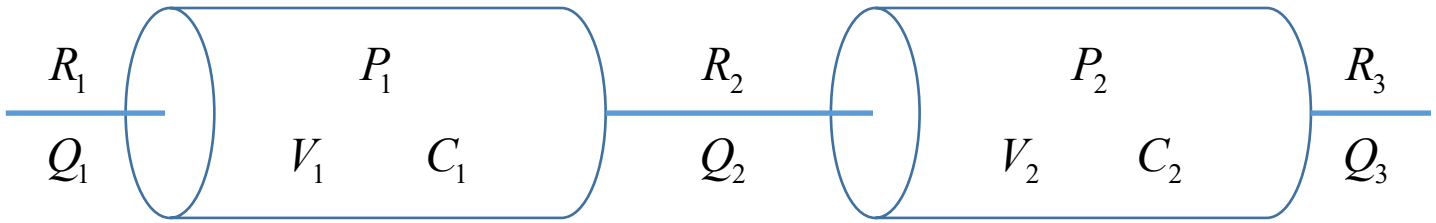


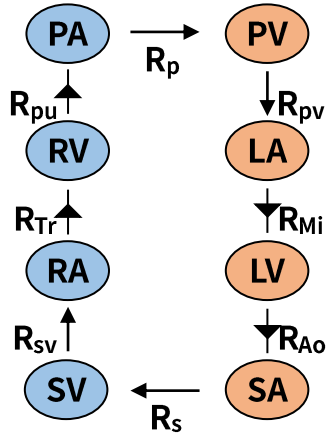


Lumped Parameter Model



Physiological Principles





- **Conservation of volume**

$$\frac{dV_1(t)}{dt} = Q_1(t) - Q_2(t)$$

$$\frac{C_{pa}dP_{pa}(t)}{dt} = \frac{S_{Pu}(t)(P_{RV}(t) - P_{pa}(t))}{R_{Pu}} - \frac{P_{pa}(t) - P_{pv}(t)}{R_p}$$

$$\frac{C_{pv}dP_{pv}(t)}{dt} = \frac{P_{pa}(t) - P_{pv}(t)}{R_p} - \frac{P_{pv}(t) - P_{LA}(t)}{R_{pv}}$$

- **Ohm's Law**

$$Q_2(t) = \frac{P_1(t) - P_2(t)}{R_2}$$

$$\frac{d(C_{RV}(t)P_{RV}(t))}{dt} = \frac{S_{Tr}(t)(P_{RA}(t) - P_{RV}(t))}{R_{Tr}} - \frac{S_{Pu}(t)(P_{RV}(t) - P_{pa}(t))}{R_{Pu}}$$

$$\frac{d(C_{LA}(t)P_{LA}(t))}{dt} = \frac{P_{pv}(t) - P_{LA}(t)}{R_{pv}} - \frac{S_{Mi}(t)(P_{LA}(t) - P_{LV}(t))}{R_{Mi}}$$

※ $L_2 \frac{dQ_2(t)}{dt} = -R_2 Q_2(t) + P_1(t) - P_2(t)$

$$\frac{d(C_{RA}(t)P_{RA}(t))}{dt} = \frac{P_{sv}(t) - P_{RA}(t)}{R_{sv}} - \frac{S_{Tr}(t)(P_{RA}(t) - P_{RV}(t))}{R_{Tr}}$$

$$\frac{d(C_{LV}(t)P_{LV}(t))}{dt} = \frac{S_{Mi}(t)(P_{LA}(t) - P_{LV}(t))}{R_{Mi}} - \frac{S_{Ao}(t)(P_{LV}(t) - P_{sa}(t))}{R_{Ao}}$$

$V_{LV}(t)$, $Q_{in}(t)$, $Q_{out}(t)$

- **Definition of compliance**

$$V_1(t) = V_{1,d} + C_1(t) \cdot P_1(t)$$

※ $V_{1,d}$ is the volume at $P_1(t) = 0$

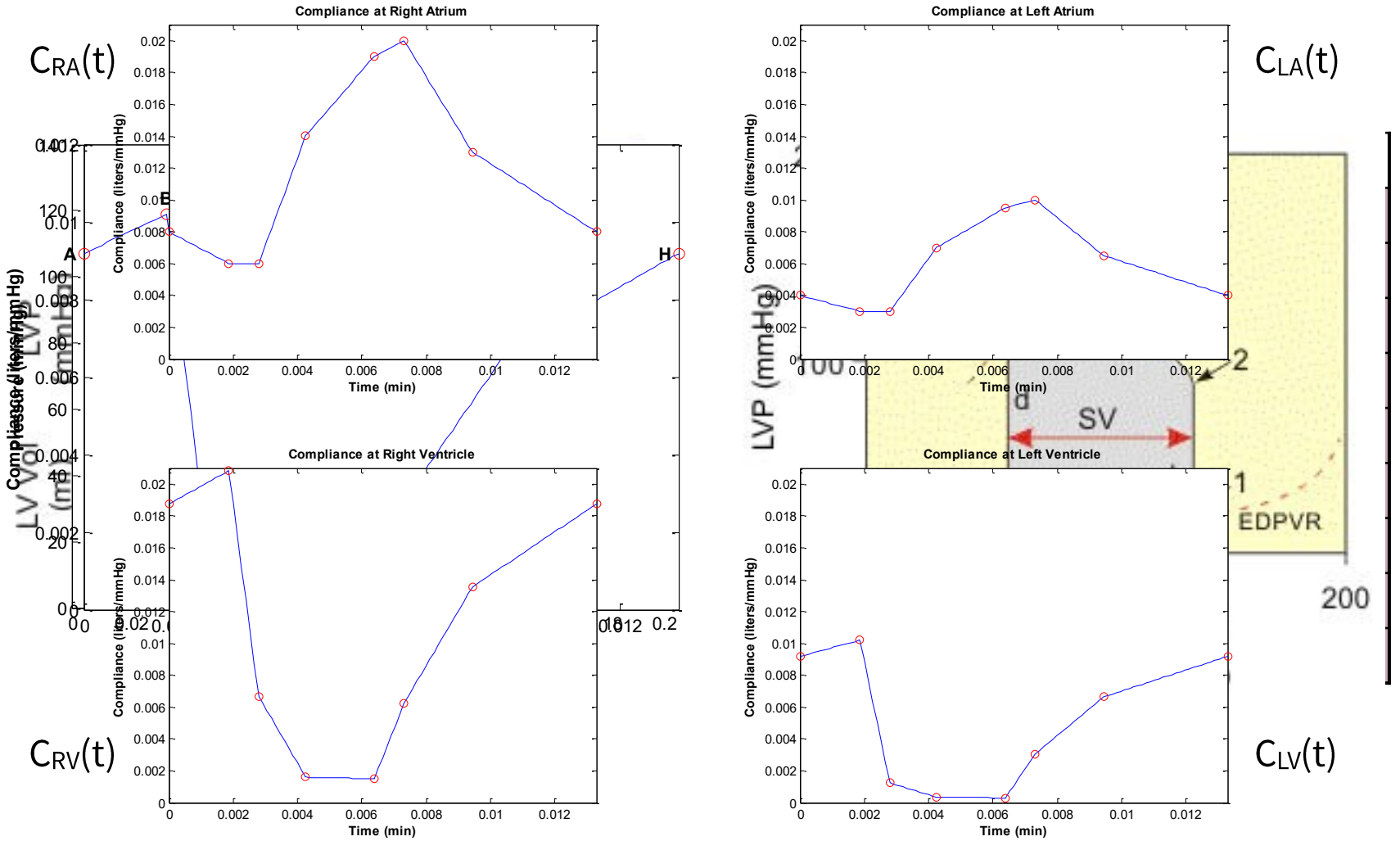
$$\frac{d(C_1(t)P_1(t))}{dt} = Q_1(t) - Q_2(t)$$

$$\frac{C_{sv}dP_{sv}(t)}{dt} = \frac{P_{sa}(t) - P_{sv}(t)}{R_s} - \frac{P_{sv}(t) - P_{RA}(t)}{R_{sv}}$$

$$\frac{C_{sa}dP_{sa}(t)}{dt} = \frac{S_{Ao}(t)(P_{LV}(t) - P_{sa}(t))}{R_{Ao}} - \frac{P_{sa}(t) - P_{sv}(t)}{R_s}$$

$$S_{Mi} = \begin{cases} 1 & P_{LA} > P_{LV} \\ 0 & otherwise \end{cases} \quad S_{Ao} = \begin{cases} 1 & P_{LV} > P_{sa} \\ 0 & otherwise \end{cases} \quad S_{Tr} = \begin{cases} 1 & P_{RA} > P_{RV} \\ 0 & otherwise \end{cases} \quad S_{Pu} = \begin{cases} 1 & P_{RV} > P_{pa} \\ 0 & otherwise \end{cases}$$

Pumping Function: C(t)



Numerical Method

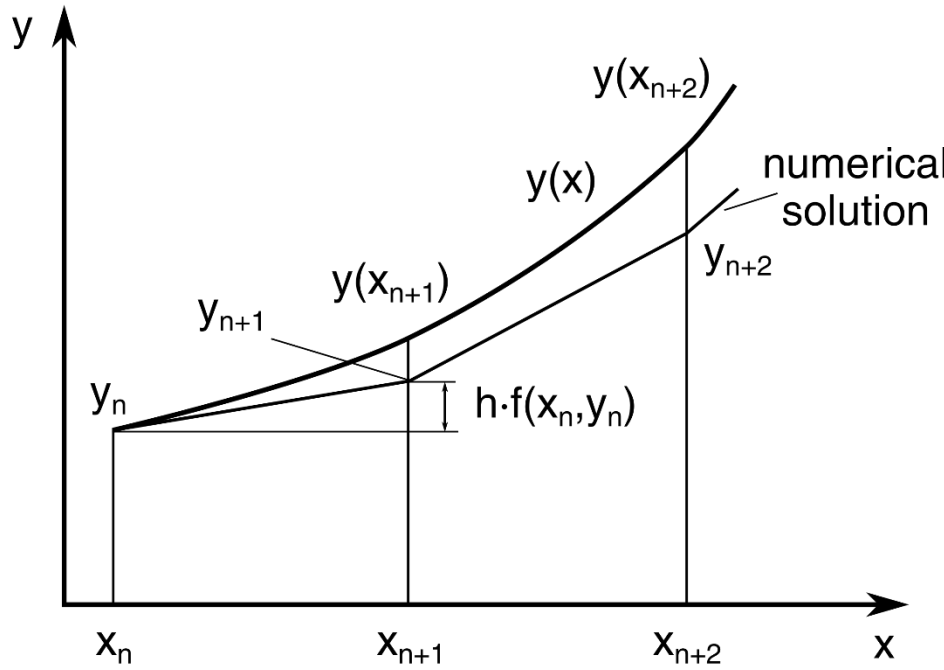
- Backward Euler Method

Governing equation at LV

$$\frac{d(C_{LV}(t)P_{LV}(t))}{dt} = \frac{S_{Mi}(t)(P_{LA}(t)-P_{LV}(t))}{R_{Mi}} - \frac{S_{Ao}(t)(P_{LV}(t)-P_{sa}(t))}{R_{Ao}}$$

Discrete equation

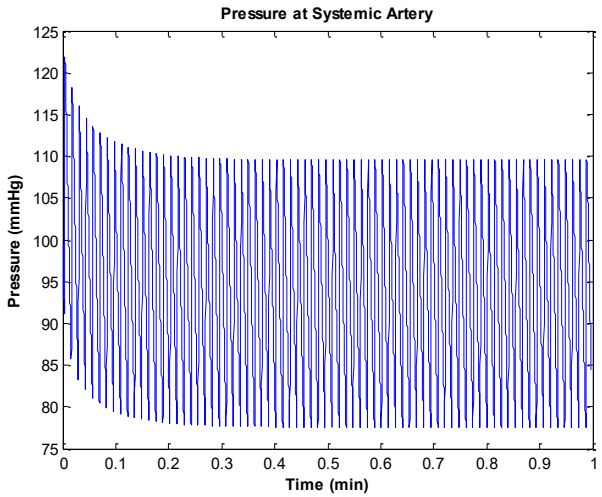
$$\frac{C_{LV}^{n+1}P_{LV}^{n+1}-C_{LV}^{n}P_{LV}^{n}}{\Delta t} = \frac{S_{Mi}^{n+1}(P_{LA}^{n+1}-P_{LV}^{n+1})}{R_{Mi}} - \frac{S_{Ao}^{n+1}(P_{LV}^{n+1}-P_{sa}^{n+1})}{R_{Ao}}$$



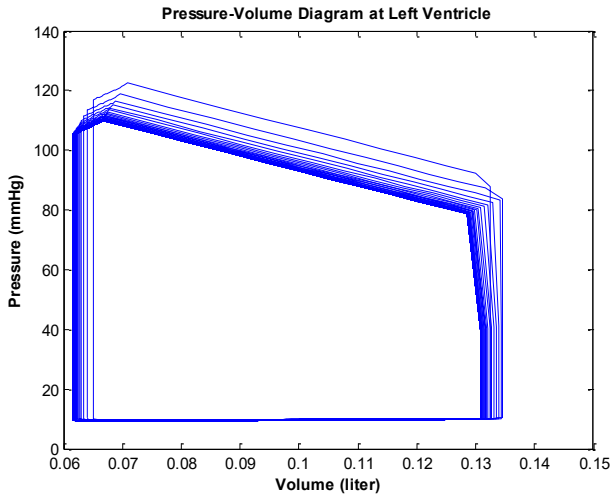
We need to solve a 8×8 matrix system for updated pressures.

Normal Case

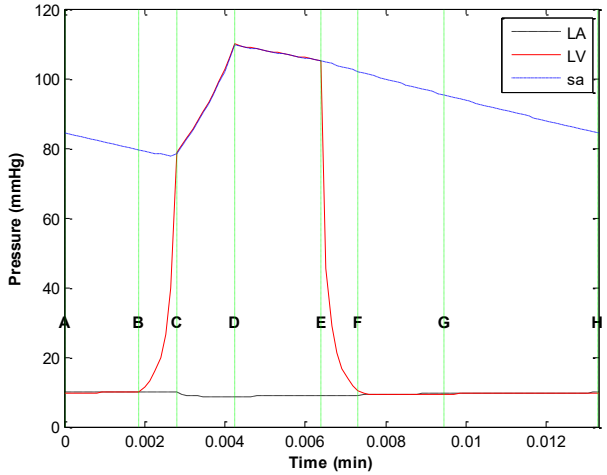
Psa during 1 min



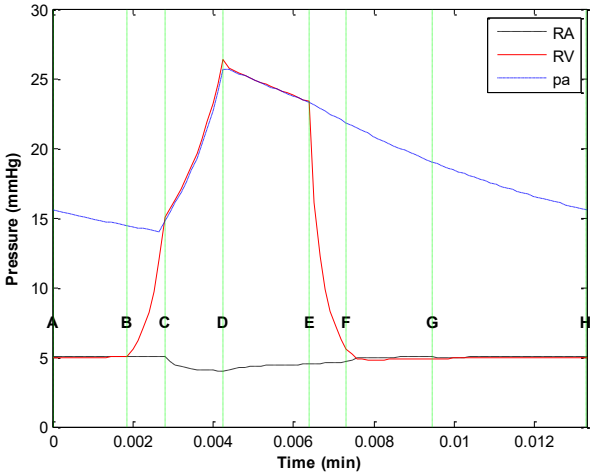
P-V diagram at LV

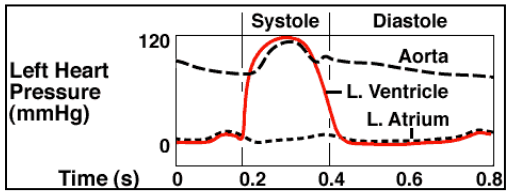


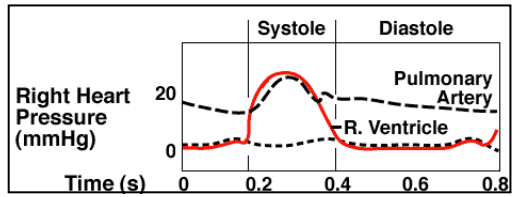
Left heart pressures



Right Heart pressure







After the periodic steady state…

- Pressures are 109.5 / 77.6 mmHg
- Stroke volume is around 0.07 liter
- Heart rate is 1.25 Hz
- Cardiac output is equal to 5.41 liter/minute

Although we use linear functions for cardiac compliances as a pumping source, all curves approximate representative curves for normal human.

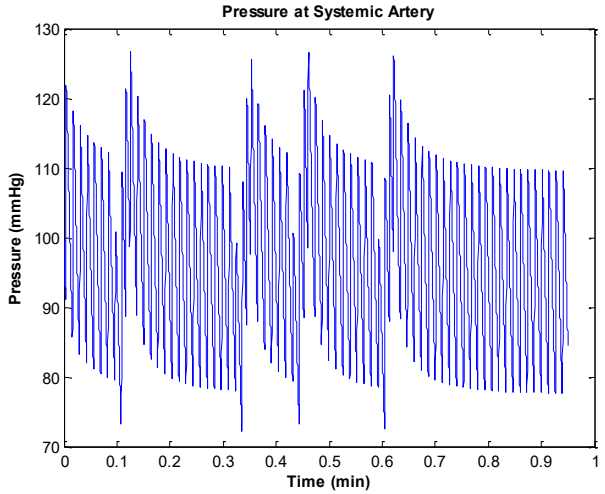
Arrhythmia Case

Irregular pumping: ΔV=0.05, T=0.0133

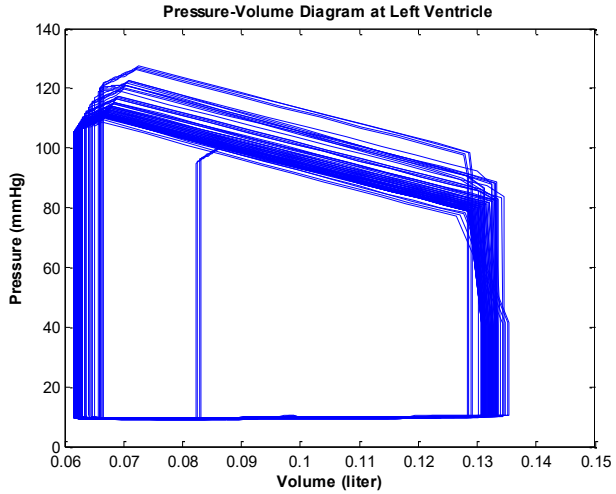
After irregular pumping (2 times): ΔV=0.07, T=0.0133*2/3

Normal Case : ΔV=0.07, T=0.0133

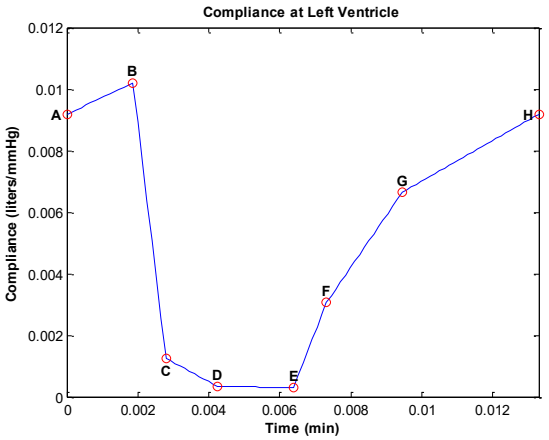
Psa during 0.9646 min



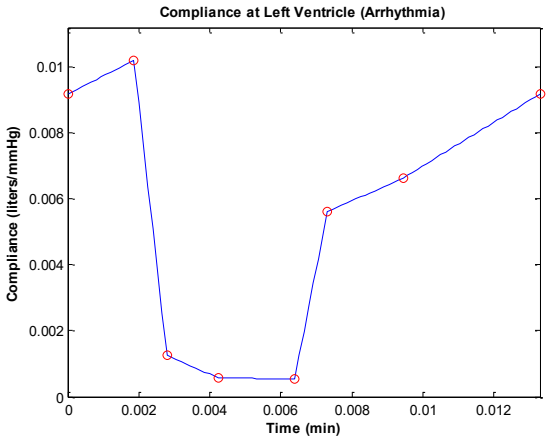
P-V diagram at LV



(Normal Case $C^{LV}(t)$)



(Arrhythmia Case $C^{LV}(t)$)



When heartbeat is irregular…

- 8th, 26th, 35th, and 48th beats are irregular
- Pressures are 99.8 / 72.1 mmHg
- Stroke volume is around 0.05 liter

After irregular pumping…

- Pressures are 125.9 / 97.9 mmHg

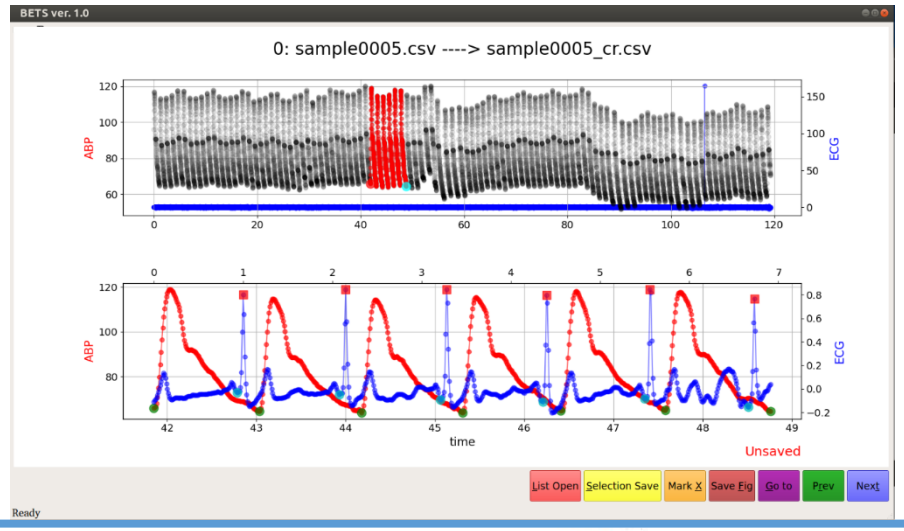
Prediction of Left Ventricular Ejection Fraction(EF)

- 병원으로부터 제공받은 데이터
  - Data set1 : 연구대상자(환자) 속성 데이터 + 대동맥 혈압 시계열 (n = 2250)
  - Data set2 : 연구대상자(환자) 속성 데이터 + 대동맥 혈압 시계열 + 심전도 시계열 (n = 103)

	vessel	procedure	action	file	검사일	성별/나이						
108	LAD MID	PRE	ADO IV	0124_LAD MID_PRE_ADO IV_CFR	2012-12-10	M/67세	BP: 142 / 88	Ht: 168cm	Wt: 78kg	BSA: 1.88㎡		
109	RCA MID	POST STENT	ADO IV	0125_RCA MID_POST STENT_ADO IV			과거검사 : Yes					
110	RCA MID	PRE		0126_RCA MID_PRE			----------					
111	LAD MID	PRE	ADO IV	0127_LAD MID_PRE_ADO IV_CFR								
							M-Mode data		MV Doppler			
							LVIDd: 46mm	IVSd : 9mm	E: 0.59m/s	e`: 0.057m/s		
							LVIDs: 27mm	LVPWd: 8mm	A: 0.81m/s	a`: 0.121m/s		
							LA: 42mm	E/A: 0.73	E/e`: 10.35			
							LVEF: 66%	Ao: 32mm	DT: 297.0msec	LAVI: 29ml/m2		
							A-L (19.6 / 17.4 / 5.3)					
							LVMI : 67.9g/㎡					
							RWT : 0.35					
							[RWMA]----------					
								Ant	A-S	I-S	Inf	I-L	A-L
							Basal	1	1	1	1	1	1
							Mid	1	1	1	1	1	1
							Apical	1		1	1		1
							Apex	1					
							1:Normal, 2:Hypokinesia, 3:Akinesia, 4:Dyskinesia, 5:Aneurysm, 99:Invisible						

index	patient_id	file_name	gender	age	height	weight	BSA	EF	heart_rate	bp_max	bp_min
1	233	3394_LAD	M	51	179	71.4	1.89	64	61	100	63
2	234	3397_RCA	F	54	147	43.65	1.33	48.7	89	130	63
3	235	3400_DIA(	M	69	160	67	1.7	38.6	92	131	95
4	235	3403_LCX	M	69	160	67	1.7	38.6	92	131	95
5	236	3406_LAD	M	50	160	80	1.83	17.8	113	149	96
6	236	3409_RCA	M	50	160	80	1.83	17.8	113	149	96
7	237	3412_LAD	M	49	181	64.9	1.83	67	88	127	76
8	238	3415_LAD	M	73	156	40.2	1.34	44.3	72	126	65
9	239	3417_LAD	M	66	169	67.9	1.78	62	92	130	80
10	240	3421_LAD	F	82	151	55.1	1.5	28.3	80	95	51
11	241	3428_RCA	M	66	169	69.1	1.79	61	93	139	72
12	242	3431_RCA	F	85	145	57	1.48	68	76	152	89
13	242	3434_LCX	F	85	145	57	1.48	68	76	152	89

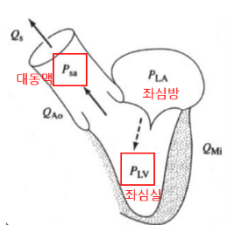
- 환자별 rest 상태에서의 성별, 나이, 키, 몸무게, BSA, 심박출률, 심박수, 혈압 최저/최고값을 추출하여 table로 정리함

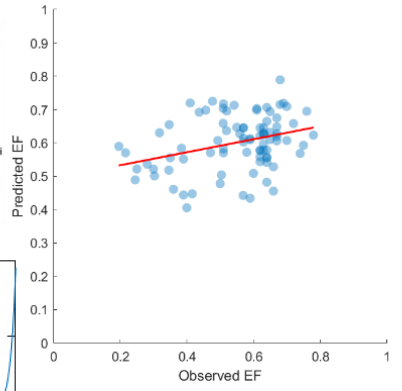


- 심박출률(Ejection Fraction, EF) : 심장 수축시 전신으로 나가는 혈액의 체적분율

$$EF = \frac{\text{심실 수축시 나가는 혈액량}}{\text{심실내의 최대 혈액량}} = \frac{\text{심실 최대 부피} - \text{심실 최소 부피}}{\text{심실 최대 부피}}$$

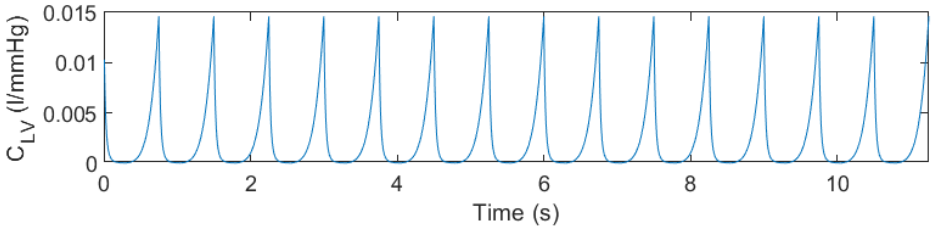
Prediction of Left Ventricular Ejection Fraction(EF)

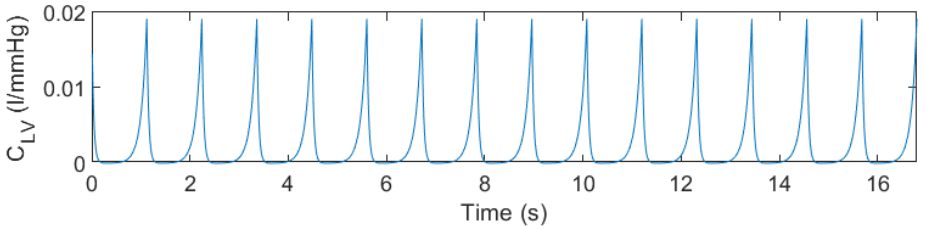


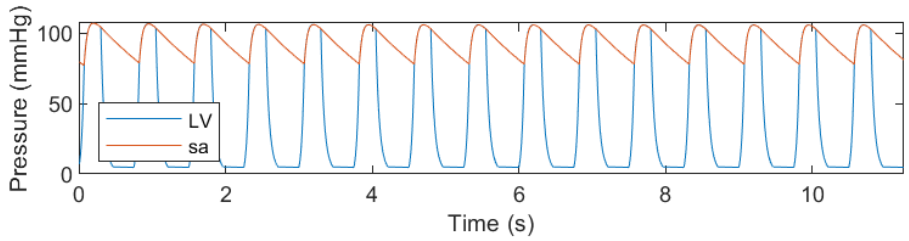


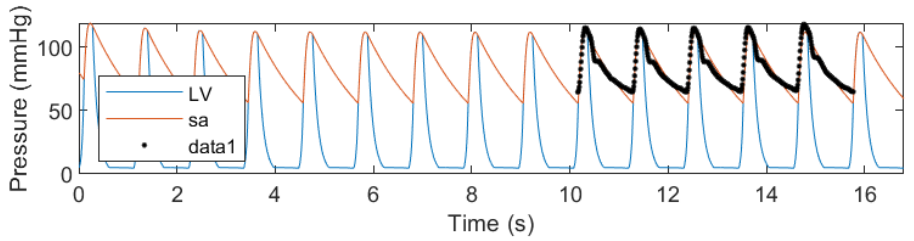
- 좌심실의 compliance 값 $C_{LV}(t)$ – 주기적 진동하는 것으로 모델링.
  * 수축 주기 T_s, 최대값 C_{LVd}(최대 이완시), 최소값 C_{LVs}(최대 수축시) → fitting parameters로 사용됨.

input



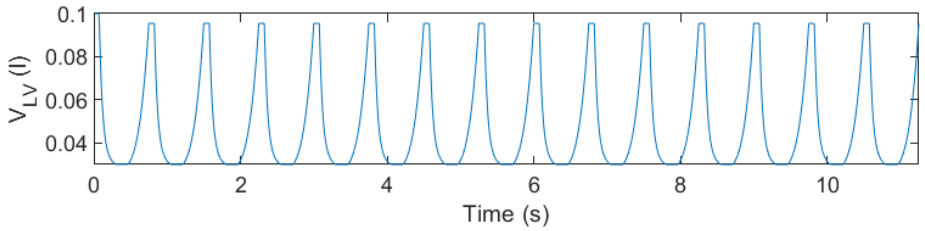


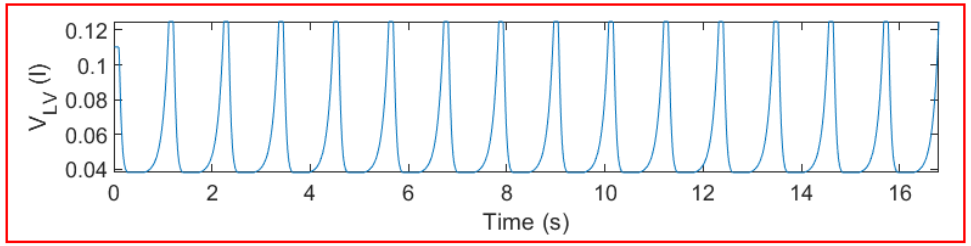




대동맥혈압 Fitting: Least Squares Method

output





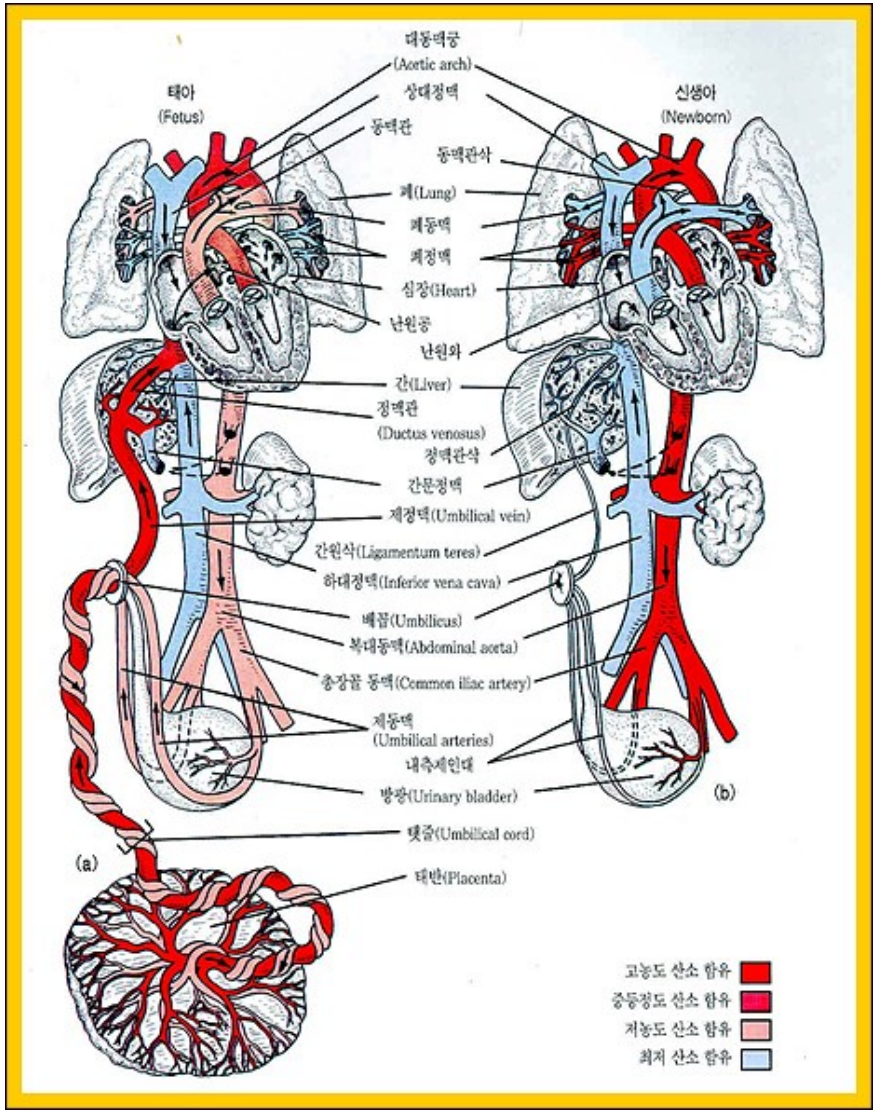
모델 좌심실 부피 변화

input -> compliance function

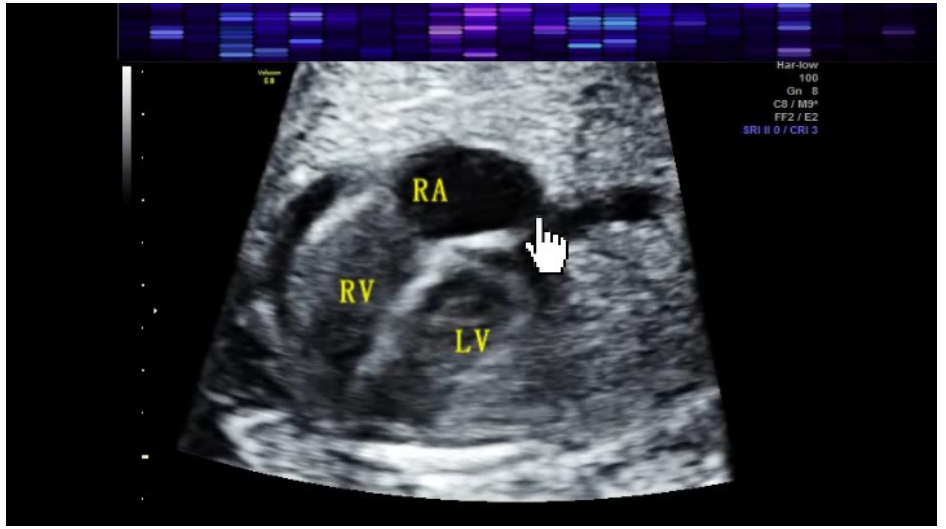
$$C_{LV}(t)=\begin{cases} C_{LVd}\left(\dfrac{C_{LVs}}{C_{LVd}}\right)^{\frac{1-\exp(-t/\tau_s)}{1-\exp(-T_s/\tau_s)}}, & 0\le t\le T_s \\ C_{LVs}\left(\dfrac{C_{LVd}}{C_{LVs}}\right)^{\frac{1-\exp(-(t-T_s)/\tau_d)}{1-\exp(-(T-T_s)/\tau_d)}}, & T_s\le t\le T \end{cases}$$

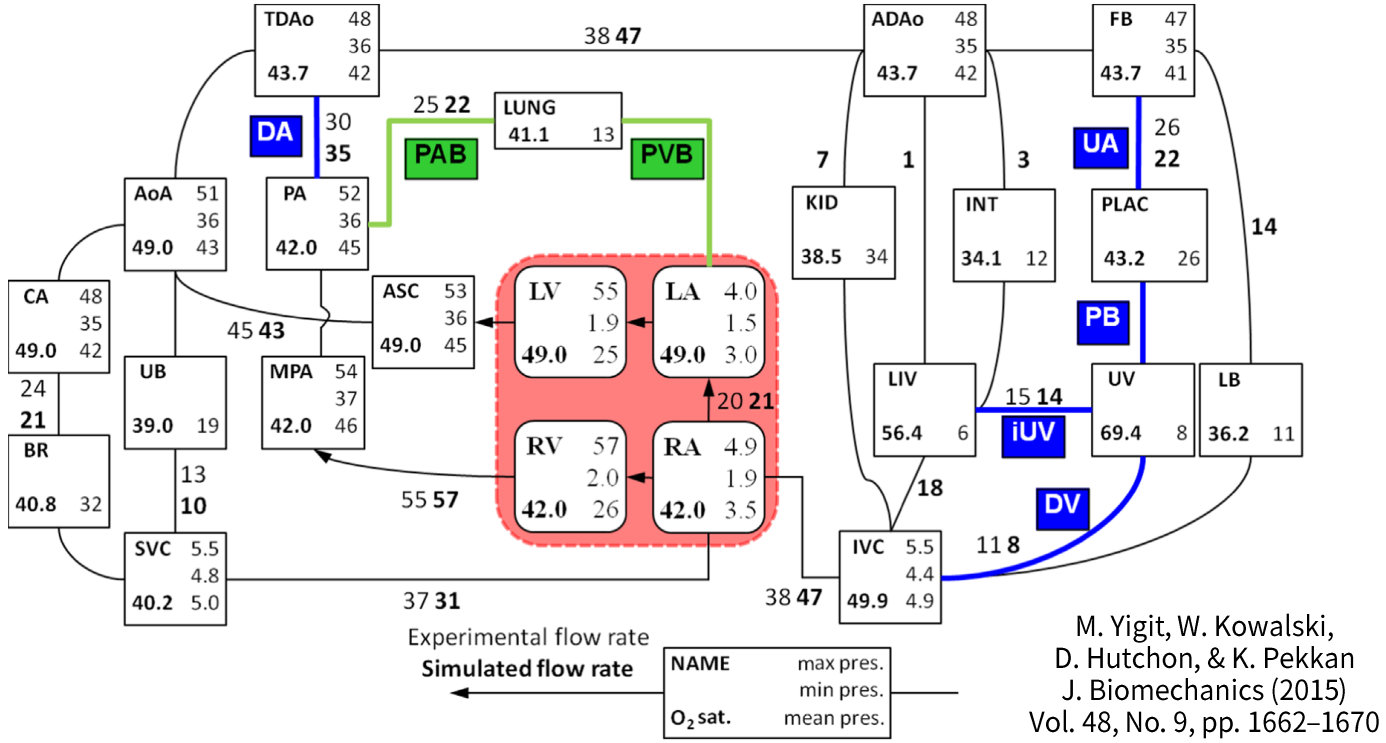
EF = (Vd-Vs) / Vd = 0.67
(정상 0.45~0.67)

Blood Circulation in the Fetus and Newborn



- 태아기에만 있는 구조물
  - 동맥관(Ductus arteriosus)
  - 정맥관(Ductus venosus)
  - 난원공(Foramen ovale)
  - 제대(탯줄, umbilical cord)





M. Yigit, W. Kowalski,
D. Hutchon, & K. Pekkan
J. Biomechanics (2015)
Vol. 48, No. 9, pp. 1662–1670

Governing Equations

- Hemodynamic model

$$\frac{d(CP)_i}{dt} = \sum_{j=1}^{N} \frac{P_j - P_i}{R_{ji}}$$

- Elastance (1/C)

$$E(t) = (E_{max} - E_{min})E_n(t) + E_{min}$$

- Gas exchange model

$$\frac{d(V[O_2])_i}{dt} = \sum_{\substack{Q_{ji}>0 \\ j=1}}^{N} Q_{ji}\left([O_2]_j + [O_2]_{in,ji}\right) - \sum_{\substack{Q_{ij}>0 \\ j=1}}^{N} Q_{ij}[O_2]_i - \dot{M}_i$$

$$[O_2]_{in,PB} = r[O_2]_U - rH_M^{-1}\left(\frac{\mathrm{H}([O_2]_{in,PB} + [O_2]_{PLAC})}{\gamma_{PB}} + \frac{(1-\gamma_{PB})\mathrm{H}([O_2]_{PLAC})}{\gamma_{PB}}\right)$$

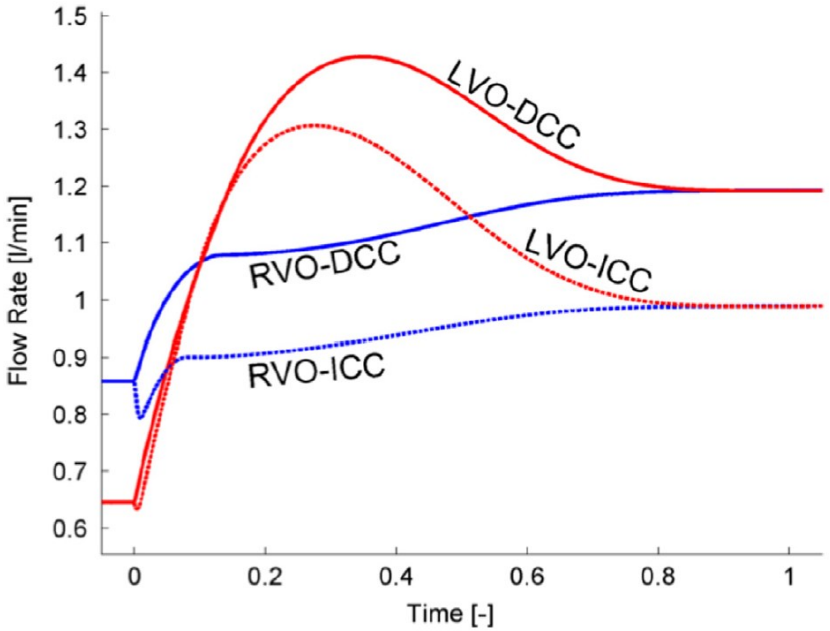
- Ventricle

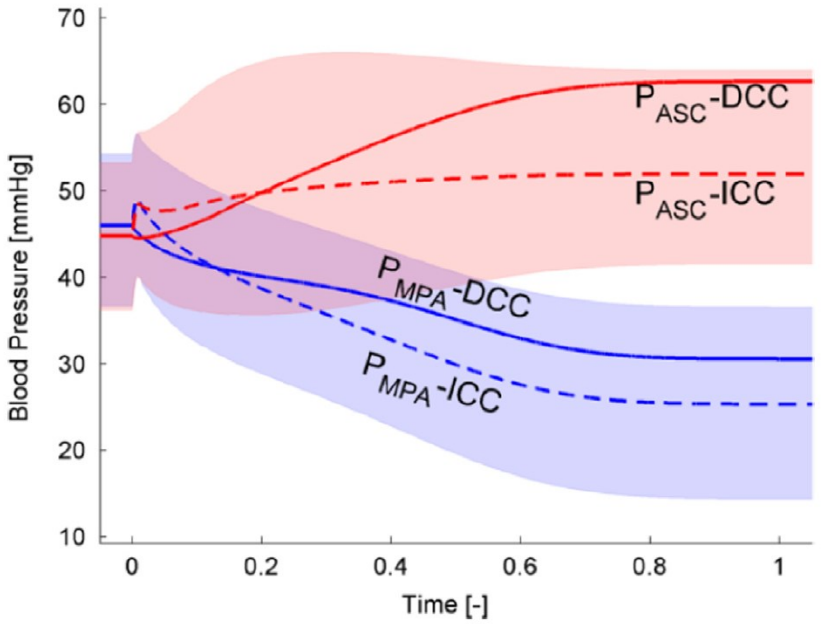
$$E_n(t) = 1.67\left[\frac{(t.\mathrm{HR}/0.303)^{1.32}}{1+(t.\mathrm{HR}/0.303)^{1.32}}\right]\left[\frac{1}{1+(t.\mathrm{HR}/0.508)^{21.9}}\right]$$

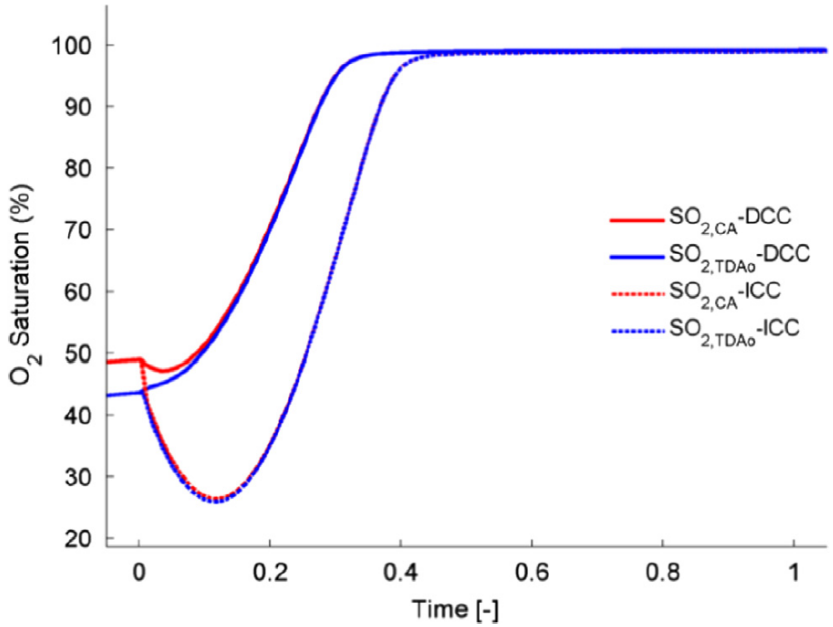
- Atrium

$$E_n(t) = 2.70\left[\frac{(t.\mathrm{HR}/0.303)^{1.32}}{1+(t.\mathrm{HR}/0.303)^{1.32}}\right]\left[\frac{1}{1+(t.\mathrm{HR}/0.25)^{21.9}}\right]$$

The Transition in Immediate and Delayed Cord Clamping







혈액량 및 심장 출력 증가

DCC는 ICC에 비해 신생아의 혈액량을 11.7% 증가시키며, preload 압력과 심장 출력을 20% 증가

동맥혈압

DCC는 ICC에 비해 20% 더 높은 동맥 혈압을 유지하며, 이는 더 나은 혈관 안정성에 기여

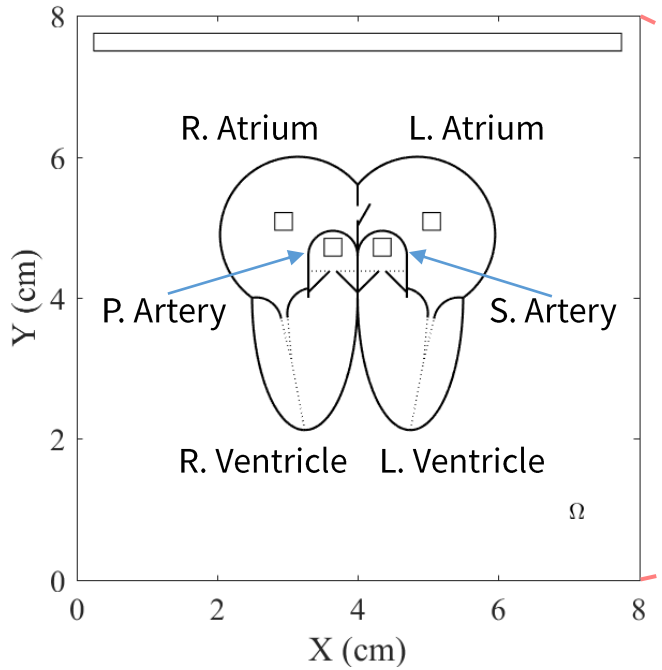
산소화

DCC는 폐 기능이 미흡하거나 지연될 경우 산소화를 유지하는 반면, ICC는 같은 조건에서 산소 포화도가 유의하게 감소

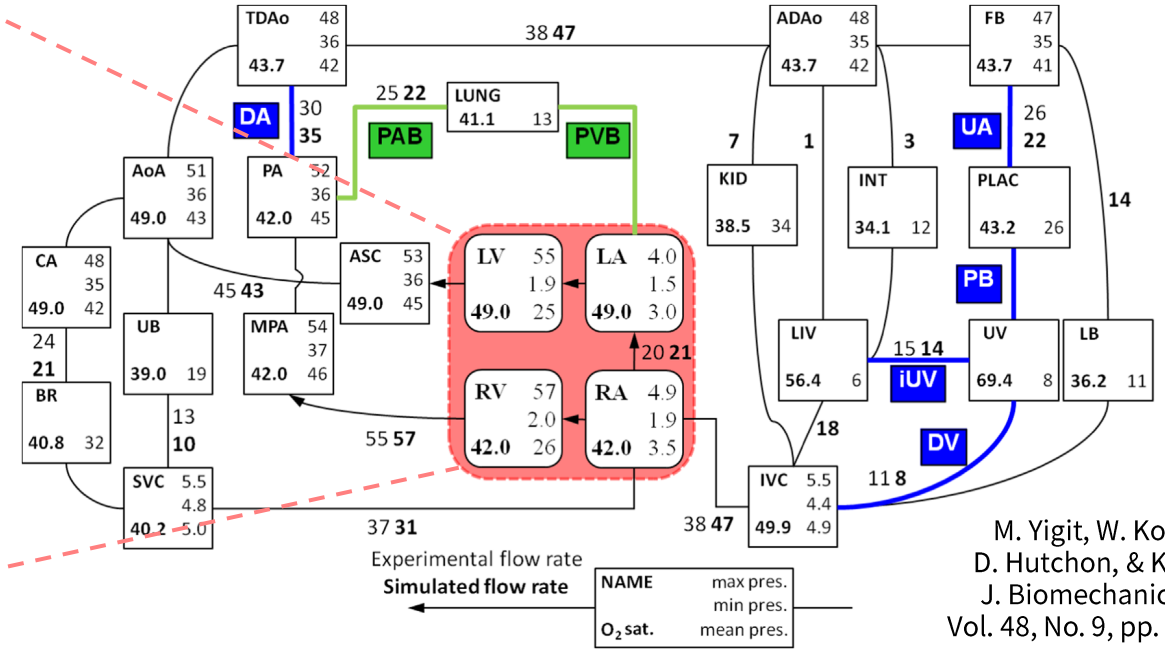
DCC가 ICC에 비해 혈액량 및 지속적인 태반 호흡으로 인한 개선된 심혈관 기능과 산소화로 인해 신생아 혈관생리학에 미치는 영향이 크다

Fetal Circulation Model

PDE Heart model



ODE Circulation model



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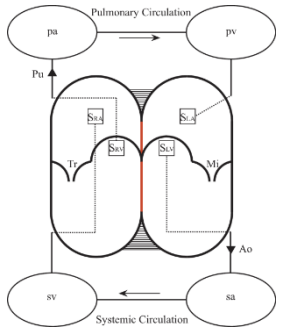
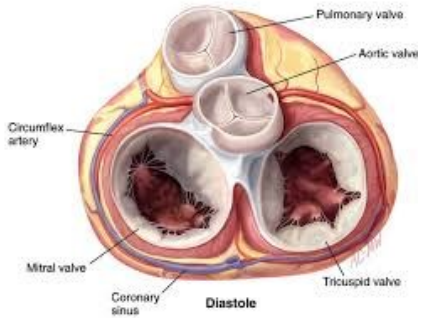
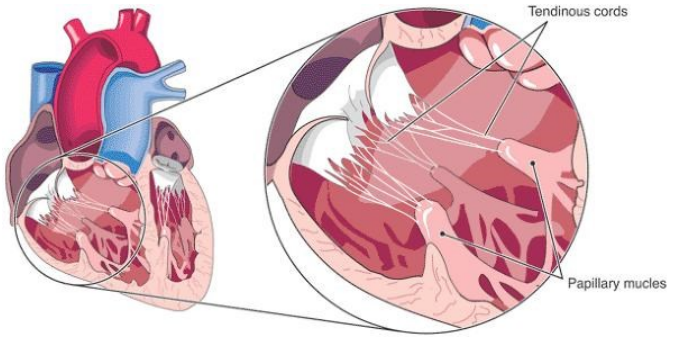
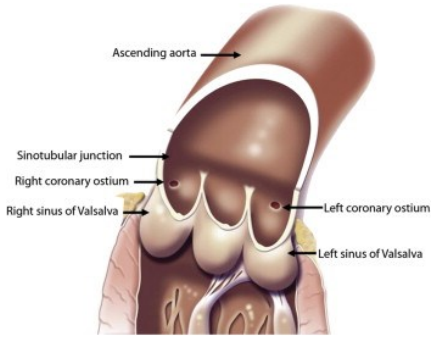
Adult model



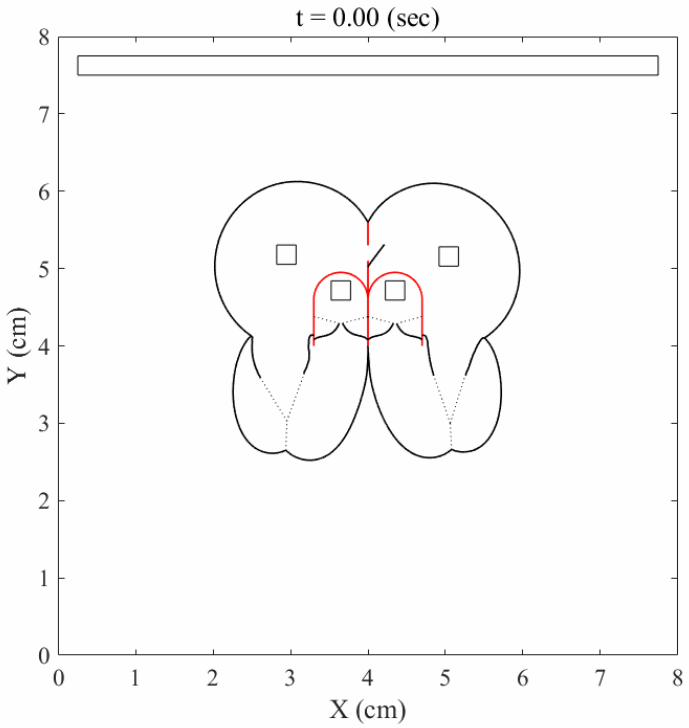


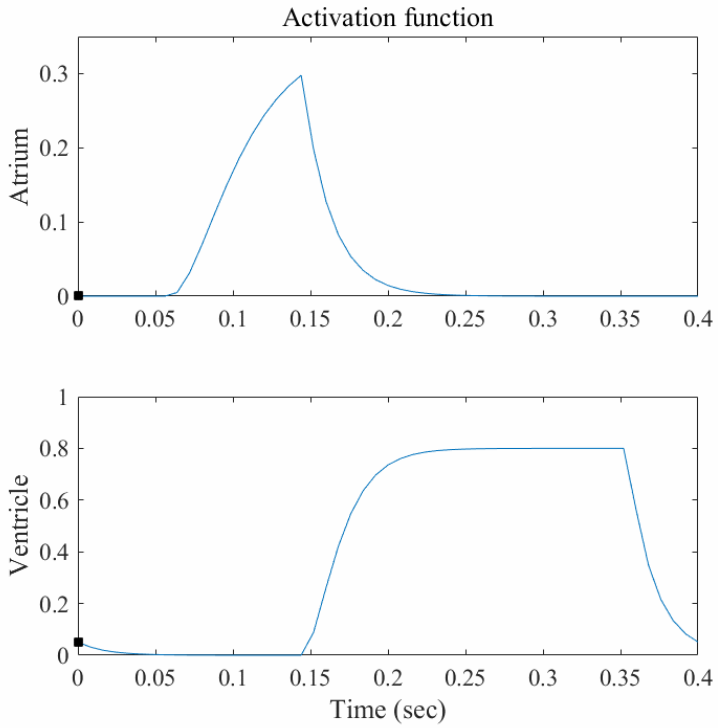
Physical valve configuration

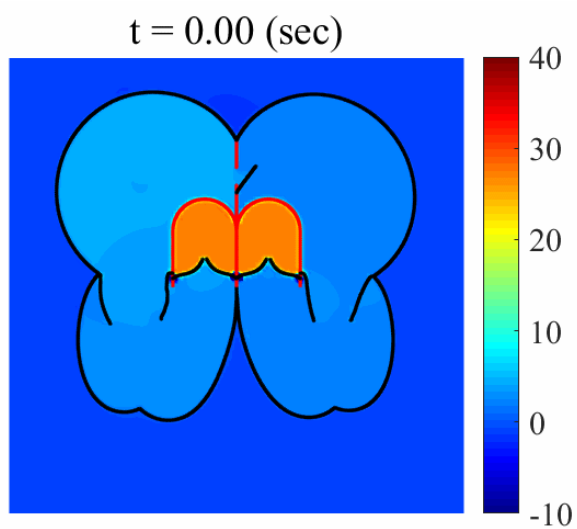




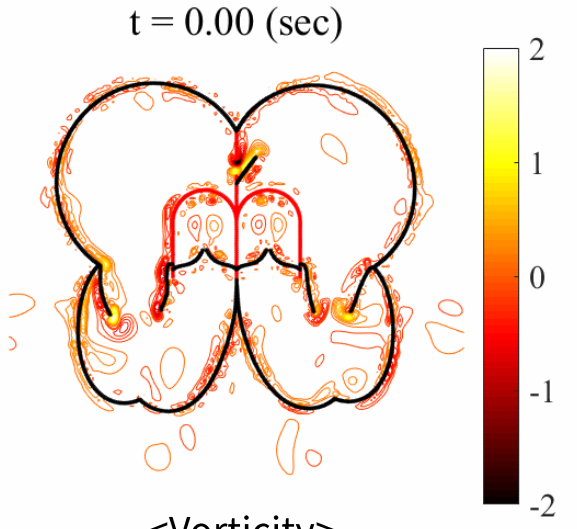
Heart Motion, Fluid Pressure, and Vorticity





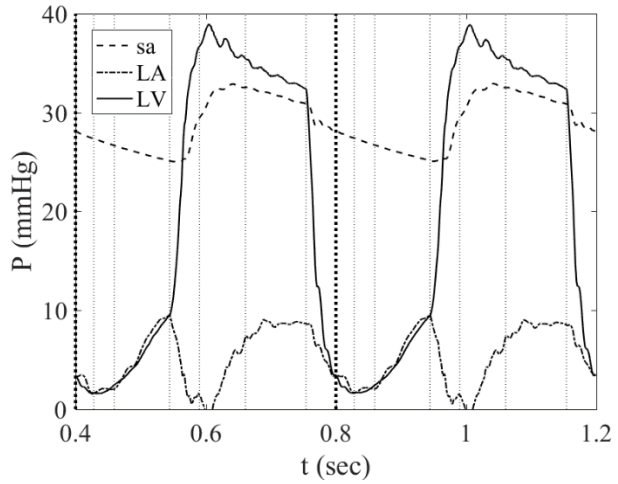


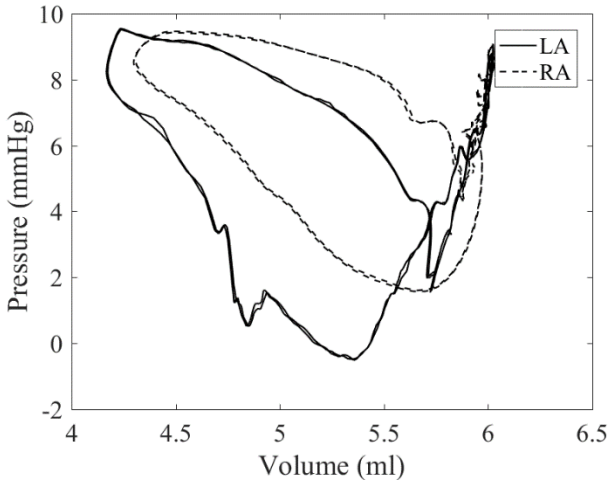
<Fluid pressure field>

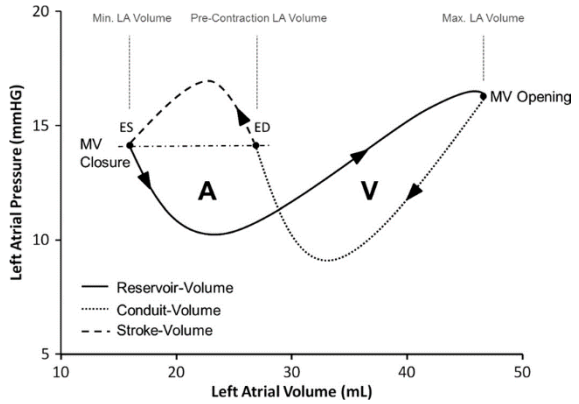


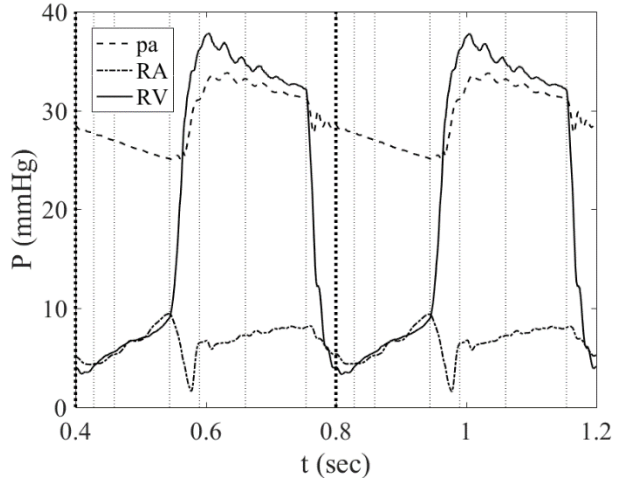
<Vorticity>

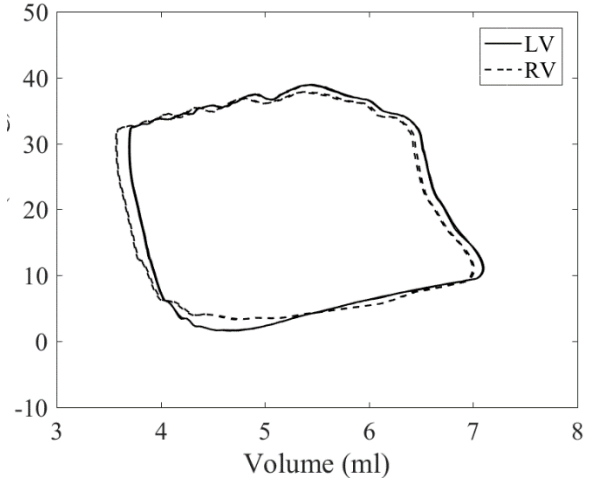
Blood Pressure and Volume in the Heart

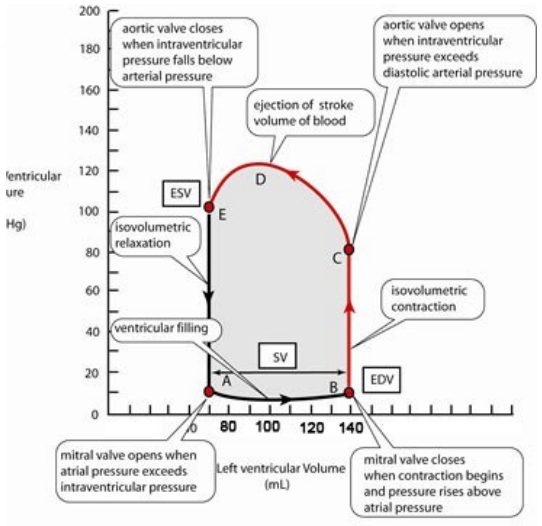








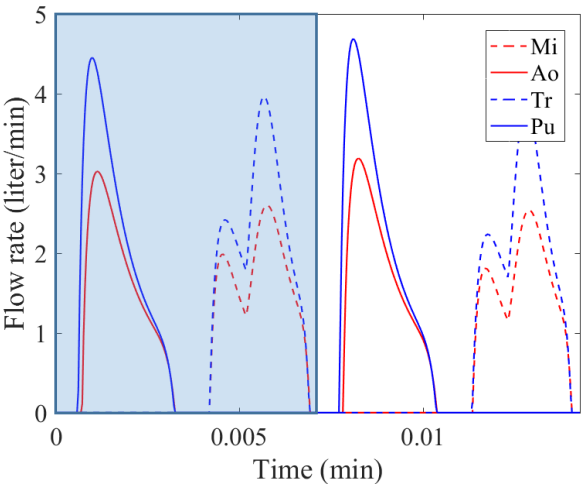




Fact: The **blood pressure** in the fetal aorta is approximately 30 mmHg (20 weeks) and **45 mmHg (40 weeks)**
The fetal **pulse pressure** is 20 mmHg (20 weeks) and **30 mmHg (40 weeks)**.

Blood Flow through Heart Valves and Foramen Ovale

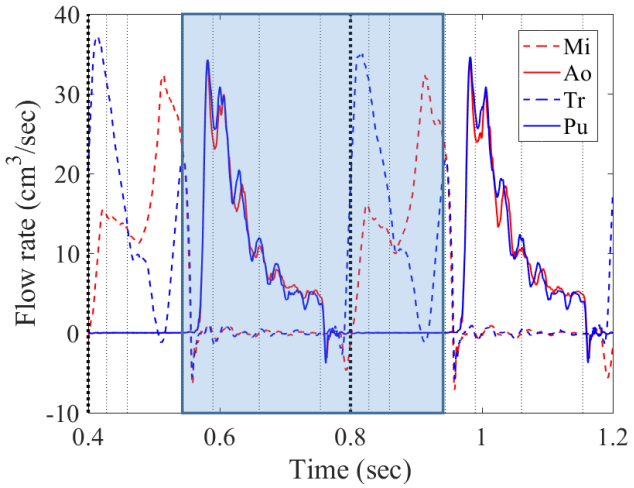
Only LP model



Stroke Volume (ml)

Mi: 4.4, Ao:4.4, Tr: 5.9, Pu: 5.9

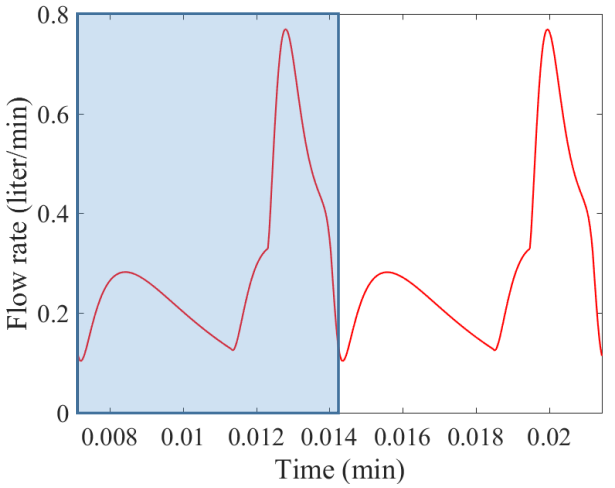
Combined model



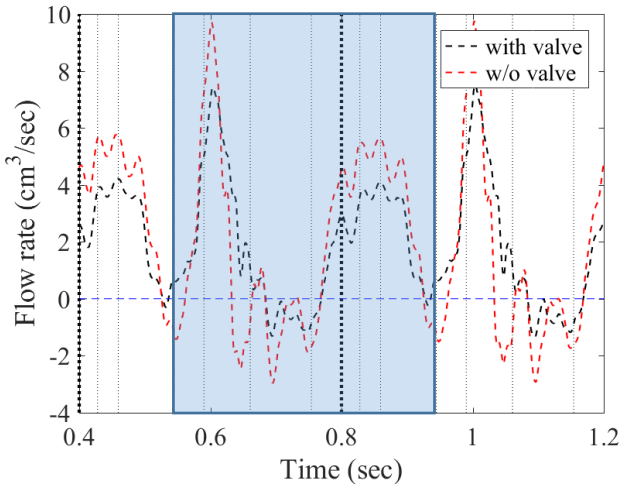
Stroke Volume (ml)

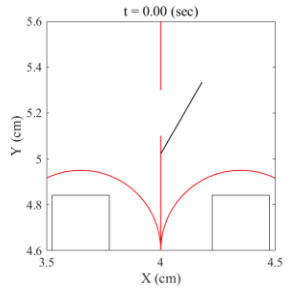
Mi: 2.50, Ao:2.36, Tr: 2.56, Pu: 2.38

Only LP model



Combined model





Fact: The left and right stroke volume

12 weeks: 0.02 mL, 0.01 mL, 20 weeks: 0.30 mL, 0.32 mL,

34 weeks: 2.07 mL, 2.67 mL

Fact: 난원공은 심장주기동안 두번 열고 닫힌다.

1. 심실 수축기 동안 열리고, 심실 확장이 시작되면 닫힌다.
2. Tricuspid valve가 열리고 심방이 수축하는 동안 열리고, 심방킥이 끝나면 닫힌다.

-> 수축기에는 짧게, 이완기에는 길게 열린다.

Conclusions

- **Pharmacokinetics(PK)와 Pharmacodynamics(PD)**는 **의약품의 체내 행동과 효과에 관한 연구**를 다루는 분야입니다. 이러한 연구들은 특정 의약품이 체내에서 어떻게 흡수, 대사, 분포, 배설되는지를 이해하고 그 효과를 예측하는 데 중요합니다. **Fluid mechanics**는 **액체나 기체의 흐름, 압력, 속도 등을 연구하는 분야**로, 여기에는 유체 역학의 다양한 이론과 원리들이 포함됩니다.

- 이 둘을 접목하는 연구는 다양한 형태로 진행될 수 있습니다. 예를 들어, **약물이 체내에서 흐름하는 동안의 유체 역학적 특성을 분석하여 약물의 흡수 속도나 분포를 이해**하는 것이 가능합니다. **약물의 경로와 동적인 흐름을 고려하여 약동학적 모델을 개발하는 등의 방법**으로 PK와 PD를 Fluid mechanics와 결합할 수 있습니다.

- 이러한 연구는 **약물의 효과를 개선**하고, **효율적인 치료 방법을 개발**하는 데 도움을 줄 수 있습니다. 또한, **약물 전달 시스템의 설계나 약물의 흡수 및 분포에 영향을 미치는 유체 역학적 변수들을 고려하여 새로운 의약품 개발**에 활용될 수 있습니다.

Thank you for your attention!

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