Heart stroke-volume variability in a murine model for heart failure with reduced ejection fraction

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(Dated: January 18, 2023)

Abstract

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I. INTRODUCTION

There is evidence that links increased sympathetic nervous system activity to increased cardiovascular morbidity and mortality, demonstrating that it has a strong predictive power for mortality and cardiovascular events [1]. On the other hand, heart rate variability (HRV) analysis has been widely used as a noninvasive assessment tool for autonomic nervous system function [2], and results show that decreased and/or abnormal HRV is associated with conditions such as congestive heart failure, diabetic neuropathy, post-cardiac-transplant depression, fatigue severity in chronic fatigue syndrome, and susceptibility to sudden infant dead syndrome have been associated with modified (usually lower) heart rate variability [3–6].

Aside from the sympathetic and vagal nervous systems, the Frank-Starling mechanism and the force-frequency relationship are two basic mechanisms that regulate the heart's contractile strength in vivo [7] , and changes in all of them have been reported in patients with chronic heart failure [7–11]. This raises the possibility that other variables, such as stroke volume, which are critical for heart function, may be altered in such pathology. This question is addressed in the present manuscript, using a murine model for heart failure with reduced ejection fraction.

II. MATERIALS AND METHODS

III. RESULTS

A. Experimental and heart variability analysis

According to the procedures outlined in Section Materials and Methods, we conducted the experiments on the control and experimental groups. We were able to calculate the

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heart's left ventricle volume as a function of time using the recorded data. This, along with the data on the ventricle pressure that was also recorded, made it possible to reconstruct for each experimental record the so-called P-V diagrams illustrated in Fig. **??**. Thereafter, we were able to extract time series of physiological interest from these diagrams, such as those of successive cardiac-cycle periods and stroke volumes.

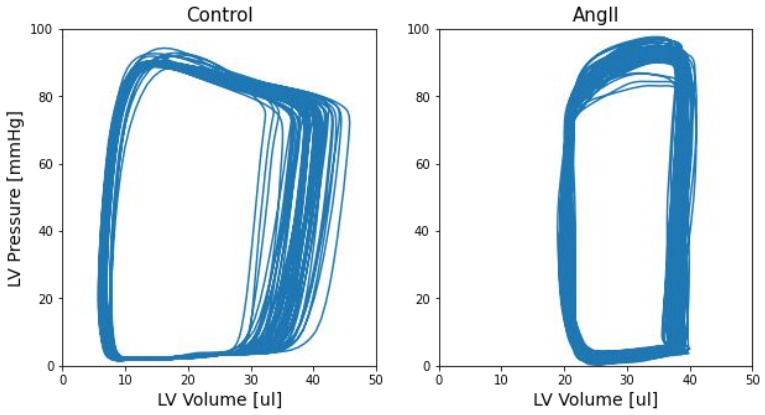

FIG. 1.

We took the time series of consecutive cardiac-cycle periods and calculated the mean cycle duration for each experimental record, then averaged all of the values obtained in each group. Figure 2A depicts the obtained results. No significative difference can be appreciated between the results of the control group and those of the group of mice with induced cardiac failure. This finding contradicts the findings of Kamen and Tonkin [3], who found that the heart rate increases in patients with chronic heart failure. However, we must remember that the sympathetic and parasympathetic nervous systems regulate heart rate. As a result, the fact that mice were anesthetized in our experimental protocol, which affected such pathways, may explain the observed results.

We also calculated the mean values for the time series of consecutive stroke volumes for every experimental record. Then we averaged the results from each group and plotted the results in Fig. 2B. As expected, there is a significant reduction in stroke volume in the group with induced heart failure when compared to the control group.

We were interested in studying the variability of heart-cycle periods and stroke volumes. In this regard, a variety of techniques have been used to measure heart rate variability. The vast majority of them are founded on the concept of signal stationarity. However, the heart

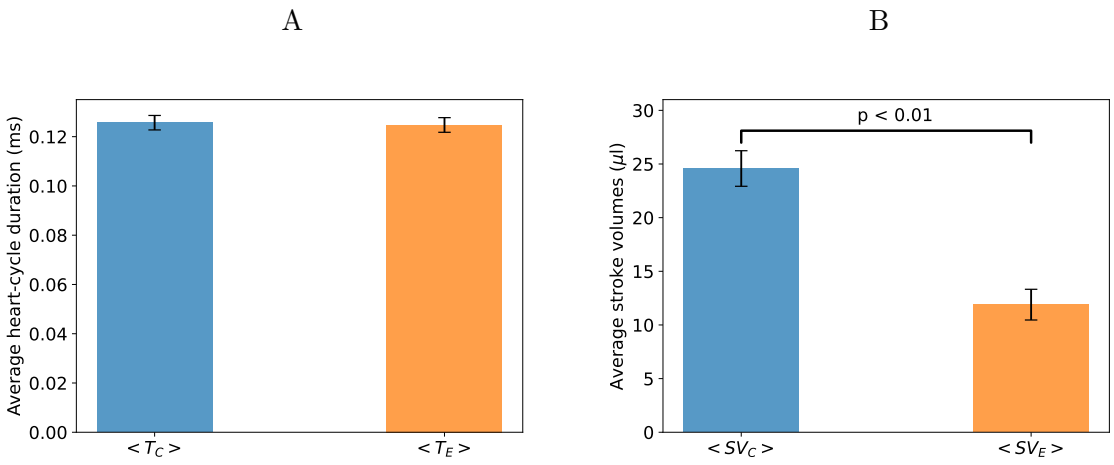

FIG. 2. A) Average cardiac-cycle periods for control and experimental groups. B) Average stroke volumes for control and experimental groups.

rate's inherent non-stationary nature—which undergoes continuous physiological change to adapt to external stimuli—presents a significant challenge that could result in inaccurate results [12]. Although several signal preprocessing methodologies have been proposed to address these issues, nonlinear analysis-based strategies are commonly employed and appear to produce reliable results. [4, 12–17]. One of them that is used in different scientific domains is the Poincairé plot [16, 18, 19]. In a Poincairé plot, all values in a time series are plotted against previous values, resulting in an ellipsoidal point cloud. The standard deviations of the point projections along the lines $y = x$ (SD2) and $y = -x$ (SD1) can be used to quantitatively analyze this diagram. The transverse axis of the ellipse (SD1) is a measure of the short-term changes in the the time series, while the longitudinal axis (SD2) reflects long-term changes. In the particular case of heart-beat duration time-series, SD1 is considered as an indicator of the parasympathetic activity, whereas SD2 is considered as an inverse indicator of the sympathetic activity [20].

We measured the above described Poincaré-plot indices of heart-cycle period variability for every experimental record, and averaged the results corresponding the the control and experimental groups. The outcomes are plotted in Fig. 3A. Observe that no statistically significative difference exists between the indices corresponding to the control and experimental groups. This suggests that, under our experimental conditions, heart failure does not affect heart rate variability (HRV). This finding contradicts Kamen and Tonkin [3] and other authors, who have reported that HRV decreases in patients with hart failure and we

believe that it is also related to the fact that mice are anesthetized in our experimental protocol. Recall the anesthesia affects the sympathetic and parasympathetic pathways and that they, in turn, influence heart rate variability.

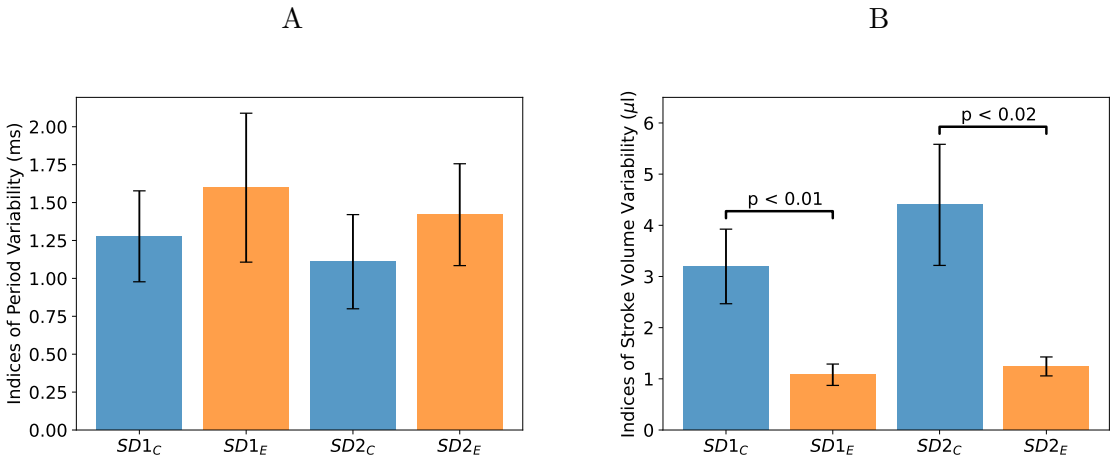

FIG. 3.

The same methodology was used to investigate the variability of stroke volumes. The results are shown in Fig. 3B. The experimental group's SD1 and SD2 values are significantly lower than those of the control group. This suggests that heart failure affects the mechanisms in charge of controlling stroke volume. Furthermore, the absence of changes in HRV suggests that both types of variability are dissociated.

B. Mathematical Model

We found that, in our experimental protocol, there is no difference in the heart rate of mice with induced heart failure compared to those in the control group. The same is true for heart rate variability. These findings contradict previous findings, but we believe this can be explained by the fact that the mice in our experiments are sedated. On the other hand, we found that, as expected, stroke volume decreases in mice with heart failure, as does stroke volume variability. Reduced HRV has not only been observed in heart failure patients, but it has also been shown to be a strong predictor of cardiovascular events and mortality. Furthermore, HRV has been linked to a number of vascular risk factors, including hypertension, diabetes, depression, and subclinical inflammation [5]. We find it intriguing that the variability of another variable, such as stroke volume, which is also critical to heart

function, is reduced in a pathology such as heart failure. What is more, our findings indicate that this decreased variability is caused by mechanisms other than those involved in HRV control. To gain some insight into this last question, we examine a simple Frank-Starling model of the cardiovascular system that was previously introduced by Upton and Ludbrook [21].

The model by Upton and Ludbrook is schematically represented in Fig. 4. It divides the blood in circulation into arterial and venous compartments. The pressure (P_x) and blood volume (V_x) in each compartment are related by the corresponding compliance (C_x):

$$P_x = V_x/C_x,$$

where subindex x can have the values A or V to represent the arterial and venous compartments. The flow of blood from the arterial compartment to the venous compartment is assumed to be passive. Hence, the blood volume exchanged during period Δt is:

$$V_R = \Delta t(P_A - P_V)/R,$$

in which R denotes the peripheral vascular resistance. Finally, according the the Frank-Starling Law [22], the volume of blood transferred from the venous compartment to the arterial compartment by the heart pumping (stroke volume), is assumed to depend lineally on the venous pressure:

$$SV = \beta P_V.$$

This is the model's most daring assumption, as it integrates the pulmonary circulation of blood and its passage through the heart auricles and ventricles in a single step. The possible implications of this assumption will be discussed later.

We now employ the Upton and Ludbrook model to investigate how the system's current state influences its evolution over successive cycles. To that end, we assume that the heart stroke occurs first, followed by passive diffusion of blood from the arterial compartment to the venous compartment. Let $V_{V,i}$ and $P_{V,i}$ denote the venous volume and pressure at the end of the i-th heart cycle. From this, the stroke volume in the next cycle is

$$SV_{i+1} = \beta P_{V,i}.$$

With this, the venous and arterial volumes after the heart stroke are:

$$V_{V,i+1/2} = V_{V,i} - SV_{i+1} \quad \text{and} \quad V_{A,i+1/2} = V_{A,i} + SV_{i+1}.$$

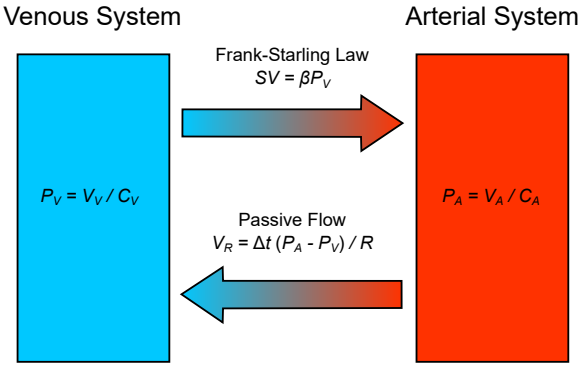

FIG. 4. Schematic representation of the model

After some algebra, these expressions can be rewritten as

$$V_{V,i+1/2} = V_{V,i}\left(1 - \frac{\beta}{C_V}\right) \quad \text{and} \quad V_{A,i+1/2} = V_T - V_{V,i}\left(1 - \frac{\beta}{C_V}\right),$$

where V_T is the total blood volume, which is assumed constant because the system is closed. After the heart stroke, a volume $V_{R,i+1}$ of blood passively diffuses back to the venous compartment. This volume is given by

$$V_{R,i+1} = \frac{1}{R}\left[\frac{V_T}{C_A} - V_{V,i}\left(1 - \frac{\beta}{C_V}\right)\left(\frac{1}{C_A} + \frac{1}{C_V}\right)\right].$$

The venous and arterial volumes at the end of the $i+1$-th heart cycle can then be computed as:

$$V_{V,i+1} = V_{V,i} + V_{R,i+1} \quad \text{and} \quad V_{A,i+1} = V_{A,i} - V_{R,i+1}.$$

After performing the corresponding algebra, this last result leads to

$$V_{V,i+1} = V_{V,i}\left(1 - \frac{\beta}{C_V}\right)\left[1 - \frac{1}{R}\left(\frac{1}{C_A} + \frac{1}{C_V}\right)\right] + \frac{V_T}{RC_A}.$$

Finally, taking into account that $SV_{i+1} = \beta V_{V,i}/C_V$, it follows that

$$SV_{i+1} = \mathcal{A}\, SV_i + \mathcal{B},$$

with

$$\mathcal{A} = \left(1 - \frac{\beta}{C_V}\right)\left[1 - \frac{1}{R}\left(\frac{1}{C_A} + \frac{1}{C_V}\right)\right],$$
$$\mathcal{B} = \frac{V_T \beta}{RC_A C_V}.$$

In other words, we derived a recursive expression for the stroke volume in consecutive heart cycles from the Upton and Ludbrook [21] model. It can be straightforwardly proved that such recursive equation converges to the stationary value

$$\overline{SV} = \frac{\mathcal{B}}{1-\mathcal{A}},$$

whenever $|\mathcal{A}| < 1$. Furthermore, the closer $\mathcal{A}$ is to 0, the faster the recursive equation converges to its stationary value.

The previous results imply that when additive noise is included in the model, stroke volume variability is reduced for smaller $\mathcal{A}$ values. Take note, in particular, that $\mathcal{A}$ is a decreasing function of β. The decrease in short-term stroke volume variability observed in our experiments could then be explained by an increase in parameter β, which is related to the Frank-Starling mechanism. Interestingly, Holubarsch *et al.* [7] discovered, despite previous controversy, that the Frank-Starling mechanism is maintained in end-stage failing human hearts. They also found evidence that diastolic compliance was reduced in isolated preparations of failing human ventricles, indicating that higher end-diastolic stresses and pressures are required in failing hearts compared to normal hearts to achieve optimal contractile force. This might be translated into changes of parameter β in our model.

IV. CONCLUDING REMARKS

The available epidemiological and clinical data link increased sympathetic nervous system activity to increased cardiovascular morbidity and mortality, demonstrating that it has a strong predictive power for mortality and cardiovascular events [1]. Heart rate variability (HRV) analysis has been widely used as a noninvasive assessment tool for autonomic nervous system function [2], and results show that decreased and/or abnormal HRV is associated with conditions such as congestive heart failure, diabetic neuropathy, post-cardiac-transplant depression, fatigue severity in chronic fatigue syndrome, and susceptibility to sudden infant dead syndrome have been associated with modified (usually lower) heart rate variability [3–6].

We found that stroke volume variability (SVV) decreases in a murine model for heart failure with reduced ejection fraction. Our results indicated that stroke volume variability is independent HRV, and the analysis of a simple model of the cardiovascular system suggests

that the observed SVV reduction may be related to changes in the Frank-Starling mechanism.

The Frank-Starling mechanism, along with the force-frequency relationship and the sympathetic and vagal nervous systems, is one of the basic mechanisms that regulate the contractile strength of the heart in vivo [7]. Significant changes in the force-frequency relationship and the β-adrenoceptor system have been described in detail for failing human myocardium [8–11], with the latter resulting in reduced HRV. Through a carefully planned set of experiments at the cell, organ, and organism levels, Holubarsch *et al.* [7] demonstrated that the Frank-Starling mechanism is well preserved in failing human myocardium. They also discovered significant changes in diastolic myocardial distensibility in patients with chronic heart failure. We speculate that these changes are at the root of the observed SVV reduction.

ACKNOWLEDGMENTS

We wish to acknowledge Prof. Fernando Angulo-Brown for fruitful discussion and advice.

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