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Cardiovascular disintegration: A conceptual, model-based approach to heart failure hemodynamics

Kardiyovasküler ayrışma: Kalp yetersizliği hemodinamisine düşünsel, model temelli bir yaklaşım

Emre Aslanger, M.D.,[1] Özlem Yıldırımtürk, M.D.,[2] Ayça Türer Cabbar, M.D.,[1] Muzaffer Değertekin, M.D.[1]

[1]Department of Cardiology, Yeditepe University School of Medicine, İstanbul, Turkey
[2]Department of Cardiology, Health Sciences University, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: The current understanding of heart failure (HF) largely centers round left ventricular (LV) function; however, disorders in serial integration of cardiovascular system may cause a hemodynamic picture similar to left-sided HF. Therefore, focusing only on LV function may be a limited and misleading approach. We hypothesized that cardiovascular system has four major integration points, and disintegration in any of these points may produce the hemodynamic picture of HF.

Methods: We used a computational model in which mechanical properties of each chamber were characterized using time-varying elastance, and vascular beds were modeled by series of capacitances and resistances. The required percent changes in stressed volume ($V_{stressed}$) was presented as a measure of congestion susceptibility.

Results: As mean systemic pressure is closely correlated with pulmonary capillary wedge pressure (PCWP), arteriovenous disintegration can create a diastolic dysfunction pattern, even without any change in diastolic function. For 10%, 20%, 30%, 40%, and 50% interventricular disintegration, required $V_{stressed}$ for reaching a PCWP over 20 mmHg was decreased by 42.0%, 31.2%, 22.5%, 15%, and 8.3%, respectively. Systolodiastolic disintegration, namely combined changes in the end-diastolic and systolic pressure-volume curves and ventriculoarterial disintegration significantly decreases the required percent change in $V_{stressed}$ for generating congestion.

Conclusion: Four disintegration points can produce the hemodynamic picture of HF, which indicates that combination of even seemingly mild abnormalities is more important than an isolated abnormality in a single function of a single chamber. Our findings suggest that a "cardiovascular disintegration" perspective may provide a different approach for assessing the HF syndrome.

ÖZET

Amaç: Kalp yetersizliğine (KY) dair mevcut anlayış büyük ölçüde sol ventrikül (SV) işlevlerine odaklanmaktadır, ancak kalp-damar sisteminde ardışık tümleşmeye dair bozukluklar da sol taraflı KY'ye benzer bir tablo oluşturabilir. Bu nedenle sadece SV işlevlerine odaklanmak sınırlı ve yanıltıcı bir yaklaşım olabilir. Mevcut çalışmada kalp-damar sisteminde dört ana tümleşme noktası olduğunu ve bu noktalardaki ayrışmanın KY hemodinamik tablosunu oluşturabileceğini kurguladık.

Yöntemler: Her odacığın zamana bağlı elastans, damar yataklarının ardışık kapasitans ve dirençler şeklinde temsil edildiği bir bilgisayar modeli kullandık. Konjesyona yatkınlık için sıkıştırılmış hacimde ($V_{sıkıştırılmış}$) yüzdesel değişiklikleri hesapladık.

Bulgular: Ortalama sistemik basınç, pulmoner kapiller tıkalı basınç (PKTB) ile yakından ilişkili olduğundan arteriyovenöz ayrışma diyastolik fonksiyonlarda herhangi bir değişiklik olmadan da diyastolik disfonksiyon paterni oluşturabildi. Ventriküller arası ayrışmanın %10, %20, %30, %40 ve %50'lik değerleri için PKTB'ı 20 mmHg üzerine çıkaracak gerekli $V_{sıkıştırılmış}$ sırasıyla %42.0, %31.2, %22.5, %15 ve %8.3 azaldı. Diyastol sonu ve sistolik basınç-hacim eğrilerindeki eş zamanlı değişiklikler ile temsil edilen sistolodiyastolik ayrışma ve ventriküloarteriyal ayrışma konjesyon oluşturmak için gerekli $V_{sıkıştırılmış}$ mikarını belirgin derecede azalttı.

Sonuç: Dört tümleşme noktasındaki bozukluklar KY'nin hemodinamik tablosunu oluşturabilmektedir, bu da ilk bakışta hafif gibi gözüken anormallikler bütününün tek bir odacığın tek bir işlevindeki bozukluktan çok daha önemli olduğunu göstermektedir. Bu açıdan bakıldığında "kalp yetersizliği" sendromunun "kardiyovasküler ayrışma" temelinde incelenmesi yeni bir perspektif sağlayabilir.

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Correspondence: Emre Aslanger, M.D. Department of Cardiology, Yeditepe University School of Medicine, İstanbul, Turkey
Tel: +90 532 510 97 96 e-mail: mr_aslanger@hotmail.com

Despite major advances in the understanding of heart failure (HF) pathophysiology, the current framework of HF hemodynamics still largely centers around left ventricular (LV) function.[1,2] Even the term "failure" itself comes from a more than a century-old view that defines HF as the failure of LV to pump sufficient blood to meet the body's requirements, resulting in high LV filling pressures transmitting "backwards."[3] When it became clear that nearly half of the patients with HF syndrome do not fail in LV systolic performance, diastolic dysfunction was proposed as the new candidate for the underlying abnormality. Accordingly, current guidelines recommend use of echocardiographic indices of diastolic dysfunction for the diagnosis of HF with preserved ejection fraction (HFpEF).[1,2] However, these indices were actually derived from patients with high diastolic pressures, not necessarily diastolic function per se, which might be explained by mechanisms other than abnormal diastology.[4] Furthermore, it is not clear how the presence of low ejection fraction (EF) automatically excludes the isolated presence of abnormalities blamed for HFpEF.

The cardiovascular system is a continuous closed circuit comprising successive hemodynamic compartments necessitating a seamless integration of their differing mechanical properties. Any disturbance in this serial integration may cause abnormal pressure or volume loading in the upstream compartment, despite not having an inherent structural abnormality in the first place. If the inflow of a cardiovascular compartment temporarily exceeds its outflow, the compartment becomes fluid overloaded and its pressure increases. When the mechanisms governing inflow and outflow are not the same and respond differently to this increased pressure, this compartment continues to be pathologically overloaded until a new equilibrium is achieved; that is, any transition from one cardiovascular compartment to the other with different inflow and outflow mechanisms can be regarded as an integration point. For example, right and left ventricles have to pump the same cardiac output (CO) to keep a steady state, but their contractile properties and corresponding vascular systems are governed by independent mechanisms. If right ventricular (RV) output temporarily exceeds LV output, excess volume has to accumulate in the intermediary (pulmonary) vascular compartment, which is frequently explained with diastolic dysfunction in the current view. Therefore, focusing only on LV function rather than the serial integration of the whole system may be a limited and misleading approach to HF.

Abbreviations:

C	*Compliance*
CO	*Cardiac output*
E_a	*Arterial elastance*
EDPVR	*End-diastolic pressure volume relationship*
E_{es}	*End-systolic elastance*
EF	*Ejection fraction*
ESPVR	*End-systolic pressure volume relationship*
HF	*Heart failure*
HFpEF	*Heart failure with preserved ejection fraction*
HFrEF	*Heart failure with reduced ejection fraction*
LV	*Left ventricular*
SV	*Stroke volume*
P_{ms}	*Mean systemic pressure*
PCWP	*Pulmonary capillary wedge pressure*
R	*Resistance*
RA	*Right atrium*
R_c	*Characteristic impedance*
RV	*Right ventricular*
$V_{stressed}$	*Stressed volume*

We proposed four integration points in cardiovascular system, as follows (Figure 1): (1) As the heart redistributes blood from veins to arteries, emptying of veins behaves different from filling of arteries. We defined this point as *arteriovenous integration*. (2) The integration between two ventricular outputs, as described above, is defined as *interventricular integration*. (3) Ventricular filling and emptying should be equal, but these functions are operated by completely different mechanisms. We defined this point as *systolodiastolic integration*. (4) Transfer of hydraulic energy from ventricles to the arterial system defined as *ventriculoarterial integration*. Until recently, it was impossible to study the complex interaction of these numerous components of cardiovascular system because any intervention on a hemodynamic parameter inevitably results in significant changes in the others, which severely complicates the interpretation. However, powerful computer models now permit the exploration of the effects of various hemodynamic parameters either in isolation or in combination.[5-10]

In this study, we hypothesized that the cardiovascular system has four major integration points, and disintegration in any of these points may produce the congestion picture of HF, even if the LV does not have any systolic or diastolic dysfunction. We used a hemodynamic model and sought how disintegration in cardiovascular system caused fluid redistribution and congestion.

METHODS

Our study did not require institutional review board approval because we used a well-validated compu-

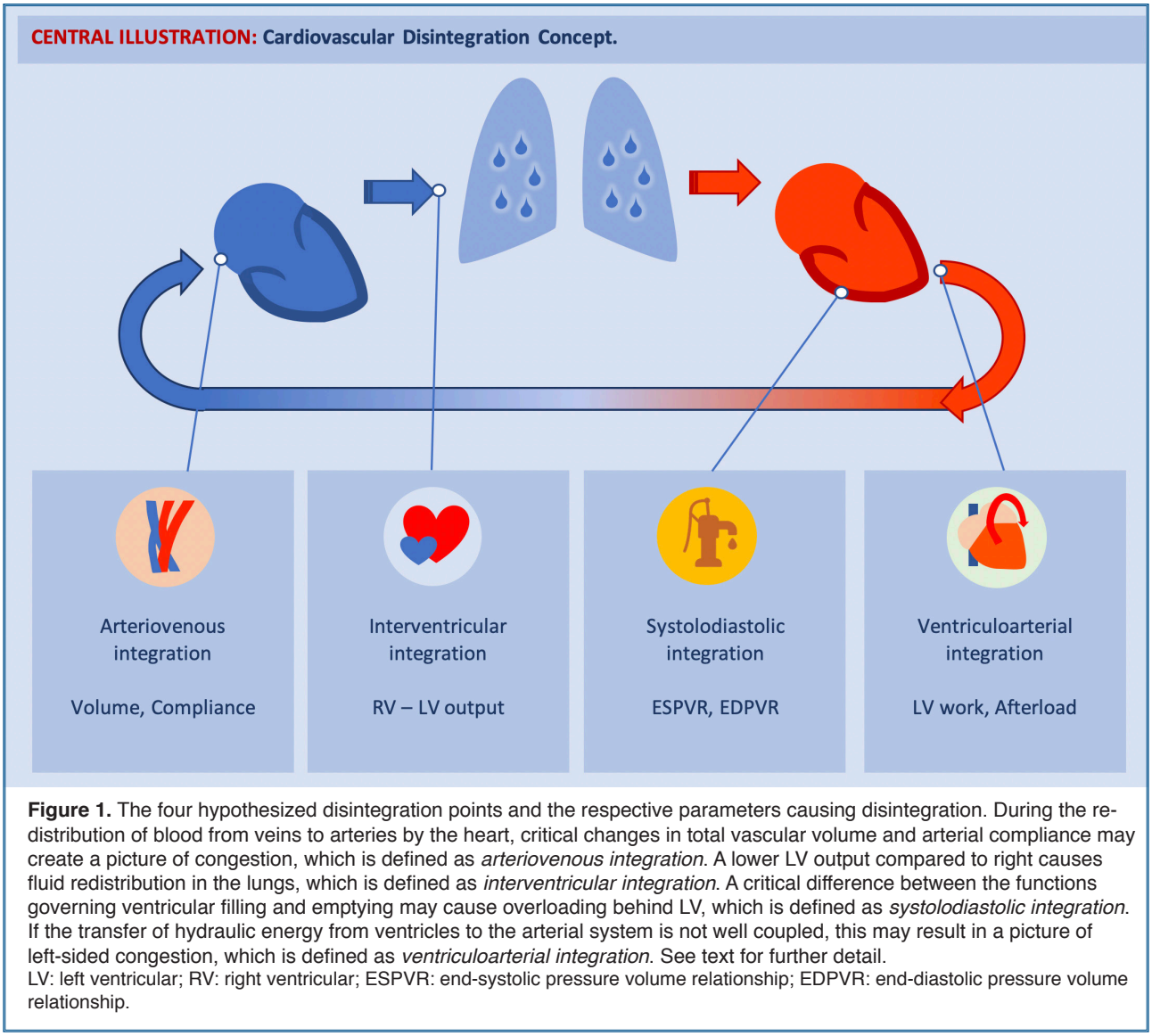

Figure 1. The four hypothesized disintegration points and the respective parameters causing disintegration. During the redistribution of blood from veins to arteries by the heart, critical changes in total vascular volume and arterial compliance may create a picture of congestion, which is defined as *arteriovenous integration*. A lower LV output compared to right causes fluid redistribution in the lungs, which is defined as *interventricular integration*. A critical difference between the functions governing ventricular filling and emptying may cause overloading behind LV, which is defined as *systolodiastolic integration*. If the transfer of hydraulic energy from ventricles to the arterial system is not well coupled, this may result in a picture of left-sided congestion, which is defined as *ventriculoarterial integration*. See text for further detail.
LV: left ventricular; RV: right ventricular; ESPVR: end-systolic pressure volume relationship; EDPVR: end-diastolic pressure volume relationship.

tational model, and normal values for baseline hemodynamic variables were collected from literature (Table 1).[5-13] The cardiovascular model used in this study has been described in detail elsewhere, and the basic governing equations are discussed in the Supplementary File 1.[5] In brief, mechanical pump properties of each chamber were characterized using a time-varying elastance model. Pulmonary and systemic vascular beds were modeled by series of capacitances and resistances. The reproducibility of the used model is 100%. Simulation results were illustrated as pressure-volume loops of RV and LV, aortic, pulmonary arterial, and ventricular pressure waveforms over time, average systemic and pulmonary outputs, as appropriate. A pulmonary capillary wedge pressure (PCWP) above 20 mmHg is used as the congestion endpoint.[14] The required percent changes in stressed volume ($V_{stressed}$) is presented as a measure of congestion susceptibility.

For the evaluation of *arteriovenous integration*, we assessed the effects of changing static components of circulation during arteriovenous fluid redistribution; namely $V_{stressed}$, mean static pressure (P_{ms}) and individual vascular compliances. Systemic and pulmonary arterial and venous compliance values (C_a, C_v, $C_{PA,}$ and C_{PV}, respectively) were decreased by 0.01 mL.mmHg^{-1}, and $V_{stressed}$ was increased by increments of 5 mL until PCWP reached to 20 mmHg. P_{ms} was calculated as $V_{stressed}$ divided by total compliance. For the evaluation of *interventricular integration*, ef-

Table 1. Normal parameters used in simulation

Parameter group/name	Symbol	Units	Values			
Common parameters						
Heart rate	HR	min^{-1}	60			
AV delay	AVD	msec	160			
Stressed blood volume	$V_{stressed}$	mL	1200			
Heart			RA	RV	LA	LV
End-systolic elastance	E_{es}	$mmHg.mL^{-1}$	0.38	1.00	0.48	2.21
Volume axis intercept	V_o	mL	10	45	10	5
Exponent for EDPVR	α	mL^{-1}	0.046	0.028	0.058	0.029
Scaling factor for EDPVR	ß	mmHg	0.44	0.34	0.44	0.34
Time to end-systole	T_{max}	msec	125	200	125	200
Time constant of relaxation	Tau	msec	20	25	20	25
AV valve resistance	R_{av}	$mmHg.sec.mL^{-1}$	0.0025		0.0025	
Circulation			Pulmonary	Systemic		
Characteristic impedance	R_c	$mmHg.sec.mL^{-1}$	0.03	0.04		
Arterial resistance	R_a	$mmHg.sec.mL^{-1}$	0.03	0.82		
Venous resistance	R_v	$mmHg.sec.mL^{-1}$	0.015	0.025		
Arterial compliance	C_a/C_{PA}	$mL.mmHg^{-1}$	20	1.83		
Venous compliance	C_v/C_{PV}	$mL.mmHg^{-1}$	7	70		

AV: atrioventricular; EDPVR: end-diastolic pressure-volume relationship; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

fects of differing LV and RV outputs were explored. LV and RV end-systolic elastances (E_{es}) were decreased and increased by increments of 0.01 $mmHg.mL^{-1}$, respectively. Corresponding EF, pressure-volume loops, ventricular and arterial waveforms were calculated. If necessary, additional 5 mL increments of $V_{stressed}$ was used until PCWP reached 20 mmHg. For the evaluation of *ventricular systolodiastolic integration*, we compared the reciprocity of end-diastolic pressure-volume relationship (EDPVR) and end-systolic pressure volume relationship (ESPVR). The exponent of EDPVR (a value) was increased and E_{es} was changed in a range similar to the published results,[15-18] and $V_{stressed}$ was increased by increments of 5 mL until PCWP reached 20 mmHg. Ventricular volume at 20 mmHg (V_{20}) were calculated according to the following formula:

$$V_{20} = \frac{\ln(\frac{20}{ß} + 1)}{\alpha} + V_0$$

where V_0 is unstressed volume of left ventricle, a is exponent for EDPVR and ß is scaling factor for EDPVR. For the evaluation of *ventriculoarterial integration*, we sought to simulate a disordered ventriculoarterial coupling within normal E_{es} limits (2.2±0.8 $mmHg.mL^{-1}$) for not letting significant interventricular or systolodiastolic disintegration to occur. Arterial elastance (E_a) was calculated as end-systolic pressure divided by stroke volume (SV). Ventriculoarterial coupling ratio was defined as E_a/E_{es} and values out of its normal range, which is typically between 0.5 and 1.2 for maximal cardiac power output and efficiency, were aimed by changing E_{es} and E_a.[15-18] E_a was changed by changing arterial resistance (R_a), characteristic impedance (R_c), and compliance (C_a). Any decrease in C_a was compensated by a similar amount of increase in C_v to keep total compliance constant.

RESULTS

Arteriovenous integration

Without changing any cardiac or vascular parameter, a 56.7% increase in $V_{stressed}$ is required to bring PCWP above 20 mmHg. However, when C_a is reduced to 75%, 50%, and 33% of its normal value, a 48.7%, 37.5%, and 27.9% increase in $V_{stressed}$ is sufficient for reaching this level, respectively. A decrease in C_{PA} in

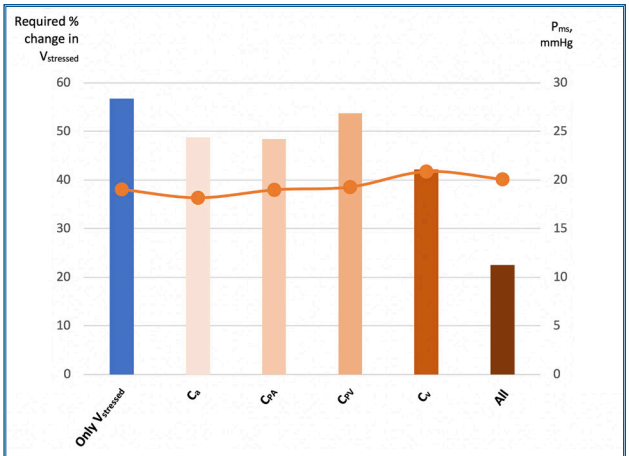

Figure 2. Required change in $V_{stresssed}$ (bars) and corresponding P_{ms} (orange line) for increasing PCWP over 20 mmHg. A P_{ms} around 20 mmHg consistently causes a PCWP over 20 mmHg with a 25% lower arterial (C_a), pulmonary arterial (C_{PA}) and venous (C_{PV}), systemic venous (C_v) and total compliance values.
$V_{stresssed}$: stressed volume; P_{ms}: mean systemic filling pressure; PCWP: pulmonary capillary wedge pressure.

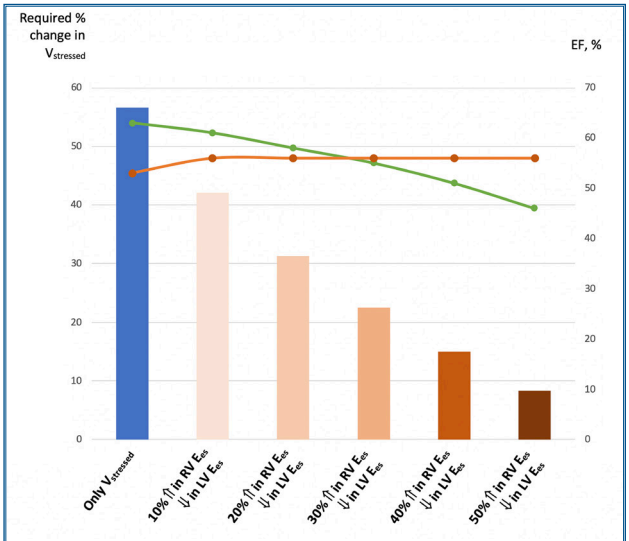

Figure 3. Required change in $V_{stresssed}$ (bars) according to percent increase in RV and decrease in LV E_{es} (horizontal axis) for increasing PCWP over 20 mmHg. Corresponding LV (green dotted line) and right ventricular EFs are also presented (orange dotted line). Even mild depression in LV, EF can be compatible with high filling pressures when right ventricular contractility is sufficiently increased.
$V_{stresssed}$: stressed volume; RV: right ventricular; LV: left ventricular; E_{es}: end-systolic elastance; PCWP: pulmonary capillary wedge pressure; EF: ejection fraction.

similar proportions results in a gradual decrease in required $V_{stressed}$ 48.3%, 40%, 36.2%, whereas these values are 53.7%, 53.3%, 50.8% for C_{PV} and 42%, 27.5%, and 17.9% for C_V, respectively. When all of the compliances are reduced by 25% and 33%, the required $V_{stressed}$ increase becomes 22.5% and 12%. Despite varying combinations of increased $V_{stressed}$ and decreased compliance to reach a PCWP of 20 mmHg, associated P_{ms} is generally approximately 20 mmHg (Figure 2).

Interventricular integration

An isolated 73% decrease in LV E_{es}, which corresponds to an EF of 31% (50% decrease from baseline), brings PCWP over 20 mmHg, whereas an isolated increase in RV E_{es} within normal range[11] decreases required percent change in $V_{stressed}$ for reaching a PCWP over 20 mmHg to 24.5%. For 10%, 20%, 30%, 40%, and 50% increase in RV and decrease in LV E_{es}, required $V_{stressed}$ for PCWP to exceed 20 mmHg were 42.0%, 31.2%, 22.5%, 15%, and 8.3%, respectively (Figures 3 and 4).

Systolodiastolic integration

EF corresponding to simulated E_{es} ranged between 49%-69%. For comparison with the published values in the literature,[18] we also calculated indexed ventricular volume at 20 mmHg (V_{20}) values for each simulated curve and found that 7.5%, 15%, 30%, 45%, and 60% increase in a value corresponded to 62.8, 58.6, 55.0, 48.9, and 44.1 $mL.m^{-2}$, respectively. These values were compatible with normal, hypertensive HF with preserved EF (HFpEF) patient cohorts. An extremely high, 79.3% isolated increase in exponent for EDPVR (a value) is required to bring PCWP over 20 mmHg. However, combined changes in a value and E_{es} produce reciprocal changes in required percent change in $V_{stressed}$ (Figure 5).

Ventriculoarterial integration

When E_{es} is kept within normal limits, decreasing C_a by 25%, 33%, 50% or increasing R_a by 25% or R_c by 25%, 50%, 100%, respectively, do not cause ventriculoarterial uncoupling with a high E_a/E_{es} ratio. When E_{es} is close to the upper limit of normal (2.6 to 3.0 $mmHg.mL^{-1}$), a high R_c or a low C_a can cause ventriculoarterial uncoupling with a low $E_a/E_{es;}$ but LV acts like a volume source in these scenarios, and it is hard to create a congestive state. Once R_a was increased by 50% or 100% and E_{es} was 1.4 $mmHg.mL^{-1}$, ventriculoarterial uncoupling with a high E_a/E_{es} ratio was produced. Increasing ventriculoarterial coupling ratio significantly decreases the required percent change in $V_{stressed}$ for reaching a PCWP of 20 mmHg (Figure 6).

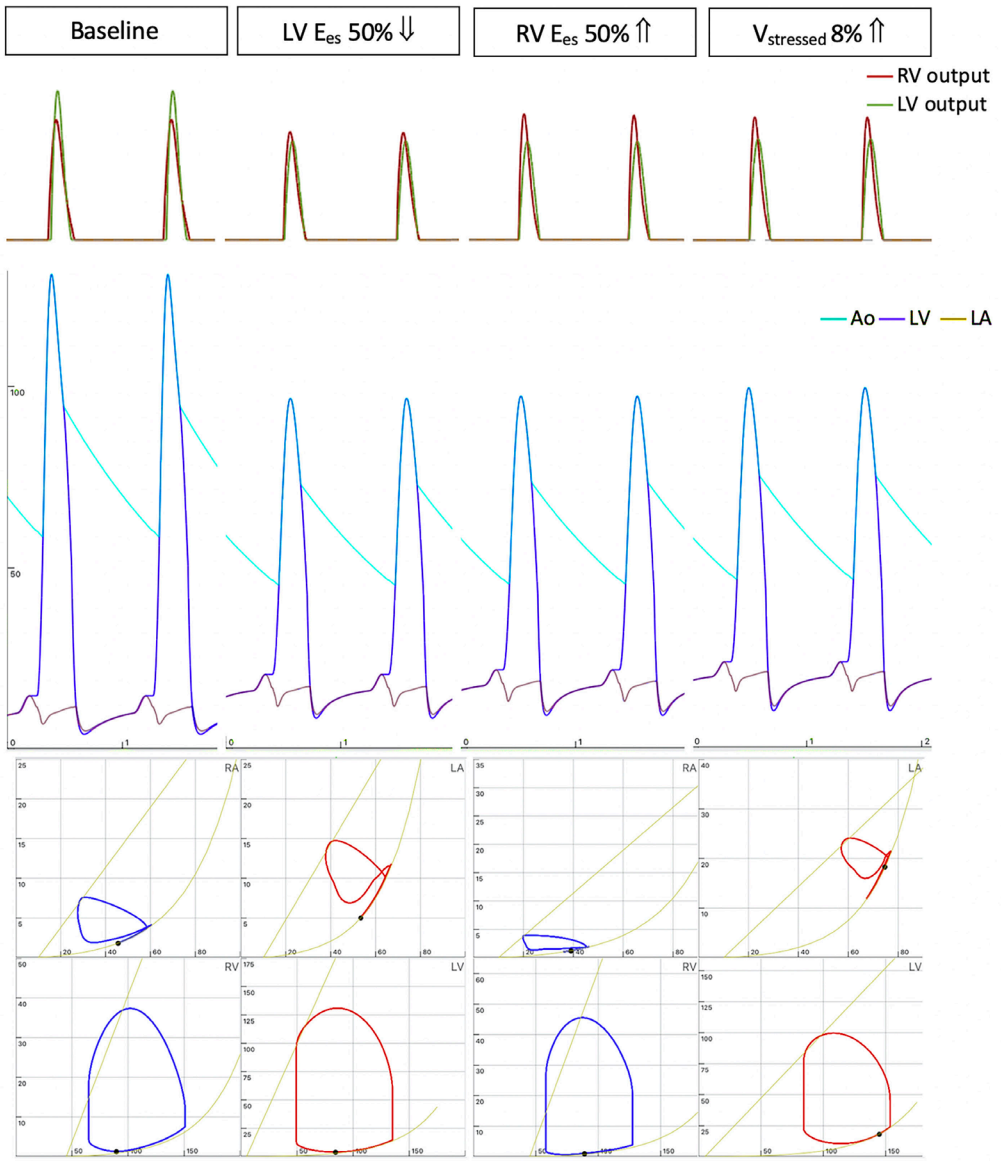

Figure 4. When sufficient decrease in LV contractility (second column), increase in RV contractility (third column) and $V_{stressed}$ (fourth column) is simulated, a significant interventricular disintegration can be produced. As right ventricular output (green) exceeds left ventricular output (red) (upper row), a hemodynamic profile similar to diastolic dysfunction can be generated (middle row) with a pulmonary capillary pressure of 20 mmHg, despite unchanging diastolic properties (lower panel).
LV: left ventricular; RV: right ventricular; $V_{stressed}$: stressed volume.

DISCUSSION

The cardiovascular system is a closed circuit, including serial compartments with different mechanical properties. Any disintegration in this serial arrangement may cause trapping of some volume in the upstream compartment and lead to a new equilibrium in which some compartments exhibit abnormal volume loading despite not having an inherent structural abnormality. In this study, we showed four such interrelated disintegration points, all with the potential for producing the hemodynamic picture of HF.

Arteriovenous integration

The changing compliance through vascular beds creates a disintegration point with two important implications. Although a thin-walled, high-compliance venous system is advantageous when used as a blood reservoir,[19] it is also the Achilles' heel of the circulatory system because veins may collapse and

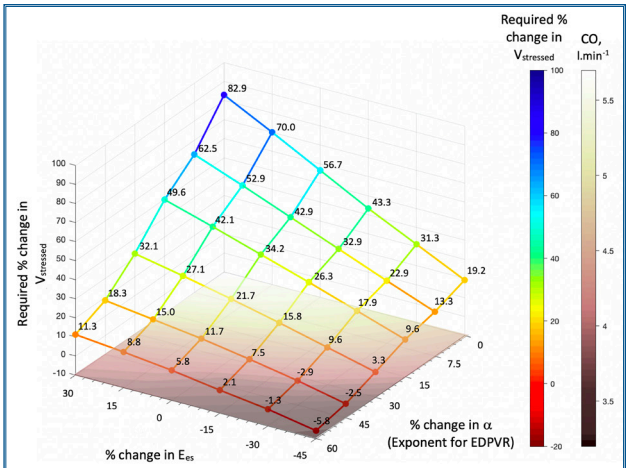

Figure 5. Required percent change in $V_{stressed}$ for bringing PCWP over 20 mmHg, according to percent changes in E_{es} and α (exponent for EDPVR). Corresponding COs are also depicted at the bottom.
$V_{stresssed}$: stressed volume; PCWP: pulmonary capillary wedge pressure; E_{es}: end-systolic elastance; EDPVR: end-diastolic pressure volume relationship; COs: cardiac outputs.

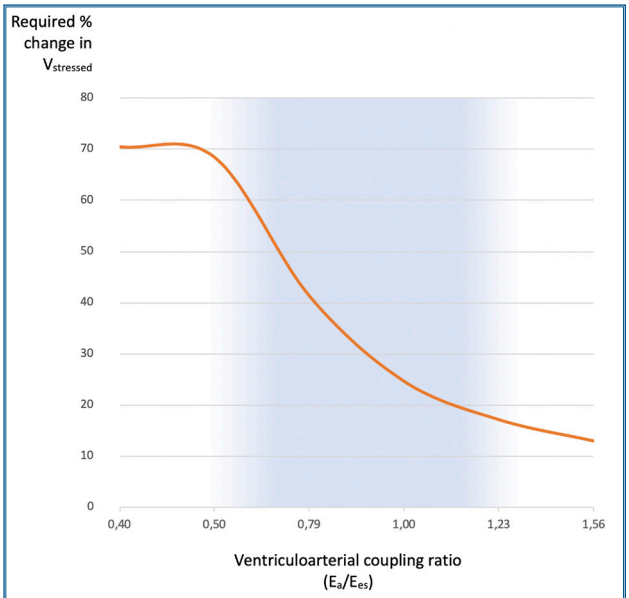

Figure 6. Required percent change in $V_{stressed}$ for bringing PCWP over 20 mmHg, according to ventriculoarterial coupling ratio. Shaded area represents the normal range for ventriculoarterial coupling ratio.
$V_{stresssed}$: stressed volume; PCWP: pulmonary capillary wedge pressure; E_a: arterial elastance, E_{es}: end-systolic pressure-elastance.

impede circulation when venous transmural pressure difference drops below zero. Therefore, if the blood flow was at a standstill in such a collapsible system, an initial pressurization would be necessary for enabling ventricular filling and commencement of circulation. This theoretical pressure is known as mean systemic pressure (P_{ms})[19] and proportional to $V_{stressed}$ and total vascular compliance (C_{total}) (Equation 1). After pumping activity begins, pressure in the arteries increases and pressure in the veins decreases, but there would be a neutral point at which the pressure neither increases nor decreases. Starling[20,21] reasoned that this point lies on the venous side of the capillaries, and the pressure difference between this point and right atrium (RA) governs CO (Equation 2). As further ventricular filling is not possible owing to venous collapse when RA pressure drops to zero; no cardiac parameter, neither contractility nor heart rate, could increase CO above this level. Thus, vascular, not cardiac, parameters set the upper limit of CO permitted in human cardiovascular system.[22-24]

Equation 1: $$P_{ms} = \frac{V_{stressed}}{C_{total}}$$

Equation 2: $$CO = \frac{P_{ms} - P_{RA}}{R_v} \quad \text{and} \quad CO_{max} = \frac{P_{ms}}{R_v}$$

Second, because of the presence of two serial circulations, another neutral point at which pressure neither increased nor decreased should be present on the pulmonary vascular system. Although a high P_{ms} is favorable in systemic circulation for increasing CO, it is disadvantageous in pulmonary circulation as it can cause alveolar transudation. As the pulmonary venous compartment has the closest average pressure to P_{ms}, any increase in P_{ms} results in or contributes to increase in PCWP, even without any LV systolic or diastolic dysfunction (Table 2).

Our results are in accordance with these predictions. Despite varying combinations of increased $V_{stressed}$ and decreased vascular compliances, a PCWP of 20 mmHg is almost always associated with a P_{ms} of approximately 20 mmHg. This means that pressure in the pulmonary venous compartment is indeed very close, if not equal, to P_{ms} and directly influenced by compliance and volume status of the vascular system. Many pathophysiological changes including aging,[25,26] sex,[27,28] obesity,[29,30] hypertension,[31] diabetes,[32] and sedentary lifestyle[26,33] can decrease vascular (involving both arterial and/or venous) compliance similar to the amounts simulated in this study.

Table 2. Four major disintegration points, their causes, components and possible treatment targets

	Inherent cause	Problem	Components	Appears as	Possible treatment
Arteriovenous disintegration	Redistribution of $V_{stressed}$ into vascular beds with differing compliances	High P_{ms}	$V_{stressed}$ C_{total}	Diastolic dysfunction	Lowering fluid volume and increasing total compliance
Interventricular disintegration	Requirement of both ventricles to pump the same CO	Systemic to pulmonary fluid redistribution	RV E_{es} LV E_{es}	Systolic and/or diastolic dysfunction	Suppression of RV contractility, increasing LV contractility or efficiency
Systolodiastolic disintegration	Different responses of the contractile and diastolic functions to volume loading	Trapping of some volume in LV to force a higher SV	ESPVR EDPVR	Systolic and/or diastolic dysfunction	Increasing contractility according to the degree of diastolic dysfunction
Ventriculoarterial disintegration	Rightward shift of LV pressure-volume loop	Inappropriately high afterload	E_{es} E_a	Diastolic dysfunction	Lowering afterload, increasing contractility

CO: cardiac output; C_{total}: total vascular compliance; E_a: arterial elastance; EDPVR: end-diastolic pressure-volume relationship; E_{es}: end-systolic elastance; ESPVR: end-systolic pressure-volume relationship; LV: left ventricle; P_{ms}: mean systemic pressure; RV: right ventricle; $V_{stressed}$: stressed volume.

Although they have all been linked to diastolic dysfunction owing to ventricular stiffness in LV-centered approach, our results indicate that a decrease in compliance of any vascular compartment may increase PCWP via P_{ms}, and the hemodynamic picture is indistinguishable from what is interpreted as diastolic dysfunction. Although volume receptors sense an 8%-10% change in volume and prompt fluid excretion,[34] approximately a combined 25% compliance decrease in all compartments lowers the required $V_{stressed}$ expansion below this sensing threshold or a moderate decrease in compliance combined with disorders in volume sensing and excretion has a potential to sustain itself. Importance of total compliance may also have therapeutic implications; for example, although it is hard to reverse the effects on aging on arterial compliance, venous compliance may serve as a surrogate target to this end.

Interventricular integration

Although RV and LV are inherently coupled as a connected anatomical structure in a shared pericardial space, this design is a byproduct of evolution rather than being a functional necessity. This collocation mandates RV and LV to beat at the same heart rate and pump the same SV and CO, even though they have different contractile properties; and they are facing completely different vascular beds with different responses to diverse pathophysiological processes. Thus, coupling of both ventricular outputs creates another integration point.

The increased PCWP in HF is commonly, and erroneously, interpreted as backward transmission of increased pressure of the failing LV; however, even if the heart stops to beat as the ultimate "heart failure" state, LV pressure (by definition equal to P_{ms} in this situation, which is normally around 10 mmHg)[35] falls short of the pressure required for generating pulmonary edema (>25 mmHg) unless significant arteriovenous disintegration is present. However, when RV output temporarily exceeds LV output, some of $V_{stressed}$ has to be redistributed from systemic to pulmonary circulation, and LV filling pressure increases to keep up with the output of the more efficient RV, even though LV diastolic parameters are unchanged.[36,37]

Our results confirm these predictions. A subclinical decrease in LV systolic function combined with normal-to-high RV systolic function[18,38,39] seems to lower the required $V_{stressed}$ expansion significantly for creating a hemodynamic profile indistinguishable from diastolic dysfunction, despite diastolic pressure-volume curve is unchanged (Figure 4). These findings are interesting because although interventricular disintegration may cause HFpEF with inappropriate RV output, it can provide another explanation for the clinical picture what

we currently call HF with reduced ejection fraction (HFrEF). The real cause may be excess RV energy input compared with LV; this explains why subsequent RV failure decreases the episodes of pulmonary edema in patients with HFrEF. Beta-blockers may, at least in part, exert their effect through limiting RV output especially during sympathetic stimulation. Although interventricular disintegration due to an exaggerated isolated increase in RV output seems possible; in real clinical practice, it is probably much more commonly due to the other 'LV disintegrations' discussed below.

Systolodiastolic integration

According to Frank-Starling law, an increase in LVEDP translates into an increase in SV. On the other hand, EDPVR follows completely different curve since it is independent of contractile mechanism governing Frank-Starling law. For a certain amount of increase in SV, required additional volume and corresponding LVEDP increase in Frank-Starling curve and EDPVR may not coincide. Thus, systolic and diastolic functions of a ventricle create an integration point.

Although our results indicate that severe degrees of isolated systolic or diastolic dysfunction can result in high LV filling pressures, mild-to-moderate degrees of combined systolic and diastolic dysfunction may also cause a similar hemodynamic picture. In our simulation, the degree of isolated diastolic dysfunction causing a PCWP over 20 mmHg is more severe than generally reported values in the literature,[15-18] which suggests that pure diastolic dysfunction is probably less frequent than systolodiastolic disintegration. This also suggests that an increased degree of systolic function can compensate for a certain degree of diastolic dysfunction and an inadequate compensation may be the cause of high filling pressures. Several investigators[40,41] found subtle systolic abnormalities in patients diagnosed as HFpEF, but this may the reason why these patients had manifest "diastolic dysfunction," whereas others with normal-to-high systolic function did not. Once systolodiastolic disintegration is moderate-to-severe, it has a potential to outgrow itself both by lowering CO, which prompts fluid accumulation, inducing interventricular disintegration, which contributes to pulmonary congestion.

Ventriculoarterial integration

The relation between LV and its opposing hydraulic load has been well studied, and afterload reduction already constitutes the keystone of HF management.[1,2,13,15] As LV pressure-volume loop has to remain within the boundaries of ESPVR and EDPVR, any increase in E_a carries the pressure-volume loop rightward, forces it to climb the ascending part of EDPVR, increases internal work, and decreases LV efficiency.[15-17] Our results indicate that when there is substantial ventriculoarterial disintegration (with a high E_a/E_{es} ratio), even minor increases in $V_{stressed}$ can generate significant pulmonary congestion. Although isolated increases in afterload (E_a) or decrease in LV contractility (E_{es}) may produce ventriculoarterial disintegration, combined disorders can much easily produce uncoupling and are probably more common in the real clinical practice.[15-17] As E_{es} is still in normal limits, hemodynamic picture resembles HFpEF, despite EDPVR remaining unchanged.

Limitations

Our study had several limitations. Although the hemodynamic model used in this study is well validated,[5,11] human cardiovascular system is a complex network of interacting mechanisms; and therefore any model, no matter how comprehensive, would be inadequate in simulating the real world. Normal values of several hemodynamic parameters were collected from the literature, but there is a paucity of data in many areas, and reported values sometimes show a wide variation. Some of the changes tested in the study may not be proven to occur in real clinical practice, but the data on the behavior of many of these parameters in different clinical scenarios are scarce, and further studies are needed to clarify whether these predictions have a real pathophysiological role in HF. Moreover, in this study, our main aim was to demonstrate that the interaction between cardiovascular compartments can cause apparent LV dysfunction even without affecting LV function themselves, rather than claiming these simulations with the exact amount of changes used in the study are the cause of the hemodynamic picture of HF. The selection of 20 mmHg as the surrogate for congestion is arbitrary as many patients with HF and higher PCWPs may not exhibit symptoms and signs of congestion.

Finally, all integration points interact with each other, and complete isolation of one abnormality is generally not possible. Several disintegrations do co-exist or follow each other. For example, after a myocardial infarction, ventriculoarterial, systolodia-

stolic, and interventricular disintegration may all be possible; and once failure of RV ensues owing to pulmonary hypertension, arteriovenous disintegration can take over as the prevailing cause of congestion. Similarly, in our simulations, changing C_a for testing arteriovenous or LV E_{es} for interventricular disintegration also cause some ventriculoarterial disintegration. In some situations, we tried to compensate these changes, but we deliberately did not complicate calculations in others to focus on the effects of isolated changes. It should be underlined; however, our hypothesis is not to claim that an isolated disintegration causes HF; but any disintegration in cardiovascular system, either in isolation or combination, can cause apparent LV dysfunction.

Conclusion

Our study, for the first time, quantitatively showed that disintegration in several cardiovascular points can produce a hemodynamic picture of HF. Although resulting hemodynamic picture resembles diastolic or systolodiastolic dysfunction, this may not necessarily reflect the real underlying abnormality. Our results also indicate that a combination of even seemingly mild abnormalities is much more important than an isolated abnormality in a single function of a single chamber. This new perspective may offer a better appreciation of underlying hemodynamic pattern and may lead to better tailoring of treatment according to hemodynamic subcategories. Therefore, our findings suggest that the cardiovascular disintegration approach may provide a broader perspective for assessing the HF syndrome. Further studies are needed to elucidate the implications of this new perspective.

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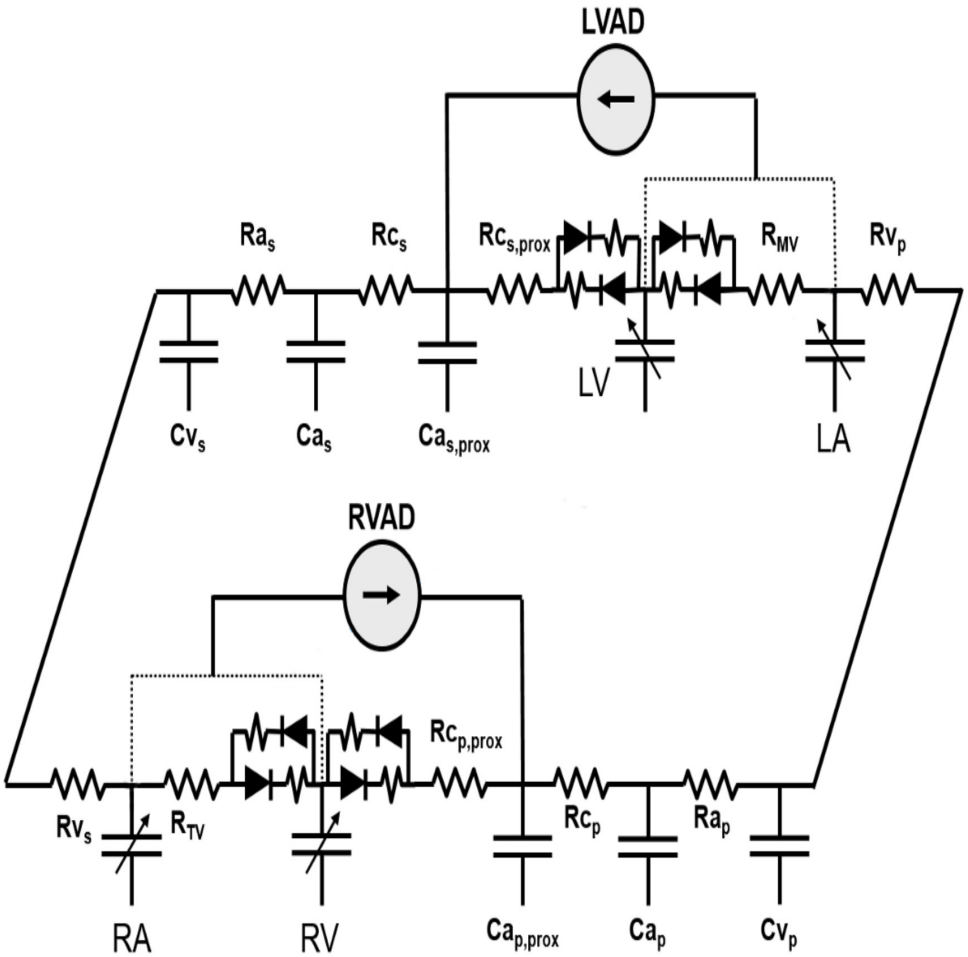
Keywords: Diastolic dysfunction; heart failure; hemodynamics; pressure-volume loop; ventriculoarterial coupling

Anahtar Kelimeler: Diyastolik disfonksiyon; kalp yetersizliği; hemodinami; basınç-hacim ilmiği; ventriküloarteriyal eşleşme

Supplementary Figure 1. Details of used hemodynamic model



Harvi is a hemodynamic model wherein the cardiovascular system is modeled using an electrical analog as shown above. Ventricular and atrial pump features were represented by alterations of the time-varying elastance (E[t]) theory that relates time-varying ventricular pressure (P[t]) to time-varying ventricular volume (V[t]). Each cardiac chamber is modeled as follows:

$$P(t) = P_{ed}(V) + (1-e[t])P_{es}(V) \qquad (1)$$

In equation (1), the values are calculated as follows:

$$P_{ed}(V) = \beta\,(e^{\alpha[V-Vo]}-1)$$
$$P_{es}(V) = E_{es}(V-V_o)$$

and

$$e(t) = \begin{cases} \tfrac{1}{2}\,(\sin[\{\pi/T_{max}\}t - \pi/2] + 1) & 0 < t \le 3/2\ T_{max} \\ \tfrac{1}{2}\,e^{-(t-3/2Tmax)/\tau} & t > 3/2\ T_{max} \end{cases}$$

where $P_{ed}(V)$ is end-diastolic pressure and $P_{es}(V)$ is end-systolic pressure—both being functions of volume—E_{es} is end-systolic elastance, V_o is the volume axis intercept of the end-systolic pressure–volume relationship, α and β are parameters of the end-diastolic pressure–volume relationship, T_{max} is the point of maximal chamber elastance, τ is the time constant of relaxation, and t is the time during the cardiac cycle. The systemic and pulmonary circuits are each modeled by lumped venous capacitance and arterial capacitance (C_v and C_a, respectively), a proximal characteristic impedance (R_c), a lumped arterial resistance (R_a), and a resistance to return of blood from the venous capacitance to the heart (R_v). The heart valves permit flow in only one direction through the circuit. The total blood volume (V_{total}) contained within each of the capacitive compartments is divided into 2 pools: the unstressed blood volume (V_0) and the stressed blood volume ($V_{stressed}$). V_0 is defined as the maximum volume of blood that can be placed within a capacitive vessel without raising its pressure above 0 mmHg. The blood volume within the capacitive compartment that is more than V_0 is $V_{stressed}$ such that $V_{total} = V_0 + V_{stressed}$. Pressure within the compartment is assumed to rise linearly with $V_{stressed}$ relative to compliance (C) as $P=V_{stressed}/C$. Differential equations corresponding to the circuit are solved numerically using simple Newtonian method with a 2 ms time step size. The normal value of each parameter of the model was set as shown in Table 1 of the main text.