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Rogério Manuel Pedro Medeiros

Brain-heart interaction: the effect of cardiac activity on visual perception

Dissertation to obtain a Master's Degree in Biomedical Engineering in the field of Neurosciences, advised by PhD. Prof. Maria J. Ribeiro, PhD. Prof. Marco Simões and PhD. Prof. Paulo de Carvalho, presented to the Faculty of Sciences and Technology of University of Coimbra / Physics Department.

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(There is no scientific study more vital to man than the study of his own brain. Our entire view of the universe depends on it)

Francis Crick

Resumo

Durante o quotidiano, o nosso ritmo cardíaco tende a adaptar-se às várias circunstâncias da vida. Numa tarefa de discriminação visual, estudos mostram que uma pista auditiva evoca um estado de preparação onde a atenção é orientada para o estímulo alvo caracterizado por uma desaceleração cardíaca. Relativamente às duas fases do ciclo cardíaco, sístole e diástole, a perceção de estímulos tácteis é facilitada quando o estímulo é apresentado na diástole. Nesta dissertação, apresentamos dois estudos: um que analisa a capacidade de identificar a sístole e a diástole utilizando o electrocardiograma (ECG), a sua validade em indivíduos com e sem doença cardiovascular, e o impacto do exercício e da frequência cardíaca nesta identificação; e outro que mostra, utilizando uma base de dados diferente, a variação da resposta cardíaca numa tarefa de discriminação visual, bem como a influência das fases do ciclo cardíaco na exactidão da resposta dos participantes. A sístole é a fase cardíaca que começa e termina com a abertura e fecho da válvula aórtica. No nosso primeiro estudo, quantificamos as diferenças temporais entre as ondas do ECG e a abertura e o fecho da válvula aórtica estimadas a partir do ecocardiograma, para quantificar o erro associado à utilização do ECG para definir a sístole. Verificámos que este erro aumentou após o exercício e foi modulado pelo ritmo cardíaco. Relativamente ao segundo estudo, observamos uma desaceleração cardíaca invocada por um estado de preparação. A desaceleração cardíaca não foi significativamente diferente quando comparamos ensaios em que os participantes foram capazes de identificar corretamente o estímulo visual com ensaios em que os participantes responderam incorretamente. Quanto à influência da apresentação dos estímulos nas diferentes fases do ciclo cardíaco na percepção visual, verificamos que não havia diferença significativa na exatidão dos participantes quando comparamos ensaios em que o estímulo foi apresentado na sístole com ensaios em que o estímulo foi apresentado na diástole. Em conclusão, os resultados indicam que o erro associado à utilização dos eventos do ECG para estimar o início e o fim da sístole é pequeno, particularmente em participantes saudáveis em condições de repouso. Além disso, verificamos que a desaceleração cardíaca e as fases do ciclo cardíaco não modularam significativamente a percepção visual na tarefa de discriminação visual utilizada neste estudo.

Palavras-Chave

Neurociências, Perceção Visual, Sistema cardiovascular, Ciclo Cardíaco, ECG

Abstract

During everyday life, our heart rate tends to adapt to the various circumstances of life. In a visual discrimination task, studies show that an auditory cue evokes a state of attentive preparation characterized by a heart deceleration. Regarding the two phases of the cardiac cycle, systole and diastole, perception of tactile stimuli is facilitated when the stimulus is applied in diastole. In this dissertation, we present two studies: one that analyzes the ability to identify systole and diastole using the electrocardiogram (ECG), its validity in individuals with and without cardiovascular disease, and the impact of exercise and heart rate on this identification; and another that shows, using a different database, the variation of the cardiac response in a visual discrimination task, as well as the influence of the phases of the cardiac cycle on the accuracy of the participants' response. The systole is the cardiac phase that starts and ends with the opening and closing of the aortic valve. In our first study, we quantified the time differences between the ECG waves and the opening and closing of the aortic valve, estimated from the echocardiogram, to quantify the error behind using the ECG to define the systole. We found that this error increased after exercise and was modulated by heart rate. Regarding the second study, we observed a cardiac deceleration invoked by a state of attentive preparation induced by the presentation of an auditory cue. The cardiac deceleration was not significantly different when we compared trials where the participants were able to correctly identify the visual stimulus with trials where the participants responded incorrectly. Regarding the influence of the presentation of the stimuli in the different phases of the cardiac cycle on visual perception, we found that there was no significant difference in the accuracy of the participants when comparing trials where the stimulus was presented in the systole with trials where the stimulus was presented in the diastole. In conclusion, the results indicate that the error associated with using the ECG events to estimate the start and end of the systole is small particularly in healthy participants in resting conditions. Moreover, we found that cardiac deceleration or the phases of the cardiac cycle did not significantly modulate visual perception in the visual discrimination task used in this study.

Keywords

Neurosciences, Visual Perception, Cardiovascular System, Cardiac Cycle, ECG

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Abbreviations

ACh Acetylcholine

AVC Aortic Valve Closure

AVO Aortic Valve Opening

BPM Beats Per Minute

CISUC Centro de Informática e Sistemas da Universidade de Coimbra

CHUC Centro Hospitalar e Universitário de Coimbra

CVD Cardio Vascular Disease

DEI Departamento de Engenharia Informática

ECG Electrocardiography

ECO Echocardiography

EEG Electroencephalography

EGG Electrogastrography

EMG Electromyography

EOG Electrooculography

ET Eye Tracker

FIR Finite Impulse Response

HEA Healthy

IBI Inter Beat Interval

i.e. That is

NE Norepinephrine

1

Motivation / Relevance

The connection between our body and the brain is a well-established reality. During the whole day we rarely are still, we tend to twitch our fingers, twist our faces and swing our bodies. It is curious that we cease all movement when we wish to pay attention in order to take in as much information as possible [1, 2]. Through the process of paying attention, our heart rate decreases as we freeze our body and dilate our pupils [2–5].

Regarding the interaction between our brain and our heart, it is known that a cardiac deceleration exists during the preparatory phase of attention in preparation for sensory stimuli processing [6–8]. However, the link between this cardiac slowing and sensory stimuli processing, particularly visual stimuli, is unclear.

With this study we want to look at the cardiac deceleration decomposed into the various phases of the cardiac cycle (systole and diastole) and measure how these events modulate visual perception.

This work has the following main scientific goals:

- Since neuroscience studies use the electrocardiogram (ECG) to define systole and diastole, we aimed to determine if this method is suitable for this type of studies. To do that we compared the electrical definition of the systole (via the ECG) with the mechanical definition (via the echocardiogram);

- Using the findings from the first research, we wanted to explain the mechanisms underlying the influence of the cardiac cycle on visual perception. We wish to see if visual perception is facilitated during diastole as compared to systole for visual stimuli, as it has been demonstrated for tactile stimuli [9].

1.1 Document Structure

Beside the state of the art, conclusions and discussions, this master's thesis will be divided in two main chapters presenting two different studies:

On chapter 3, we report how accurate it was to use the ECG to detect the onset and the offset of the systole. We used data from the echocardiography and compared the aortic valve events with the waves given by ECG to quantify the time differences in defining the systole in ECG compared to echocardiography. We also studied the effect of exercise and cardiovascular disease in the timing differences between the electrical and mechanical systole.

On chapter 4, we study the effect of the cardiac cycle in visual perception. For this, we used a different database to investigate the effect of preparatory cardiac deceleration on the duration of the systole/diastole phases and if visual perception was modulated by these two phases.

2

Physiological Background

In this chapter, we will provide the theoretical background as well as the body of published works in the field of brain-heart interactions to understand what we have done in the studies reported in this dissertation.

2.1 The Cardiac Cycle: Defining Systole and Diastole

The heart has four chambers: two atria (left and right) and two ventricles (left and right). These atria are separated from the ventricles by the atrioventricular valves (the tricuspid one on the right side and the mitral on the left side). The heart also has two other valves that separate the ventricles from the arteries that conduct the blood to the 2 different circulations. On the right side, we have the pulmonic valve that opens when the pressure inside the right ventricle is higher than the pressure inside the pulmonic artery to conduct blood to the lungs and allow for the exchange of O2 and CO2 - **Pulmonary Circulation**. On the left side, we have the aortic valve that separates the left ventricle from the aorta (artery that conducts oxygenated blood to all organs - **Systemic Circulation**). The aortic valve opens when the pressure inside the left ventricle is higher than in the aorta.

The heart also has veins that are connected into the atria. Their responsibility is to receive blood from the two circulations into the heart: the pulmonary veins to receive blood rich in oxygen, and the superior vena cava / inferior vena cava receive blood rich in carbon dioxide. [10]

The location of all these elements can be seen on figure 2.1.

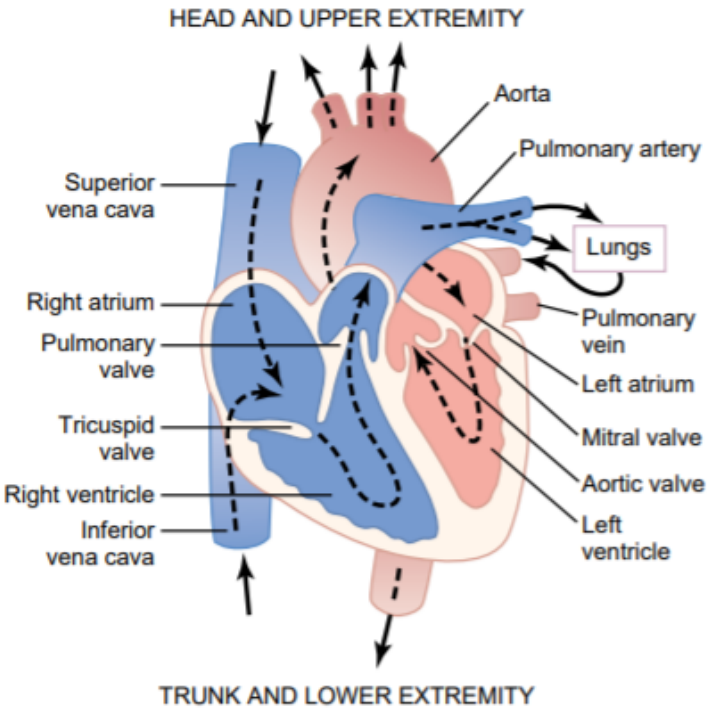

Figure 2.1: Schematic figure of all components of the heart. The pulmonary circulation is represented in blue and the systemic in red. (figure adapted from [11] - figure 9.1).

The **Cardiac Cycle**, is defined by 2 major phases: the **systole** and the **diastole**. During the **systole** there is contraction of the ventricles, which leads to the opening of the aortic valve so that the blood can circulate through the body. During **diastole**, occurs the relaxation and the filling of the ventricles with blood once the aortic valve closes. It is important to note that the opening of the aortic valve marks the onset of the systole and the closure of the valve marks its end [11].

We can define the main cardiac cycle events using different acquisition methods. Since [12] reported that the systolic events can be defined with precision using the echocardiography, in this master's thesis, we will be comparing the electrical heart events measured in the electrocardiogram with the mechanical aortic valve events given by the echocardiography.

2.2 The Electrocardiography

Electrocardiography (ECG) is a long-standing diagnostic method for cardiac problems [13]. The heart produces electrical currents that flow on the tissues around it. The ECG is a method that records, through electrodes, the depolarization and repolarization of the cardiac cells [10].

The electrode placements can be divided into two categories: bipolar (consisting of two electrodes) and unipolar (composed by one electrode) [14].

The bipolar derivations can follow three different sets of positions:

- I: the negative electrode is connected on the left arm and the positive on the right one;
- II: the negative electrode is connected on the right arm and the positive on the left leg;
- III: the negative electrode is connected on the left arm and the positive one on the left leg.

The unipolar electrode placements can vary from six different positions (V1, V2, V3, V4, V5, V6) which can be seen on fig. 2.2. Each position leads to different ECG waves morphologies.

In addition to the two types of derivations previously described, there are additional types of derivations for a variety of particular circumstances involving the diagnosis of various illnesses, such as the derivation V7 used to diagnose posterior wall myocardial infarction [14].

The electrocardiogram is composed of several waves which can be seen in fig. 2.3. We can see the P wave followed by the complex QRS composed of waves Q, R and S that in turn is followed by the T wave. Each ECG event is marked with its beginning (onset) and its ending (offset) [10].

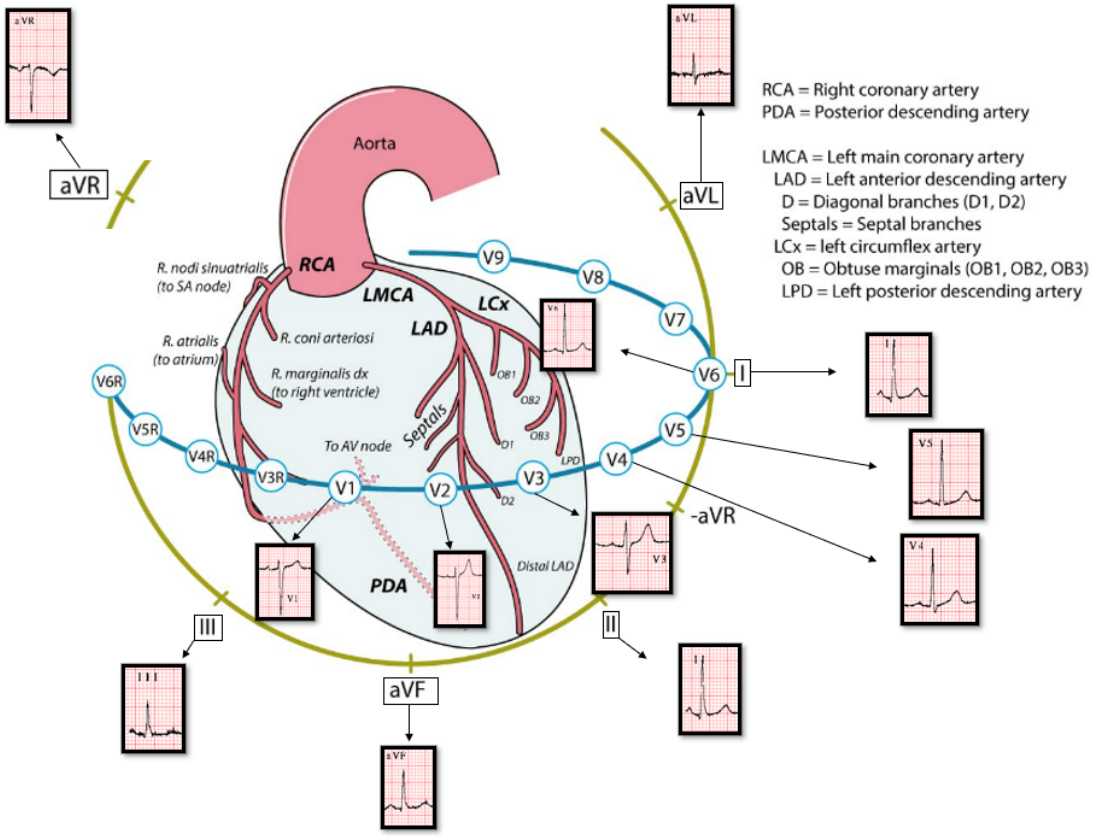

Figure 2.2: Positions of each precordial lead and the corresponding ECG shape (adapted from [15] with ECG leads from [16])

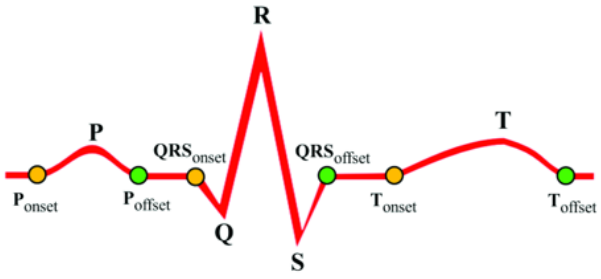

Figure 2.3: The electrocardiogram (adapted from [17] - fig. 7.)

2.3 Defining Systole and Diastole Using the ECG

Systole and diastole can be defined using the ECG, i.e., we can relate the opening and the closing of the aortic valve to the waves presented in the ECG.

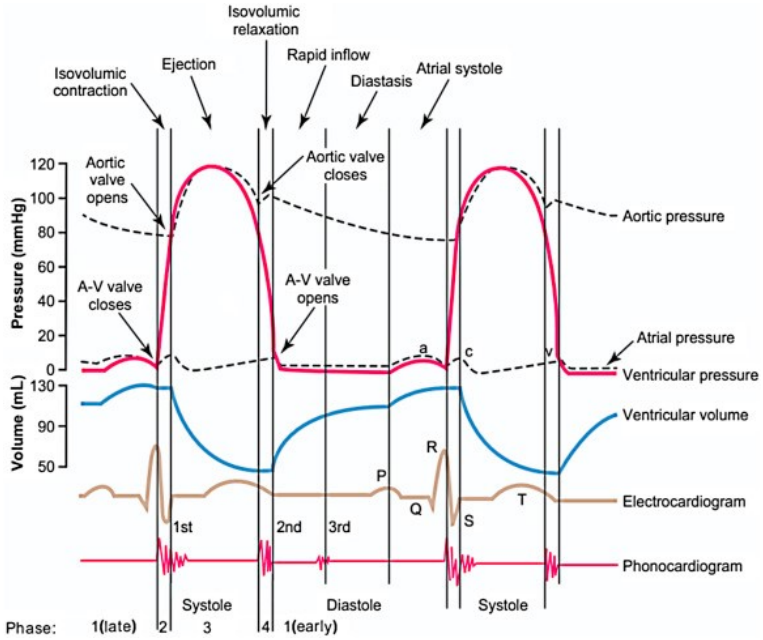

Figure 2.4: The cardiac cycle related to the phonocardiogram, ECG, ventricular volume and pressure. A-V valve is the atrioventricular valve. (adapted from [11] - fig. 9.5)

In fig. 2.4, it is shown that the aortic valve tends to close at the end of the T wave (T offset) and it tends to open up between the R peak and the end of the S wave (S offset). The systole can be defined as the time period between the opening and the closing of the aortic valve. Therefore, the systole phase tends to start between the R peak and the end of the S wave in the ECG, and finishes near the offset of the T wave [11].

Thus, the systolic phase can be defined by the opening and closing of the aortic valve (mechanical systole) or by the electrical events measures in the ECG (electrical systole). However, there is no consensus regarding the definition of the beginning and end of this cardiac phase. [18–20]. Here are three examples of studies that use different definitions of the systolic phase:

- Systole is defined by the interval between the Q wave and the second aortic valve sound (S2) [18];

- The beginning of diastole usually occurs after the T wave (on 50 % of the participants) [20];
- Systole is defined by the interval between the Q wave and the T wave [19].

We can see that, in those 3 studies, we do not have a general agreement in the definition of the systolic phase.

2.4 Interactions Between Heart and Brain: A Visual Perception Approach

It is known that our brain controls our heart. During our daily life, we can feel our heart beat faster or slower. It tends to adapt to each circumstance of our lives [21, 22]. For example, heat acclimatization allows us to change our heart rate, which can be an outcome of the autonomous nervous system's activity [23, 24].

Another example that shows the interaction between the autonomous nervous system and the heart is the freezing state. As mentions Roelofs et al. ([5]), when we are in some kind of unexpected dangerous situations, our body freezes. Some studies show that when we are in this freezing state, our heart rate tends to decrease [25–27].

Regarding visual perception, the detection of visual stimuli is more sensitive when we are in the freezing state [28]. Furthermore, some studies show that when the visual stimuli and the heartbeat are timed, our visual perception is facilitated [29,30]. Also, Sandman et al. ([31]) report that lower heart rates improved the visual stimulus perception. This also leads to the fact that the heart is controlled by the autonomic system.

In cued reaction time tasks, a cue stimulus is presented before the target presentation, indicating that the target stimulus will follow soon. The cue precedes the timing of the target and induces the orienting of attention towards the target. Therefore, a neutral auditory cue can trigger a form of selective attention [32, 33]. This attentive state leads our heart rate to decrease: some studies showed that after the presentation of an auditory cue, participants tend to focus, which causes the heart rate to decrease [6–8, 34].

We know that our autonomic nervous system controls many organs of our body including the cardiac muscle which controls our heart rate [35, 36].

The autonomous nervous system is divided by two main systems: the **parasympathetic system** which is more active during rest conditions and controls the basal organs, and the **sympathetic system** which, conversely, reacts to stressful situations. These two systems are composed by a two-neuron chain: the preganglionic neurons which are longer in the parasympathetic system than the ones in sympathetic system and the postganglionic neurons which are longer in the sympathetic system than the parasympathetic system [37].

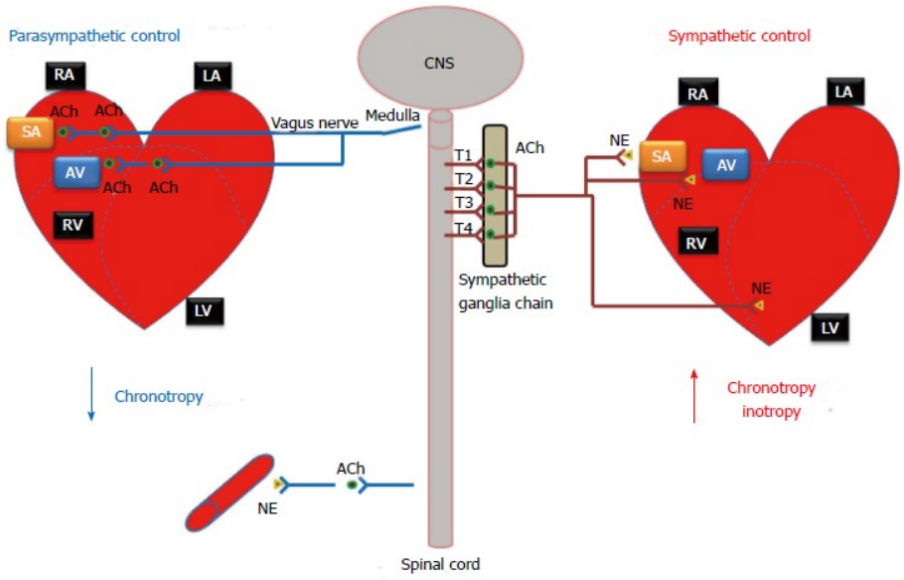

Figure 2.5: The action of parasympathetic and sympathetic systems on the heart. (adapted from [37] - fig. 1)

As we can see in fig. 2.5, the parasympathetic system operates in the heart through the long preganglionic neurons derived from the mid-brain. These nerves release the neurotransmitter acetylcholine (ACh) which binds to the muscarinic receptors (M2 and M3) in the heart, causing the heart rate to decrease. The sympathetic system operates through the shorter preganglionic nerves which arise from the spinal cord's upper thoracic portions (T1-T4). These nerves interact with the postganglionic nerves using acetylcholine as well, but the postganglionic nerves in the sympathetic nervous system release norepinephrine (NE), which binds to the adrenergic receptors in the heart (α, β), leading to an increase in heart rate [37].

This autonomic neural response can be also controlled by some brain areas such as the insular cortex, anterior cingulate cortex, the amygdala and several hypothalamic nuclei [3].

Although the neuronal mechanisms that controls the heart are well established, it is not clear how cardiac deceleration during attentive preparation might affect sensory processing.

It is known that, during diastole, the perception of somatosensory stimuli is enhanced. Some studies show that when the somatosensory stimulus is presented in diastole, the detection rate of the stimulus is higher when compared to when it is presented during systole [38, 39]. This hypothesis can also be seen in the potential evoked by the brain: it is reported that the somatosensory potential evoked by the brain, when the stimulus is presented in diastole, shows a higher amplitude compared to when the stimulus is presented in systole [9]. Even in pain, the perception of the stimuli is lower during systole when compared to diastole [40–42]. As we can see, perception of somatosensory stimuli is enhanced in diastole; however, what happens to visual stimuli is unknown.

It is known that the heart rate also influences the different phases of the cardiac cycle. Some studies point to the fact that a cardiac deceleration increases relative duration of the diastolic phase [43–46].

From all these studies we can conclude that somatosensory perception is higher during diastole than during systole. We also saw that there is a heart deceleration during attention preparation and this cardiac deceleration may be significant for somatosensory processing since there is an increase in the percentage of time spent in diastole during the cardiac cycle. So, in this master's thesis we want to combine these findings and determine if they have any impact on visual perception.

3

Using the ECG to Estimate the Onset and the Offset of the Systole

Systole can be defined using mechanical and electrical approaches. Some studies compared the electrical definition of systole with the mechanical systole to see which electrical heart events were related to the opening and the closure of the aortic valve (mechanical systole) [19, 20]. In neuroscience investigations, studies that regard the heart and the brain use an electrical systole definition as we can see in Motyka et al. ([38]).

In this chapter, we wanted to see if the electrical approach to define the systole was suitable. To do that, we compared the mechanical instants of the onset and offset of the systole (the opening and closing of the aortic valve) estimated with precision on the echocardiogram (ECHO), with the timings of the different waves that compose the electrocardiogram (ECG). We wanted to verify the method reported by [19, 20], i.e., we wanted to find the exact QRS complex event from the ECG that was related to the opening of the aortic valve and verify if the T wave was in fact related to the closure of the valve.

Furthermore, we studied how the relationship between the opening and closing of the aortic valve and the ECG waves changes in individuals with cardiovascular disease and in healthy individuals while resting or after exercise.

We also investigated the relationship between heart rate and the difference between mechanical and electrical systole instants in healthy participants while resting or after the exercise and in participants with cardiovascular diseases.

3.1 Methods

3.1.1 Participants

We analysed a database acquired in Centro Hospitalar da Universidade de Coimbra (CHUC) composed by 68 adult participants with ages between 18 and 85 years old in which 33 were healthy and 35 were diagnosed with a cardiovascular disease (table 3.1).

Table 3.1: Distribution of all of the cardiovascular diseases included.

Conditions	Nr. of participants
Acute myocardial infarction (EAM)	2
Angina pectoris	1
Aortic insufficiency	2
Aortic prosthesis	2
Aortic stenosis	2
Aortic valve post-surgery (biological prosthesis)	1
Arterial Hypertension (HTA)	3
Atrioventricular block	1
Atrioventricular Conduction Disorders	1
Atypical pain	1
Coronary Artery Disease (CAD)	8
Gastrointestinal pathology	1
Heart failure	3
Hepatic transplant	1
Hypotension	1
Incomplete right branch block	1
Interatrial communication (CIA) operated	1
Ischemia	1
Lymphoma	1
Mitral Post-surgery (mitral valve repair or replacement)	1
Myocarditis	2
Paroxysmal Atrial fibrillation	1
Stenosis of the thoracic aorta (STA)	1
Stroke	1
Syncope	1
Ventricle extra-systoles (EV)	2
Ventricular Dysrhythmia	1

The cardiac data was acquired in 5 different ways:

- Non-Invasive Continuous Cardiac Output Monitor (NICCOMO);
- Stethoscope;
- Echocardiography;
- Photoplethysmography (PPG);
- Electrocardiography (ECG).

In this master's thesis, we will be comparing the data from the echocardiography and the data from ECG.

For healthy participants, the acquisitions were obtained during two different conditions: at rest and after exercise, whereas for those with cardiovascular disease (table 3.1), only acquisitions at rest were performed.

For some participants, the acquisitions of the aortic valve events were not saved, so in some further plots no data will be presented of those subjects (for example CHC02HEA Post-Exercise (see fig. A.2)).

The healthy participant CHC05HEA was removed from the analysis due to problems in the identification of the ECG waves.

3.1.2 Analysis of the ECG data

The ECG used in the analysis was the one acquired synchronously with the stethoscope using the Welch Alyn system, which was acquired when participants were in the supine position. The ECG, while the stethoscope heart sounds were recorded, was acquired with a sampling rate of 44100Hz using a MLII lead configuration. The reason why we chose the ECG signal from the stethoscope was because it presented less noise when compared to the other acquisitions means.

The timings of the open and closure of the aortic valve were obtained from the echocardiogram using a Doppler echo with a sampling rate of 500Hz. The aortic valve mechanical events were defined in the echocardiography acquisitions with the assistance of a technician to identify the timings related to the aortic valve utilizing the images from the echocardiogram.

To analyze the ECG data, we used Matlab (version R2021b) custom scripts and the ECG toolbox from the Health Informatics Lab at Centro de Informática e

Sistemas da Universidade de Coimbra (CISUC).

Since the toolbox was designed to work with data sampled at 250Hz, we re-sampled the ECG data from 44100Hz to 250Hz and the Doppler echocardiogram data from 500Hz to 250Hz to further compare the ECG data with the aortic valve events.

After that, we used some procedures to preprocess the ECG data before it entered the toolbox:

- **Noise Reduction**: we ran a low-pass finite impulse response (FIR) zero phase filter through the ECG data with a cut-off frequency of 20Hz to reduce the noise from the signal;
- **Normalization**: we adapted all the ECG signal to take values between -1 and 1 using the normalization formula: $X_{new} = \frac{X - X_{min}}{X_{max} - X_{min}}$.

Next, we used the segmentation function of the toolbox to identify all the components from the ECG on the signal.

The ECG toolbox is composed of routines that identify the peaks of the waves and its onsets (beginnings) and offsets (endings) using the morphological derivatives as an algorithm of detection. After the identification, the toolbox outputs a variable with the timings of each ECG wave:

- **WAVES.P**: retrieves all the instants related to the P wave: P onset, P peak and P offset;
- **WAVES.QRS**: shows the events associated to all the waves presented in the QRS complex: Q onset, Q peak, R peak, S peak and S offset;
- **WAVES.T**: gives all the events related to the T wave: T onset, T peak and T offset.

3.1.3 Data Troubleshooting

When we were visually inspecting the segmentation of the data by the ECG toolbox, we detected some issues related to the identification of some ECG waves. Also, some problems on data savings of the aortic valve closure and the aortic valve opening from the echocardiography were detected.

3.1.3.1 ECG Toolbox Problems

As we can see in fig. 3.1, there were some problems related to the identification of the T wave and the S wave on the QRS complex by the ECG toolbox.

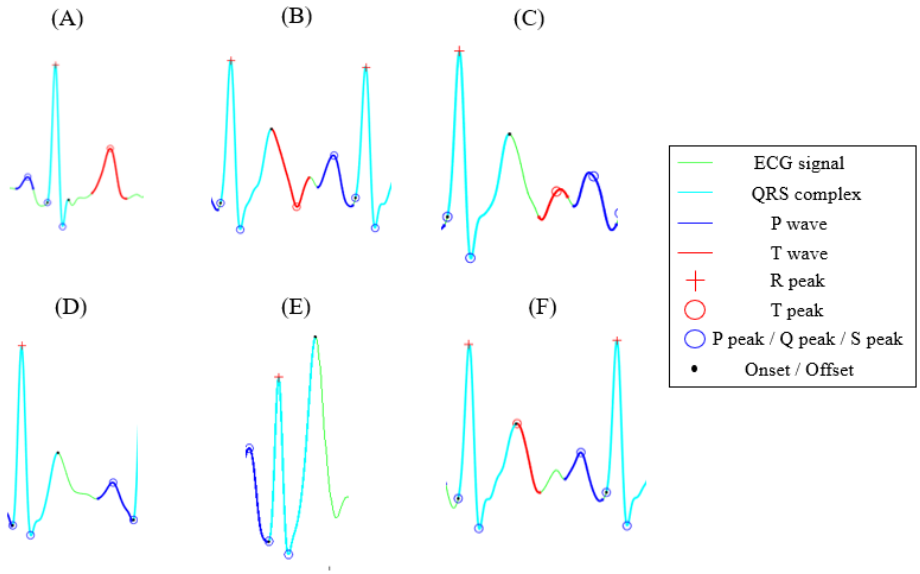

Figure 3.1: ECG toolbox output that shows waves that were wrongly identified. The time came in seconds. **(A)** Example with all waves correctly identified; **(B)** T wave which T peak is lower than T onset; **(C)** T wave that was lower than the identified QRS offset (or S offset); **(D)** T wave not identified and QRS offset higher than the next P wave; **(E)** QRS offset higher than R peak; **(F)** T onset incorrectly identified but T peak and T offset in the right place.

To solve those problems, we adopted the following strategies:

- **Fig. 3.1 (B):** We compared the ECG value of the T offset with the T peak, and when T offset value was higher than the T peak, we removed that cycle (this could happen in participants with ischemia);
- **Fig. 3.1 (C):** We compared the T peak with the QRS offset (S offset) and if the T peak value was lower than S offset, we erased that cycle from the data;
- **Fig. 3.1 (D) and (E):** We compared the S offset with the P peak, if the S offset was higher than the P peak, then we removed that cycle from the analyses;
- **Fig. 3.1 (F):** We preserved those cycles because we could measure the error based only in the T offset, the onset was not needed in this analysis.

3.1.3.2 ECG data problems

Since we will be measuring the difference between events related to the aortic valve and ECG events, it was important to ensure that those two events belonged to the same cardiac cycle.

To do that, we verified if the ECG events and the aortic valve events were between two R peaks: The R peak from the actual cycle (R peak 1) and the next one (R peak 2) as it is represented in fig. 3.2.

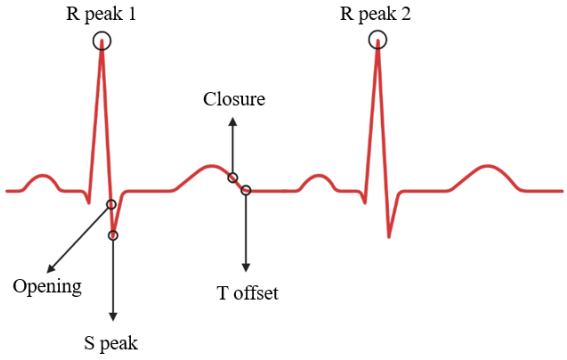

Figure 3.2: Scheme that represents the ideal case in which we have all the ECG and the aortic valve events. R peak 1 is the R peak from the same cycle as the opening, closure, S peak and T offset. The R peak 2 is the R peak from the cycle after the one represented.

These two values of R peak used in the verification above, were moved to an extra variable in which we measured the difference between those two peaks (Interbeat Interval (IBI)) and divided 60 by that value to obtain the heart rate in beats per minute (bpm).

Regarding the aortic valve events, sometimes the database revealed that, in the same cardiac cycle, the aortic valve closure appeared first than the opening. In those cases, we eliminated all the events related either to the aortic valve or to the ECG. In fig. 3.3 we can see four ECG cycles with the ideal case reported in fig. 3.2.

After verifying that the mechanical events were in the same cardiac cycle as the electrical ones, we measured the difference between both. Next, we measured the z-score (using the Matlab function "zscore") of each time interval and excluded the outliers which had absolute z-scores higher than 3.

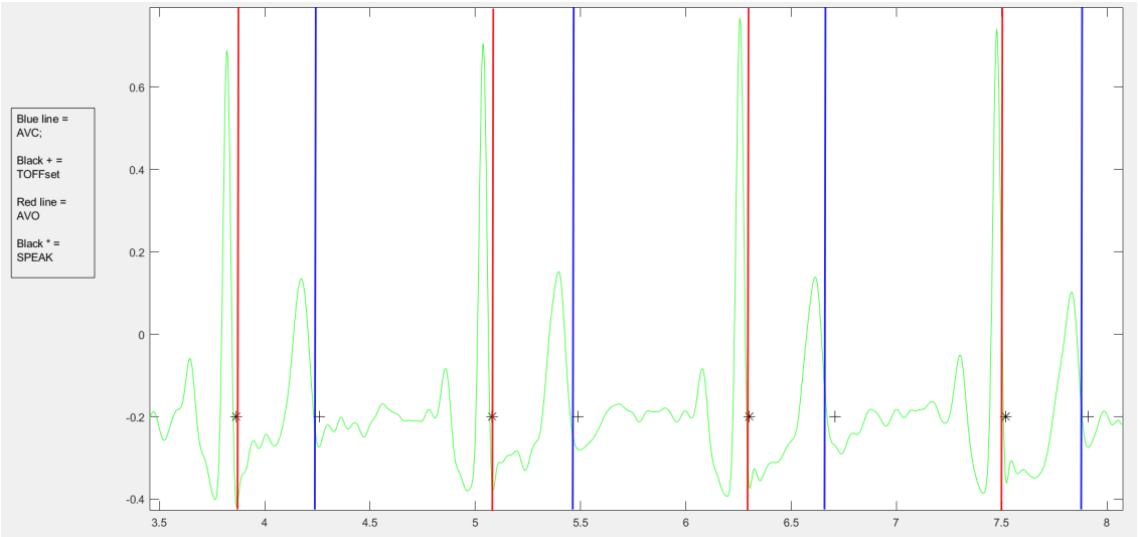

Figure 3.3: ECG cycles with annotated aortic valve mechanical events - example from one participant. We can see the mechanical systole events in vertical lines (blue line represents the aortic valve closure and red line represents the aortic valve opening) and the electrical heart events in markers (+ represents T offset and * represents S peak).

3.1.4 Statistical Analysis

To test the effect of the exercise on the time intervals in the healthy participants, we used a paired T-test between the average time intervals of the estimated during resting conditions and the average time intervals estimated after exercise. To study the effect in each participant, we compared the time intervals using an independent samples T-test and measured the percentage of the participants whose difference was significant ($p < 0.05$).

To analyse the effect of the cardiovascular condition, we compared the time intervals of the healthy participants with time intervals of the individuals with cardiovascular disease using the independent samples T-test.

To study the effect of heart rate, we ran the Matlab's function "corrcoef" between the set of time intervals and the heart rates of each participant. Next, we ran the one sample T-test in the Pearson's correlation coefficients to determine if at the group level there was a significant relationship between heart rate and the time differences between the mechanical and electrical systoles.

In all the statistical analysis, a cut-off of $p < 0.05$ was used to define significance.

3.2 Results

3.2.1 Measuring the Time Difference between the Mechanical Events and the Electrical Events

We measured the time intervals given by the difference between the aortic valve events and the ECG events. As it is shown above in section 2.3, the closure of the aortic valve is related to the T offset, however the opening could be between the R peak and the S offset [19, 20].

In a first approach, we compared the opening of the aortic valve with the R peak, S offset and S peak by making the difference between those events. The main objective of these comparisons was to determine which ECG event was nearer to the aortic valve opening. The average differences can be seen in table 3.2.

Table 3.2: Average values ± standard deviation of the time intervals between the ECG events and the Aortic Valve Opening (AVO) across participants.

Electrical event - Mechanical event	Healthy		Cardiovascular Disease (ms)
	Rest (ms)	Post-Exercise (ms)	
R peak - AVO	-40.8 ± 9.0	-27.2 ± 9.6	-42.2 ± 19.4
S offset - AVO	42.5 ± 22.5	69.3 ± 28.3	58.7 ± 34.1
S peak - AVO	-1.4 ± 9.2	12.0 ± 9.9	-2.2 ± 19.7

The negative values seen on table 3.2 are related to the fact that the aortic valve opening occurs after the electrical event. The positive values of the average differences between the S offset / S peak and the aortic valve opening means that the opening of the valve came before the end of the S wave and before the peak of the S wave.

From the obtained results, we can conclude that the S peak was the one that was closest to the opening of the valve, being this the instant that reveals a smaller time interval between the ECG event and the opening of the aortic valve. Therefore, we chose the S peak for the following analyses.

3.2.2 Comparison between the Time Intervals in the Onset and in the Offset of the Systole

After measuring the time interval between the S peak and opening of the aortic

valve, we compared the T offset with the closure of the aortic valve and the mechanical systole with the electrical systole in healthy and in cardiovascular participants (table 3.3).

According to [47], the duration of the systole varies between 300 and 400 ms. We measured the duration of mechanical systole as the difference between the closure of the aortic valve (AVC) and the opening of the aortic valve (AVO). The electrical systole, instead, was measured by the difference between the T offset and the S peak. We concluded that both systole durations matched the literature values and the duration of the electrical systole is higher than the mechanical systole for healthy participants rest (paired T-test: $p = 9.6769\text{e-}09$, $t_{31} = 7.75$) and post-exercise (paired T-test: $p = 6.3155\text{e-}08$, $t_{30} = 7.12$) and for participants with cardiovascular disease (paired T-test: $p = 9.4449\text{e-}05$, $t_{34} = 4.42$) (table 3.3).

To the average time interval, we could see that the values were higher in the offset of systole when compared to the onset of systole. Also we noted that, for the closure of the aortic valve, all the average time intervals came positive, contrarily to what can be seen in healthy participants in rest and in participants with cardiovascular disease on the aortic valve opening analysis. When the average value was positive means that the electrical event came after the mechanical event. In the negative average values, the mechanical event came after the electrical event, mostly.

Table 3.3: Across groups average information related to the time interval analysis regarding the aortic valve opening (AVO) and the aortic valve closure (AVC). From left to right we have: The average time interval in healthy participants at rest and after exercise as well as that of participants with cardiovascular disease; Average systole duration measured between the mechanical and electrical events.

Group		**Average time interval (ms)**		**Average systole duration (ms)**	
		S peak - AVO	**T offset - AVC**	**Mechanical**	**Electrical**
Healthy	Rest	-1.4 ± 9.2	22.5 ± 18.5	270 ± 21	294 ± 25
	Post-Exercise	12.0 ± 9.9	42.0 ± 25.0	245 ± 29	274 ± 30
Cardiovascular Diseased	Rest	-2.2 ± 19.7	23.8 ± 42.3	298 ± 36	328 ± 43

3.2.3 Studying the Effect of the Exercise

3.2.3.1 The Effect of Exercise on the Difference between Mechanical and Electrical Systole events

In order to study the effect of exercise on the time interval between the ECG events and the aortic valve opening and closing, we plotted for each participant all the time differences for every cardiac cycle during rest and post-exercise conditions (Appendix A.1).

In fig. 3.4 we show an example from a healthy participant. We can see that the time interval of the resting acquisitions is much lower than the post-exercise ones. This effect was seen in 22/32 individuals (Appendix A.1) in the onset (fig. A.1) and in 27/32 in the offset of systole (fig. A.2).

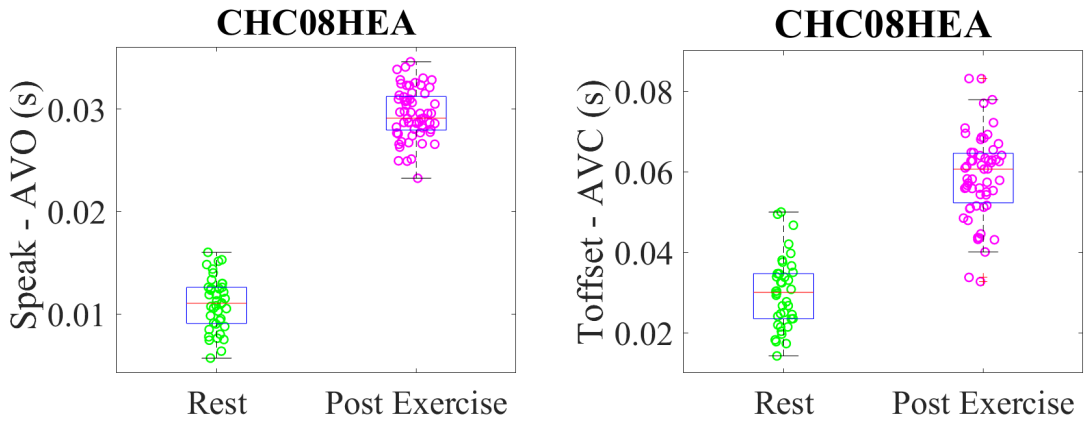

Figure 3.4: Plots with all cardiac cycles of healthy participant CHC08 separated by condition. In the left it is shown the results regarding the onset of the systole and in the right side regarding the offset. In green color we have acquisition of CHC08HEA made at rest and in magenta we have the values made after exercise.

To compare the effect of exercise in each participant, we ran the paired T-test (section 3.1.4) between the rest acquisitions and the post-exercise ones to measure the percentage of the individuals that the post-exercise time differences were significantly different from the rest ones. Relative to the interval between the S peak and the opening of the aortic valve, approximately 62.50% of the participants showed significant effect of the exercise and the T-tests showed an average T value of -11.18. To the interval between the T offset and the closure of the aortic valve, 81.30% of the participants presented significant differences between the groups and the average T value was -8.68.

After we made a comparison to each individual, we made a comparison between the average time intervals between the healthy participants rest acquisitions and the post-exercise acquisitions.

Figure 3.6 shows the same group of healthy participants. We can see the comparison of the time intervals measured between the electrical and the mechanical systole.

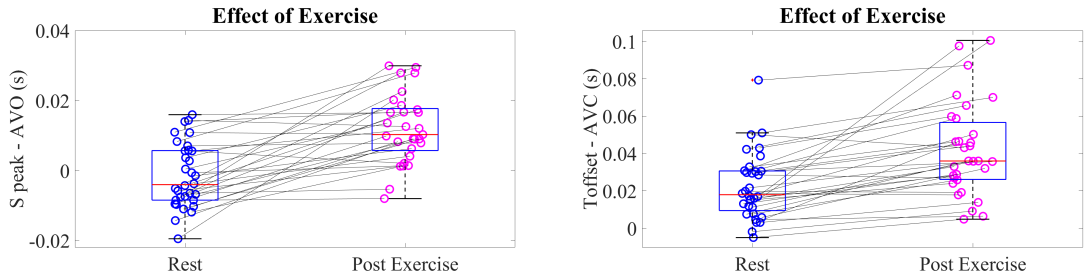

Figure 3.5: Comparison plots with the average time intervals of all healthy participants measured between the T offset and the aortic valve closure (right side) and between S peak and the aortic valve opening (left side). In blue we have the acquisitions made at rest and in magenta we have the acquisitions done after exercise.

Either to the aortic valve opening (paired T-test: $t_{28} = -5.99$, $p = 1.8977\text{e-}6$) or to the aortic valve closure (paired T-test: $t_{30} = -5.33$, $p = 9.1407\text{e-}6$), healthy individuals whose acquisition was done at rest had lower time intervals between the electrical heart events and the mechanical aortic valve events than the acquisitions done after the exercise. This observation suggests that the increase in heart rate leads to an increase in the distance between the aortic valve closure / opening and the T offset / S peak, respectively.

3.2.3.2 The Effect of Exercise on Heart Rate

In this analysis, we compared the average heart rate in each healthy participant rest acquisition with each post-exercise acquisition.

Figure 3.6 shows that the average heart rate of the post-exercise acquisitions in healthy participants was higher than the heart rate measured at rest (paired T-test: $t_{30} = \text{-}7.17$, $p = 5.6205\text{e-}8$).

The exercise described here involves the participants using the static bike for a while before the ECG acquisition.

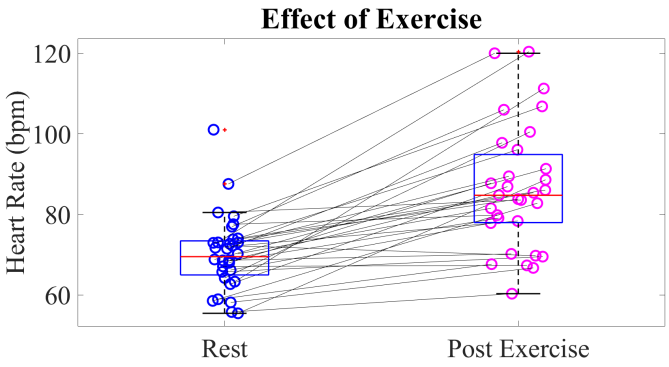

Figure 3.6: Effect of exercise on heart rate in healthy participants. In blue we can see the rest acquisitions and in magenta the post-exercise acquisitions of healthy participants.

3.2.4 Studying the Effect of Cardiovascular Disease

3.2.4.1 The Effect of Cardiovascular Disease on the Difference between Mechanical and Electrical Systole Events

To study the effect of cardiovascular disease on the difference between the mechanical and electrical systole, we box-plotted the average time intervals measured in healthy rest participants and compared them with the time intervals measured in participants with cardiovascular disease. We also studied the distribution of the time intervals of each participants with cardiovascular disease related to the difference between the S peak and the aortic valve opening (figure A.3) and related to the difference between the T offset and the aortic valve closure (figure A.4) in appendix A.2.

Figure 3.7, shows two distinct groups of participants. In green we have the time differences between the electrical heart events and the mechanical aortic valve events from healthy rest participants. In red instead, we have the time intervals of participants with cardiovascular disease at rest.

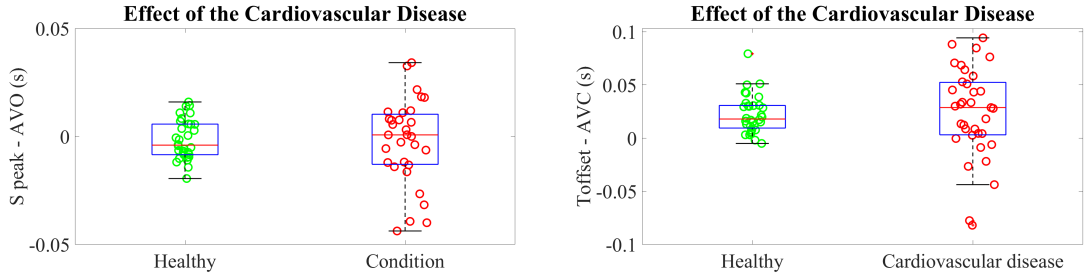

Figure 3.7: Comparison plots with the average time intervals between the electrical and mechanical systole events of healthy participants at rest (green) and participants with cardiovascular disease (red). In the left side we have the comparison related to the opening of the aortic valve (AVO) and in the right side the comparison between healthy and participants with cardiovascular disease in the closure of the aortic valve (AVC) analysis.

For both opening (independent samples T-test: $t_{61} = 0.19$, $p = 0.85$) and closing (independent samples T-test: $t_{65} = -0.17$, $p = 0.88$) of the aortic valve, it was found that the time differences are not significantly different between the participants with cardiovascular disease (fig. 3.7 in red) and healthy individuals (fig. 3.7 in green). However, it is important to note that, the dispersion of the time intervals is higher in the group with cardiovascular disease when compared to the healthy group.

3.2.4.2 The Effect of Cardiovascular Disease on Heart Rate

In this analysis, we compared the average heart rate of the healthy group with the heart rate of the group with cardiovascular disease to study the effect of the cardiovascular condition on heart rate.

Figure 3.8 shows that the average heart rate in the individuals with a cardiovascular condition was lower than the healthy participants (independent Samples T-test: $T_{65} = 0.79$, $p = 0.43$).

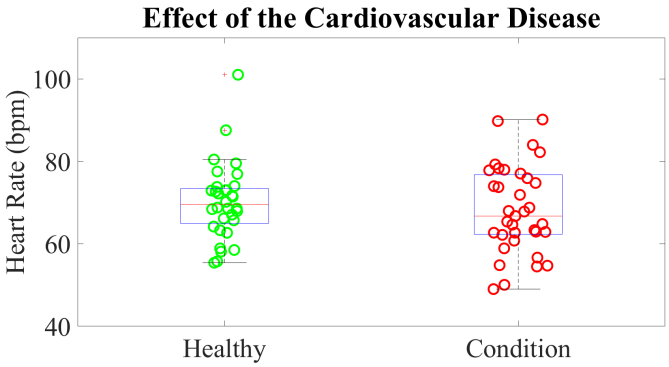

Figure 3.8: Variation of heart rate between groups. In green we can see the healthy participants and in red we can see the participants with cardiovascular disease.

3.2.5 Relationship between Heart Rate and the Time Intervals between ECG Events and the Opening and Closing of the Aortic Valve

3.2.5.1 Effect of Within-Subject Fluctuations in Heart Rate on the Time Interval between Electrical and Mechanical Systole Events

In this analysis,we investigated the effect of heart rate fluctuations on the time differences between the electrical and mechanical heart events, in each participant. The results can be seen in tables 3.4 and 3.5.

To do this analysis, for each participant, we run a correlation analysis to investigate the relationship between heart rate and the time differences between the electrical and mechanical systole events. We saw that, for the opening of the valve, 25.0 % of the healthy participants in rest condition as well as 21.8 % of the post-exercise ones and 17.1 % of the participants with cardiovascular disease showed a significant correlation between the time intervals and the heart rate values (table

3.4). To the closure of the valve, the percentages were 15.6 % of the healthy participants in rest condition as well as 25 % of the post-exercise ones and 18.2 % of the individuals with cardiovascular disease (table 3.5).

Table 3.4: Correlation between heart rate and the time intervals between the opening of the aortic valve and the S peak.

Group		**% of participants presenting a significant correlation**	**Average value of r coefficient**	**p value from one sample T-test**
Healthy	**Rest**	15.6 %	- 0.1464	5.7798 e-5
	Post Exercise	25.0 %	- 0.0857	0.1140
Cardiovascular Disease	**Rest**	18.2 %	- 0.0480	0.3898

Table 3.5: Correlation between heart rate and the time intervals between the closure of the aortic valve and the T offset.

Group		**% of participants presenting a significant correlation**	**Average value of r coefficient**	**p value from one sample T-test**
Healthy	**Rest**	25.0 %	0.1888	2.0467 e-5
	Post Exercise	21.8 %	0.1150	0.0052
Cardiovascular Disease	**Rest**	17.1 %	0.0375	0.4697

Afterwards we ran the one sample T-test in the Pearson's correlation coefficients of all participants (section 3.1.4), we saw that only for the healthy participants at rest condition in the opening of the valve analysis (table 3.4) and in healthy participants rest and post-exercise conditions in the closure of the valve analysis (table 3.5), the one sample T-test revealed a significant effect ($p < 0.05$), so we could establish a relation between the time intervals and the heart rate.

With that said, to the opening of the valve analysis, the correlation coefficient is negative. For the healthy individuals at rest in this analysis, as the heart rate increases, the time interval became more negative, i.e., the mechanical event comes further after the electrical event (table 3.4).

For the closure of the valve analysis, as the mean value of the correlation coefficient was positive for the healthy participants (rest and post-exercise acquisitions) and the one sample T-test reveled a significant effect, we could say that the time intervals increased with heart rate (table 3.5).

In the figures below, we can see one example of one participant of each group who showed a significant correlation between heart rate and the time interval and one who did not. We provided examples for both the aortic valve opening analysis and the aortic valve closure analysis.

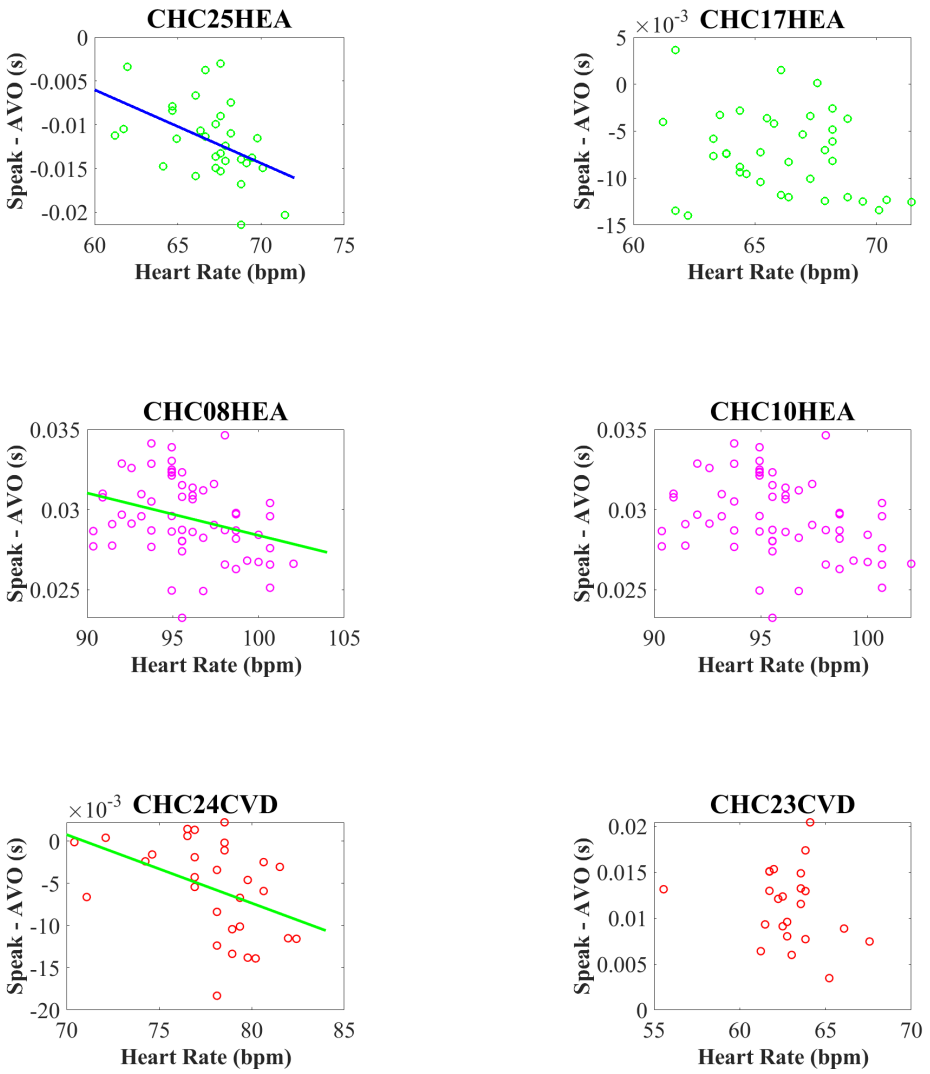

Figure 3.9: Six examples of participants related to the aortic valve opening analysis: **CHC25HEA** - healthy participant at rest presenting a significant correlation between heart rate and the time interval between T offset and the AVC. ($p = 0.0087$;r = -0.4631); **CHC17HEA** - healthy participant at rest with a non significant correlation (p = 0.1571;r = -0.2374); **CHC08HEA** - healthy post-exercise participant presenting a significant correlation (p = 0.0142;r = -0.3125); **CHC10HEA** - healthy post-exercise participant with a non significant correlation (p = 0.2041;r = -0.1976); **CHC24CVD** - participant with a cardiovascular disease presenting a significant correlation (p = 0.0181;r = -0.4288); **CHC23CVD** - participant with cardiovascular disease with a non significant correlation (p = 0.3253;r = -0.2147).

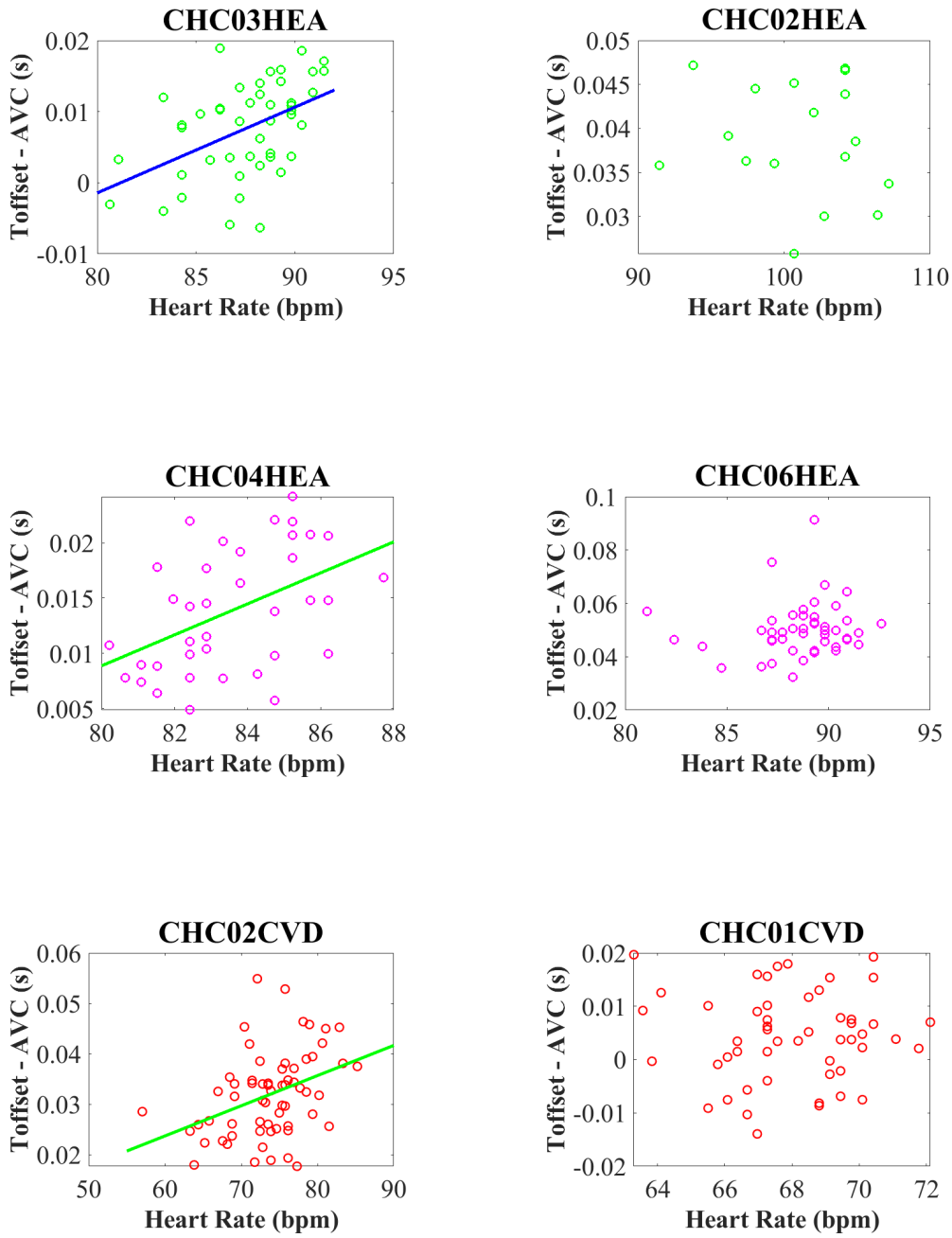

Figure 3.10: Six examples of participants related to the aortic valve closure analysis: **CHC03HEA** - healthy participant at rest presenting a significant correlation between heart rate and the time interval between T-offset and the AVC. ($p = 0.0011; r = 0.4711$); **CHC02HEA** - healthy participant at rest with a non significant correlation ($p = 0.5863; r =$ -0.1421); **CHC04HEA** - healthy post-exercise participant presenting a significant correlation ($p = 0.0037; r = 0.4653$); **CHC06HEA** - healthy post-exercise participant with a non significant correlation ($p = 0.3917; r = 0.1279$); **CHC02CVD** - participant with cardiovascular disease presenting a significant correlation ($p = 0.0022; r = 0.3786$); **CHC01CVD** - participant with cardiovascular disease with a non significant correlation ($p = 0.9878; r =$ -0.0022).

3.2.5.2 Relationship between Average Heart Rate and Average Time Differences between Electrical and Mechanical Systole Events

In this analysis, we compared the average values of the time intervals of each participant with the average heart rate values using the "corrcoef" function from Matlab to conclude if we had a correlation between those variables.

In the opening of the aortic valve analysis, we saw that the healthy participants whose acquisitions were done at rest showed a significant correlation between the heart rate and the time intervals ($p = 0.0141$) same as the post exercise acquisitions ($p = 9.6803e - 4$). For the participants with cardiovascular disease, no significant correlation was observed between the time intervals and the heart rate ($p = 0.7268$). The plots related to these observations could be proved in the left side figs. 3.11, 3.12 and 3.13.

Contrary to what we saw on the analysis when we compared the time intervals with the heart rate within each subject to the closure of the aortic valve analysis, no significant correlation was observed between the average time interval values and the average heart rate. The function returned a p value higher than 0.05 to healthy participants whose acquisitions were made at rest ($p = 0.2136$), to post-exercise acquisitions ($p = 0.5574$) and to participants with cardiovascular disease at rest ($p = 0.6315$). The plots related to these observations could be observed in the right side figs. 3.11, 3.12 and 3.13.

With this analysis we could conclude that, when we compared the average heart rate with the average time interval between all individuals we did not see the same results as the ones obtained in the analysis inside each individual.

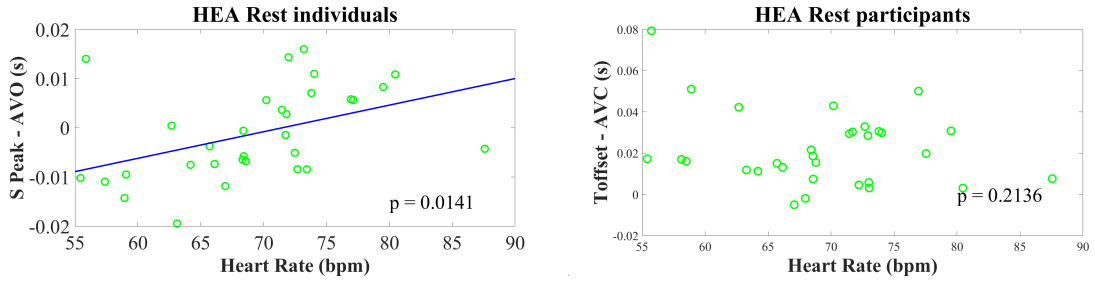

Figure 3.11: Average time intervals (in seconds) plotted against the average heart rate values (in beats per minute) of healthy (HEA) participants whose acquisition was done at rest. In the right side we have the analysis related to the aortic valve closure and the left side we had the analysis related to the aortic valve opening.

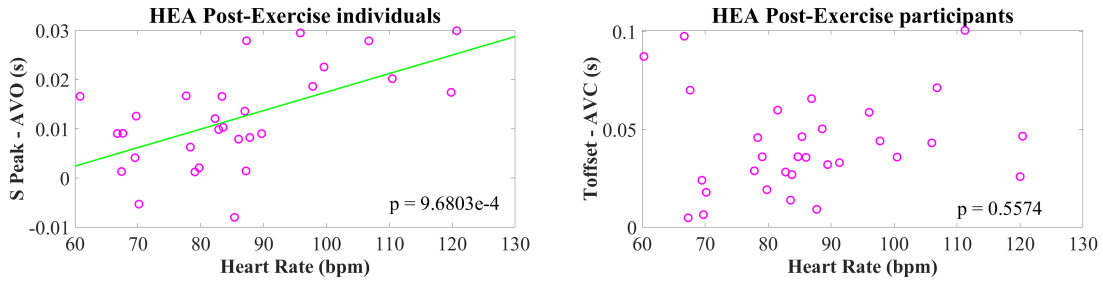

Figure 3.12: Average time intervals (in seconds) plotted against the average heart rate values (in beats per minute) of healthy (HEA) participants whose acquisition was done after the exercise. In the right side we have the analysis related to the aortic valve closure and the left side we had the analysis related to the aortic valve opening.

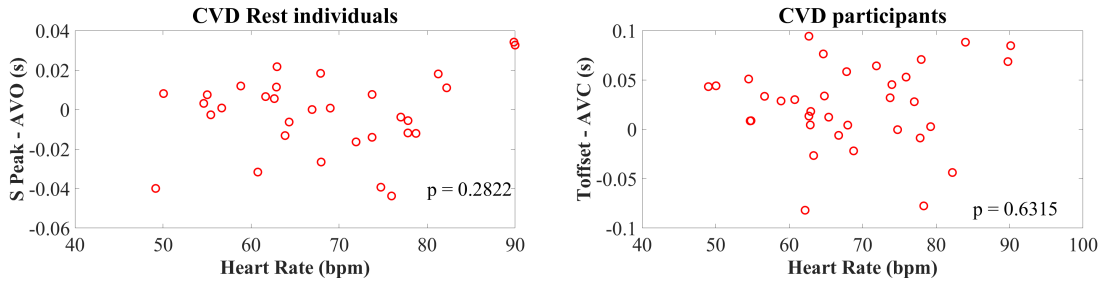

Figure 3.13: Average time intervals (in seconds) plotted against the average heart rate values (in beats per minute) of participants with cardiovascular disease (CVD). In the right side we have the analysis related to the aortic valve closure and the left side we had the analysis related to the aortic valve opening.

3.3 Discussion

In this chapter, we aimed to define which electrical event from the ECG was more closely associated with the mechanical aortic valve events (opening and closing of the valve) precisely recorded from the echocardiography. We also studied the effect of exercise and cardiovascular disease and heart rate in the time difference between the mechanical systole events and the electrical systole events.

Contrary to what was shown in [18–20], we concluded that the electrical wave with the shortest time interval to the aortic valve opening was the S peak and not the Q wave. As reported in the results, it showed the lower average value of the time intervals measured between the ECG events and the aortic valve opening in the three comparisons performed. Regarding the electrical event that can be compared to the aortic valve closing (the end of systole), our findings were in accordance with

the findings reported by the previous studies, and that ECG event was the offset of the T wave [18–20].

We also studied the effect of exercise and of cardiovascular disease in the time intervals between the electrical and the mechanical systole. A summary is presented in fig. 3.14.

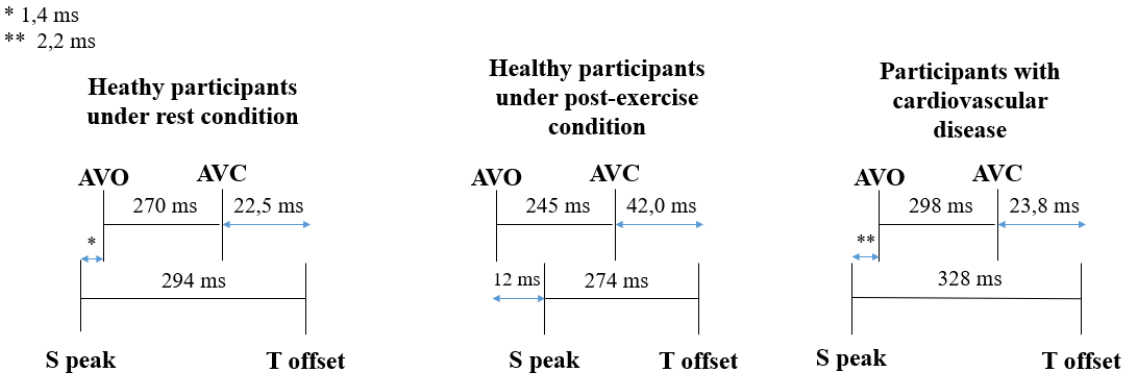

Figure 3.14: Scheme that summarizes all the results related to the time interval between electrical and mechanical systole. From left to right, the results concerning the analysis of healthy individuals whose acquisition was done at rest, of healthy individuals whose acquisition was done after exercise, and of individuals with cardiovascular disease whose acquisition was done at rest. It is important to note that the time intervals are not to scale.

In both healthy and with cardiovascular disease groups, we found that the time difference associated with the offset of systole is greater than the one associated with the onset. This can be due to wrong choice of the T offset. As we can see in fig. 2.4, the closure of the aortic valve could be located in the time interval between the T peak and the T offset. Maybe if we estimated the average point between these two events, we would obtain smaller time differences results.

From figure 3.14, we can observe that the duration of the electrical systole, in all groups, is higher than the mechanical one. Although we are expressing the same cardiac event (the systole), electrical and mechanical processes in the heart muscle are not two representations of the same pattern [48].

The effect of exercise resulted in two observations:

- The opening of the aortic valve occurs earlier than the S peak;
- The closure of the aortic valve occurs earlier than the T offset.

The fact that the S peak occurred after the aortic valve opening in the healthy participants whose acquisitions were done after the exercise could be related to the disappearance of the S wave in the ECG: Nouraei et al.([49]) reported that participants after exercising for approximately 3 minutes did not show the S wave. Maybe, the toolbox had higher difficulties in identifying the S wave leading to higher time intervals.

As we saw in fig. 3.14, the T offset appeared after the closure of the valve. This is a normal observation, because the aortic valve closure normally appear between the T peak and the T offset, as it is reported by Gil et al. ([20]).

The effect of the cardiovascular disease resulted in these two observations:

- The opening of the valve occurred after the S peak;
- The closure of the valve occurred before the T offset.

For this analysis we compared the time intervals of the cardiovascular diseased participants with the time intervals of the healthy participants on rest condition and no significant differences were found between those two. We conclude that no effect of the cardiovascular disease could be reported regarding the time intervals between the electric and mechanical systole events.

This analysis also leads us to believe that, in future visual perception analyses, we should remember that when we are using the electrical definition of the systole, we are probably including part of the onset of diastole. This is due to the fact that, as previously stated, aortic valve closure happens shortly before T offset.

We found that, in healthy participants under rest conditions, within-subject heart rate fluctuations were negatively correlated with the time interval between the S peak and the opening of the aortic valve (periods of faster heart rate are associated with earlier opening of the aortic valve). Surprisingly, this relationship was inverted in the between-subjects analyses where participants with on average faster heart rates showed later aortic valve opening. For participants with cardiovascular disease neither the within-subject nor the between-subjects analysis revealed significant correlations.

Regarding the aortic valve closure analysis, we found that, in healthy participants under rest and post-exercise conditions, there was a significant correlation, but not in cardiovascular diseased group. Within-subject heart rate fluctuations were positively correlated with the time interval between the T offset and the closure of the aortic

valve (periods of faster heart rate are associated with larger time intervals between the T offset and the closure of the aortic valve). In the between-subjects analysis, no relationship was found to be statistically significant.

4

Modulation of Heart Rate during the Attentive Anticipation and its Impact on Visual Perception

The perception of tactile stimulus is facilitated when the stimulus is presented during the diastole phase of the cardiac cycle in comparison to when the stimulus is presented during systole. [9]. In this part of the thesis, the main purpose is to study if visual perception is also modulated by the cardiac cycle..

We investigated the modulation of heart rate that occurs during the orienting of attention in preparation for the processing of sensory stimuli, how this cardiac modulation was associated with variations in visual perception, and how the different phases of the cardiac cycle (diastole and systole) might be associated with variations in visual perception.

4.1 Methods

4.1.1 Participants

We analysed a dataset that had been previously acquired as described in [50]. This dataset included data from 17 healthy participants (12 females and 5 males) with ages between 20-33 years. Several physiological signals were acquired simultaneously while the participants were engaged in a visual discrimination task:

- Electrocardiography (ECG) to study cardiac activity;
- Electrooculography (EOG) for blinking detection;
- Thoracic Circumference to measure respiration;

- Electromyography (EMG) to study muscular activity;
- Eye Tracking (ET) to study eye movements;
- Pupillography to measure modulation in arousal;
- Electrogastrography (EGG) to study stomach activity.

In the dataset from Subject S03, the 3rd and the 4th task presented unreadable ECG data because the EEG amplifier was turned off by mistake. Therefore, this subject, only had 2 runs available for the ECG analysis.

4.1.2 The Visual Discrimination Task

The visual discrimination task used is presented in fig. 4.1.

Each trial is composed by a baseline of 3-5 s before the presentation of an auditory cue. Then, after a random interval of between 2 and 6 s, the visual stimulus (which could be a car or a house) was presented very briefly for only 30 ms and was followed by a visual mask to render the image difficult to perceive. Participants were requested to report if the visual stimulus was a car or a house.

They responded it by pressing a button either with their left or right index fingers once the response prompt was presented on the screen, 510 ms after image presentation. The word related to the answer of the stimulus sometimes appeared on the left side and sometimes on the right side, to balance the answers on both fingers. If participants were not sure about the answer, they were told to guess it.

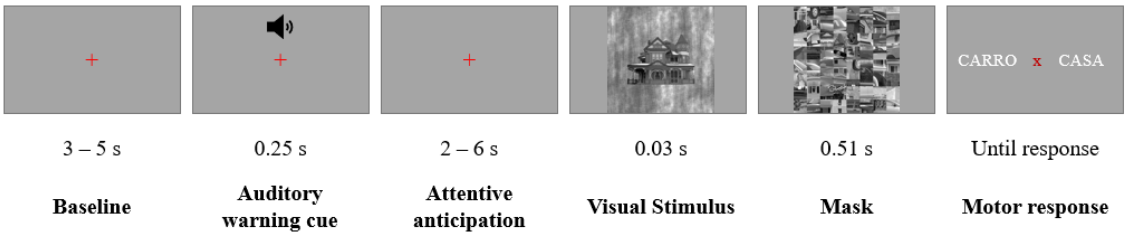

Figure 4.1: Schematic example of one trial presenting a house stimulus (the response prompt here is not to scale, the size was increased to facilitate visualization (adapted from [50]).

On this master's thesis, we only analysed the ECG data from each participant which included acquisitions of 4-5 runs of the task composed of 60 trials each. The

duration of each run was, approximately, 10 minutes (the individual trials had a maximum duration of 12 s).

4.1.3 Analysis of the ECG data

The ECG data was acquired with 2 bipolar channels (placed in the sternum according to the precordial lead V2) using the neuroscan EEG system, with a sampling rate of 500 Hz. Trigger pulses were generated at the onset of each stimulus and at every button press.

4.1.3.1 Preprocessing

To analyze the ECG data, we used Matlab (version R2021b) custom scripts, the EEGLAB toolbox [51] (version 2021.1) and the ECG toolbox from DEI.

Since the data were acquired using a sampling rate of 500Hz and the ECG toolbox was designed to work with ECG data with 250Hz, we downsampled the data from 500Hz to 250Hz.

In some runs from participants S02 and S06, there were some events missing. Luckily, events' timings were also saved in the eye tracker (ET) data, so, to solve these problems, we imported the event data from the eye tracker into Matlab.

As it is represented in fig. 4.2, the eye tracker and ECG started recording at different times. Also, in some ECG recordings the initial trigger was not recorded. In those cases, we not only had to align the data, but also check which event of the eye tracker corresponded to the first one of the ECG.

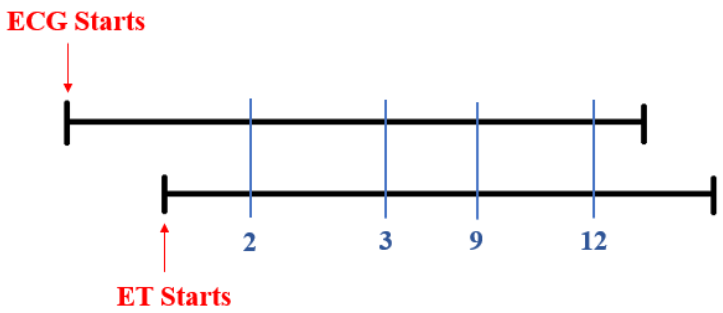

Figure 4.2: Scheme that represents the difference verified between the events of the eye tracker and the events from ECG.

The strategy here was to measure the difference between the first and the fourth event of each acquisition and compare the differences to see if the first event of each acquisition matched each other. We concluded that the first event of the ECG was related to the first one verified in eye tracker.

With all the problems solved, to align all the events we measured the difference between the first event of the eye tracker and the first event of the ECG and subtracted that difference to all the events presented in eye tracker to align them.

4.1.3.2 ECG Toolbox Troubleshooting

In order to calculate the participant's heart rate, we used the ECG toolbox, reported in section 3, to detect the R peaks. We also used custom Matlab scripts to solve some issues related to the incorrect definition of the peaks by the toolbox.

These issues were related to the fact that the ECG toolbox was designed to work with ECG data extracted using the precordial lead II. As reported in 4.1.3, the ECG acquisitions in this study followed the lead V2. We can see in section 2.2 that the shape of the ECG recordings is different for the different leads. This resulted in the ECG toolbox misidentifying some of the ECG waves.

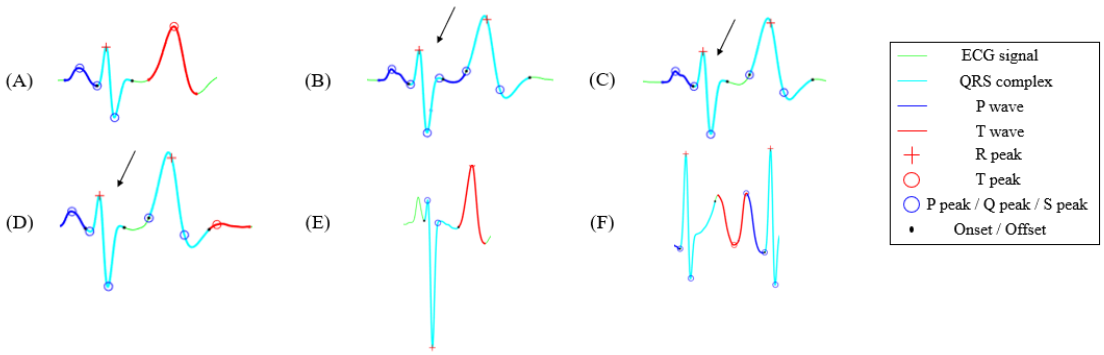

Figure 4.3: ECG toolbox output that shows ECG waves that were wrongly identified. The correct QRS complexes are pointed out with an arrow. **(A)** ECG cycle with all correct waves identified; **(B)** QRS complex detected in the place of a T wave with a P wave wrongly identified; **(C)** QRS complex detected in the place of a T wave, but no P wave nor T wave were identified; **(D)** QRS complex detected in the place of a T wave with a T wave wrongly identified; **(E)** One cycle that the P wave was not identified and the T wave had the highest positive amplitude; **(F)** T wave with T offset wrongly placed on the T peak.

As we can see in fig. 4.3, some T waves were identified incorrectly by the ECG toolbox (D, F) or were not identified (B and C). Because of its higher amplitudes, the toolbox mistook the T wave for an R peak. In these cases, we selected the real QRS complexes and eliminated the wrong ones. In other cases, the ECG toolbox identified all the waves correctly (A).

Since we will be dealing with T waves in the definition of systole / diastole, we needed to correct the cases that the ECG toolbox mistook the definition of the T peak. The strategies adopted to solve the problems were the following:

- **Fig. 4.3 (B) and (C):** we compared the QRS data array with the T wave array. If the lines of the T wave were loaded with zeros, we removed the line of the complex QRS array after the first line of zeros of the T wave array. This removed the second complex QRS that came incorrectly identified and preserved the first one (the ones marked with arrows). This method only works on cycles when the complex QRS came identified in the place of a T wave;
- **Fig. 4.3 (D):** we detected them when we saw zeros in the P wave array and the T wave had lower values than the wrong R peak identified in the wrong QRS complex. When that happened, we eliminated that QRS complex;
- **Fig. 4.3 (E):** contrarily to what we described above, we needed to preserve the data, because it is a normal ECG derivation from the V2 lead. So, when the P wave didn't came identified but T peak value was greater than the R peak, we preserved that cycle;
- **Fig. 4.3 (F):** we only changed the T peak value by the T onset value.

In the correctly identified QRS complexes, the R peaks were sometimes identified as the positive peak and other times as the negative peak. The R peaks of the correctly identified QRS complexes (red crosses on the complexes marked with an arrow in (B), (C), (D) in 4.3, and the red crosses of other letters) we can note that some of them came identified as the ones that had the most positive amplitude (A,B,C,D,F) and others came identified as the most negative (E). To find out which identification was the most correct, we confronted the normal ECG recordings from fig. 2.2 from section 2.2 and concluded, along with a cardiologist of Centro Hospitalar da Universidade de Coimbra (CHUC), that the negative peak was the one that should be identified as the R peak (the depolarization peak)

So, to correct all the cases that the ECG toolbox identified R peaks as the most

positive amplitude peaks, we compared all the values of the R peaks array and moved the wrong R peak position for the position of the negative peak.

As mentioned earlier, the ECG toolbox mistook, some QRS complexes and identified them in the place of some T waves (fig. 4.3), resulting in some zeros in the T wave vector. To further calculate the duration of systole and diastole, we needed to have T wave values identified in those zeros, otherwise the duration of these cardiac events were erroneously long.

To do that, we estimated the value of the T wave moments (T onset, T peak and T offset) based on the difference between the T wave moments and the R peak of the previous cardiac cycle (which T wave was identified).

After measuring those differences, we added them to the R peak time value of the cycle that not have the T wave identified by ECG toolbox and obtained the new T wave. We then did not use these cardiac cycles for the analysis.

4.1.3.3 Measuring the Heart Rate

After solving all the problems related to the QRS complex and to R peak itself, we measured the heartbeat by measuring the time interval between the R peaks of each cardiac cycle (Inter Beat Interval (IBI)) and converted it into beats per minute (BPM), using the equation shown in fig.4.4.

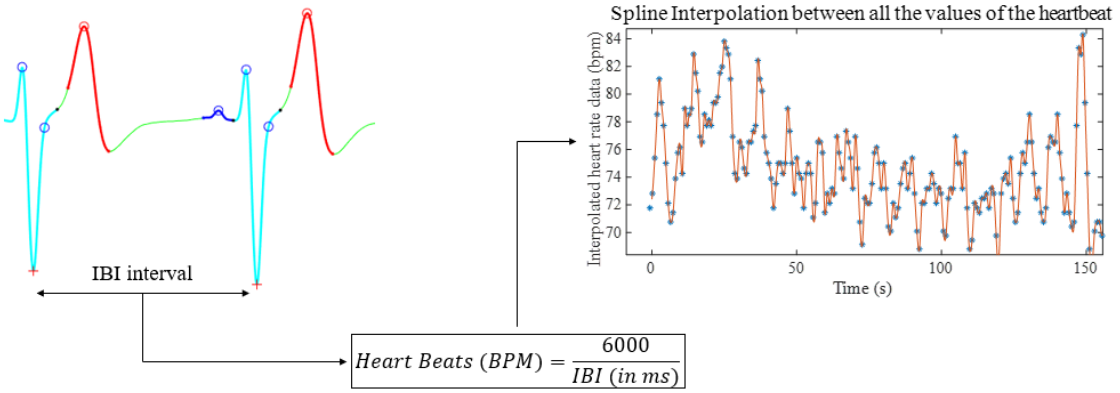

Figure 4.4: Scheme of the processes used to obtain the instantaneous heart beat data.

To exclude the ectopic beats, we calculated the z-score (using the Matlab function "zscore") and excluded the values with absolute z-scores higher than 5 (same

procedure as in [52]). It is important to note that we did not remove the trials where those ectobic beats were detected, we only eliminated the values of the heartbeat before the spline interpolation.

After that, we interpolated the values of the heart beat in beats per minute using the function "spline" of Matlab to estimate, at each time point, the instantaneous heart rate. This was necessary to align the instantaneous heart rate data with the task events - this way we have a heart rate value for each time point of the task trial.

4.1.4 Extracting Epochs Containing the Auditory Cue

To extract all the 60 epochs related to all 60 trials of the run, we first added all the events to a single variable and defined it, in EEGLAB, as the channel containing the information of the events. Then, we extracted the epochs starting 1 s before the auditory cue and ending 12 s after (we can see an epoch example in fig. 4.5)

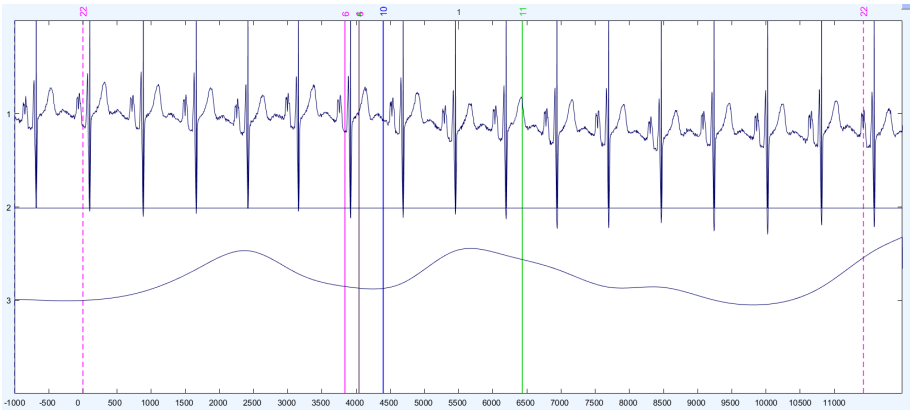

Figure 4.5: Example of one epoch locked to the auditory cue showing the ECG cycles and the heart rate fluctuations during the epoch. In the X axis we can see the time of the epoch in ms, which 0 is the auditory cue. In the Y axis we can see the data channels: channel 1 is the ECG data, channel 2 is the locations of all the R peaks, channel 3 is the linear interpolation of the heart rate in beats per minute (bpm).

Next, we separated the correct trials from the incorrect ones to study the effect of the auditory cue on the heart rate and its association with response accuracy.

To measure heart rate modulation evoked by the auditory cue, for each trial, we subtracted the heart rate values of the 12 seconds epochs by the average heart rate value measured in the 1 s immediately before the auditory cue.

4.1.5 Defining Systole and Diastole

To study what happens to the visual perception when the visual stimulus is applied during diastole or systole, it was necessary to define those cardiac events inside the ECG.

So, from section 3, we concluded that the best way to define systole from the ECG data was to define the beginning at S Peak and its end at T offset, as we can see in fig. 4.6.

We defined 2 extra events that mark the beginning and the end of the systole and added them into the variable containing all the events of the visual discrimination task to measure the duration of systole and diastole.

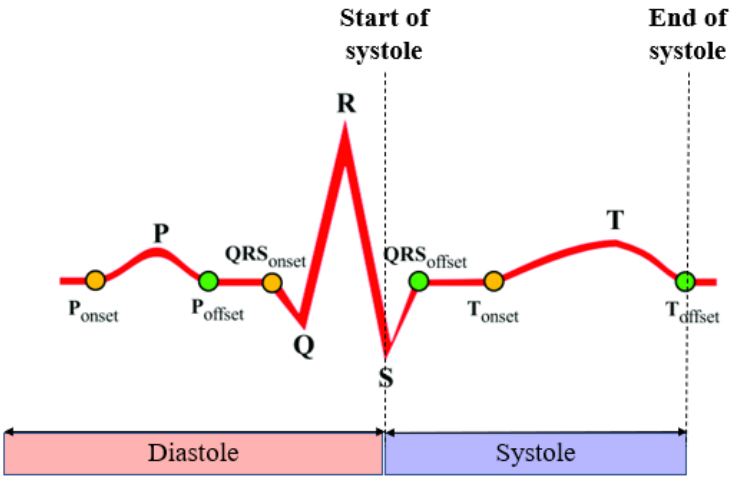

Figure 4.6: ECG cycle with the definition of systole and diastole used in this study. Systole starts at S peak and ends at T offset, and diastole starts at T offset and ends at S peak. We can see the positions of the events that mark the beginning and end of systole (figure adapted from [17] - fig. 7).

4.1.6 Measuring the Accuracy when the Visual Stimulus is Applied on Diastole and Systole

Once we had the systole and diastole identified in the events matrix, we extracted the epochs of the ECG signal locked to the auditory cue again but starting 1.5 s before the auditory cue and 11 s after (fig. 4.7).

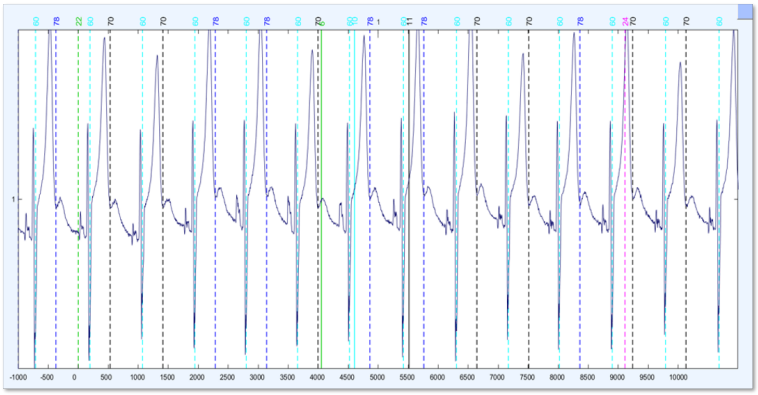

Figure 4.7: Example of one epoch locked to the auditory cue showing the ECG cycles during the epoch. In the X axis, we can see the time in ms, which 0 is the auditory cue. In the Y axis we can see the ECG data. In the events (number row on top of graph), we can see the: 70 event which symbolizes the end of the systole, 60 event which symbolizes the beggining of the systole and the 78 which symbolizes the T wave values that were predicted and should not be used in the analyses.

After the extraction of the epochs, the main goal was to see if the visual stimulus was presented inside the systole or the diastole. For that, we detected if the event related to the visual stimulus was among the events that mark the beginning and end of systole (visual stimulus applied during systole) or between the ones that mark the end and the beginning of diastole (visual stimulus applied during diastole).

Next, we evaluated the participant's accuracy when the visual stimulus was presented inside the systole or inside the diastole.

To measure the accuracy of the participant when the stimulus was applied during diastole, we quantified the amount of times that the stimulus was applied during the diastole and the number of times the participant got the correct answer and divided that number by the total of times that the visual stimulus was applied during diastole. We made that also to systole and to all trials of each individual.

4.1.7 Statistical Analysis

To study where the heart deceleration was significant in each individual heart rate variation plot (on section 4.2.1), we used a function in Matlab from David Groppe that uses the permutation method to measure the p values [53]. This function tests when the heart rate modulation during the trial is significantly different from zero (0 in fig. 4.9 plots) after controlling for multiple comparisons. This controlling was done using the "tmax" method to validate the significant time windows.

To compare the participants accuracy with the average heart rate change between 3-5 s (section 4.2.1), we used a function in Matlab from David Groppe that retrieves for each point a p value, corrected for multiple comparisons, that indicate if the cardiac modulation correlates with the performance in the visual discrimination test [54].

To compare the heart rate deceleration between correct and incorrect trials (section 4.2.2), we ran paired T-tests at every data point using the matlab "ttest" function. To control for multiple comparisons we also ran the "mult_comp_perm_t1" that corrects the p-values for multiple comparisons [53]. Since we selected a random number of correct trials, we ran those two tests 500 times when we compared the same number of correct trials to the same number of incorrect ones to obtain more consistent results.

We run a paired T-test to study if the accuracies of each participant when the visual stimulus was presented in diastole and the accuracies when the stimulus was presented in systole were significantly different (reported in section 4.2.4).

To study for each cardiac cycle after the auditory cue, if the duration of that cardiac cycle was significantly different from the duration of the cycle just before the auditory cue (section 4.2.5), we ran again the function that uses the permutation methods to measure the p values [53]. This function ran T-tests at each time point of the eight cardiac cycles after the auditory cue between the cardiac cycle duration and the duration of the cardiac cycle when the auditory cue was presented (1 in fig. 4.16) to determine the cardiac cycles where those 2 durations were significantly different from each other. The same analysis was done to the systole and diastole durations.

4.2 Results

4.2.1 Modulation of Heart Rate Evoked by the Auditory Cue

We found that the auditory cue evoked a cardiac deceleration followed by a cardiac acceleration (fig. 4.8). Here, we did an across participants' average plot to detect where the cardiac deceleration was consistent at the group level. We can see in fig. 4.8 that the maximum cardiac deceleration is located between 3s and 5s after cue onset. This observation suggests that when we pay attention to process and respond to a visual stimulus (in this case), our heart rate tends to decrease.

In fig. 4.9, we show the variation of the heart rate evoked by the auditory cue of each participant, i.e., the mean across trials. The thick black line in the graphs reports the time windows where the heart rate variation was significant ($p < 0.05$). It is apparent that the heart rate variation is mostly negative, i.e., we observe a cardiac deceleration shortly after the auditory cue.

To determine if the cardiac deceleration observed predicted task accuracy, we used a correlation analyses to test if the heart rate deceleration of each participant (average cardiac response between 3 and 5 s after the auditory cue) predicted the participant's task accuracy (fig. 4.10). The statistical analysis results showed that the correlation was not significant (r_{15} = -0.2231; p = 0.3893).

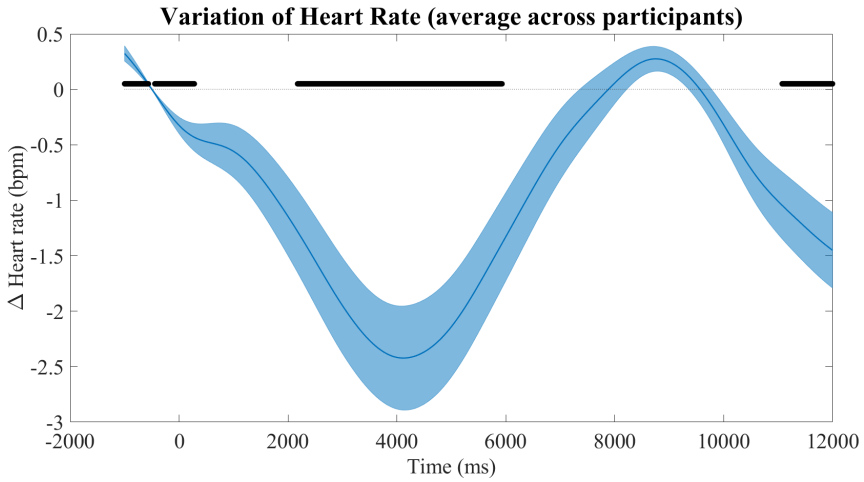

Figure 4.8: Across participants' average cardiac response locked to the auditory cue. The black line represents the significant time windows where the cardiac response is significantly different from zero ($p < 0.05$).

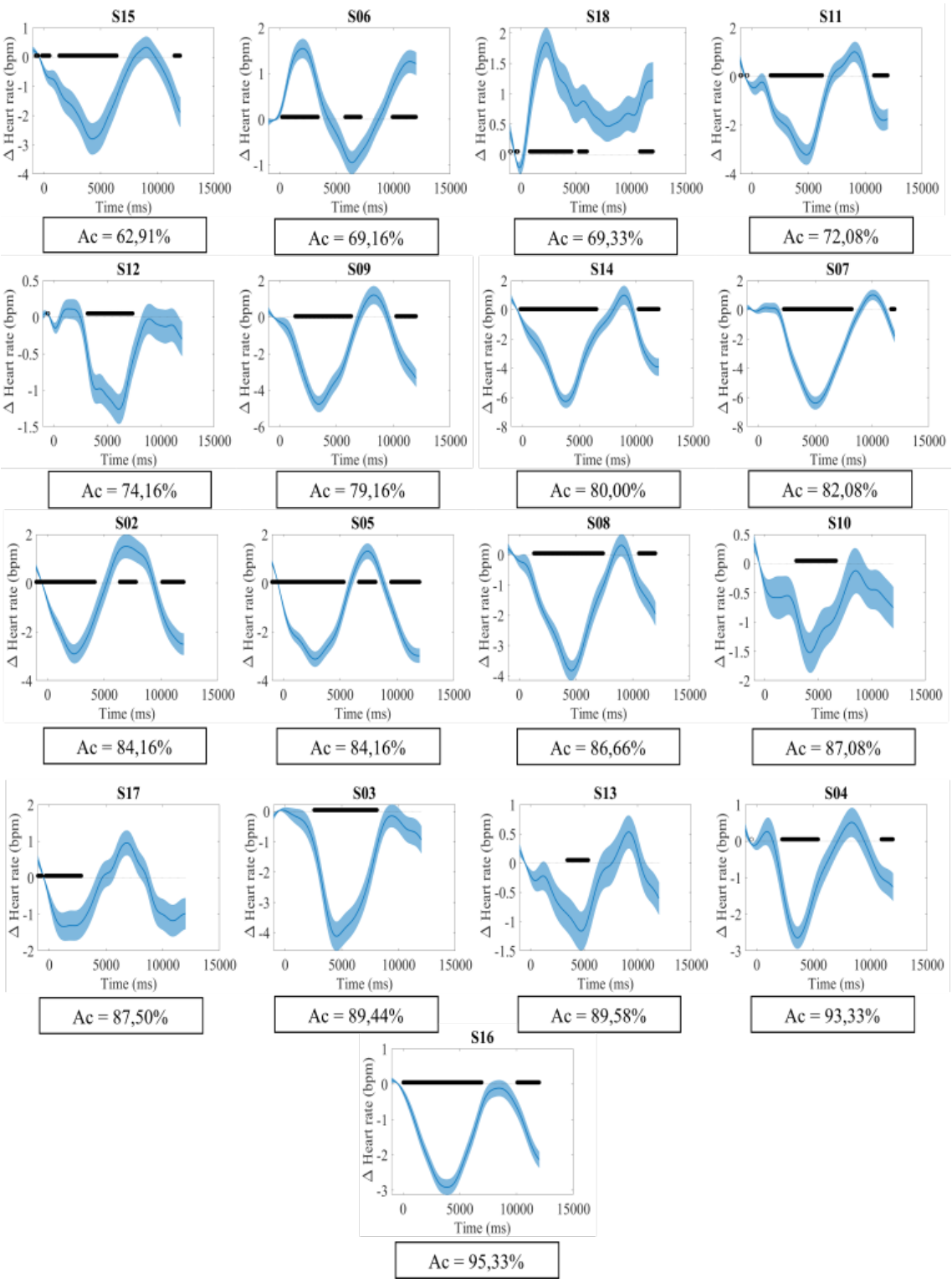

Figure 4.9: Inter-individual differences in cardiac deceleration. Here we have all cardiac responses of all participants sorted according to task accuracies (rising from left to right). The 0 in the x axis represents the presentation of the auditory cue. The black line represents the time widows where the cardiac response is significantly different from zero ($p < 0.05$) of the cardiac deceleration.

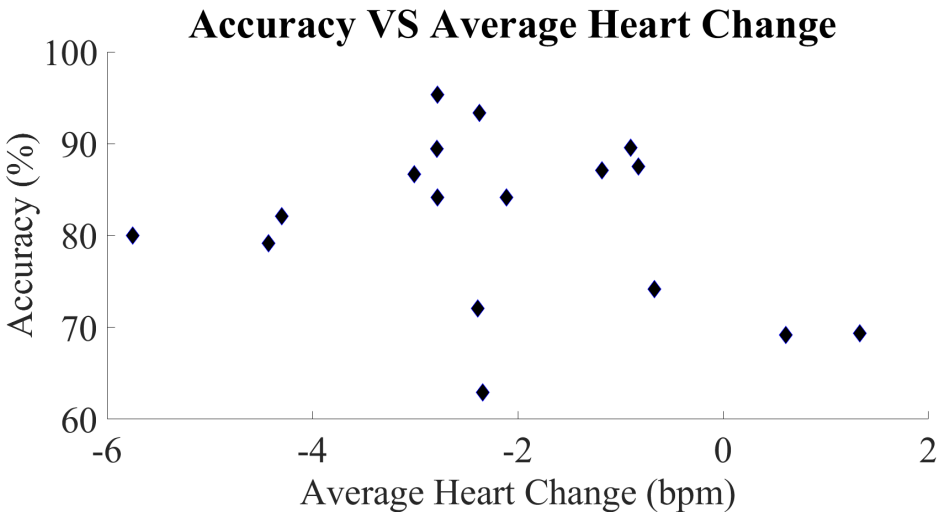

Figure 4.10: Individual accuracy values plotted against the average cardiac deceleration measured between 3 and 5 s after cue onset.

4.2.2 Differences in Cardiac Modulation between Correct and Incorrect Trials

In this analysis, we evaluated if the preparatory modulation in heart rate was different in trials where the participant correctly identified the image in comparison with trials where the participant responded incorrectly. To do that, as reported in section 4.1.4, we separated correct and incorrect trials (fig. 4.11).

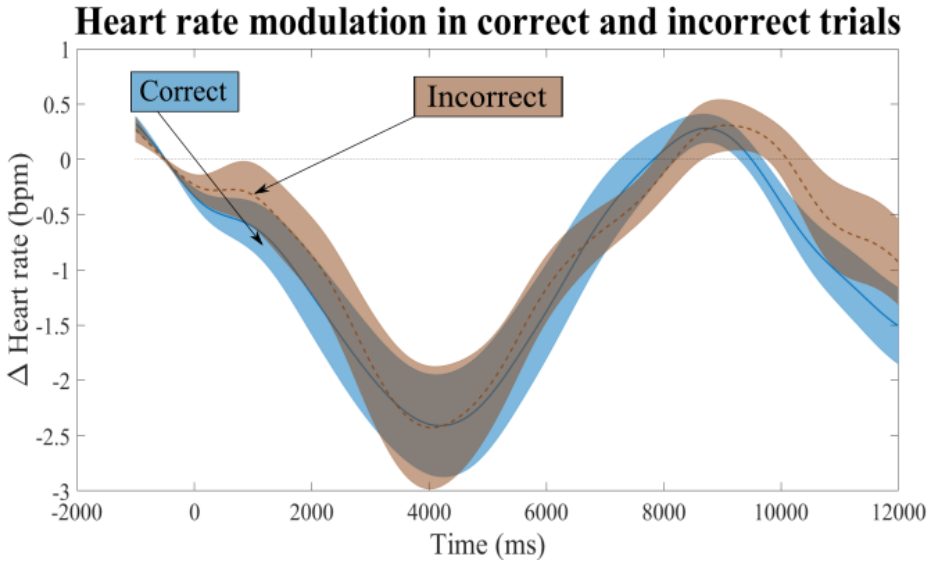

Figure 4.11: Variation of heart rate of all correct trials (blue curve) and all incorrect trials (brown curve).

Participants had more correct trials than incorrect (subject's average accuracy $= 81.5 \pm 9.23$ %), so, to correctly compare the two conditions, we randomly selected the same number of correct trials on each run as the incorrect trials.

Since we randomly selected the correct trials, we repeated the statistical analysis (T-test without correction for multiple comparisons (fig. 4.12) or the T-test with correction for multiple comparisons fig. 4.13)) 500 times.

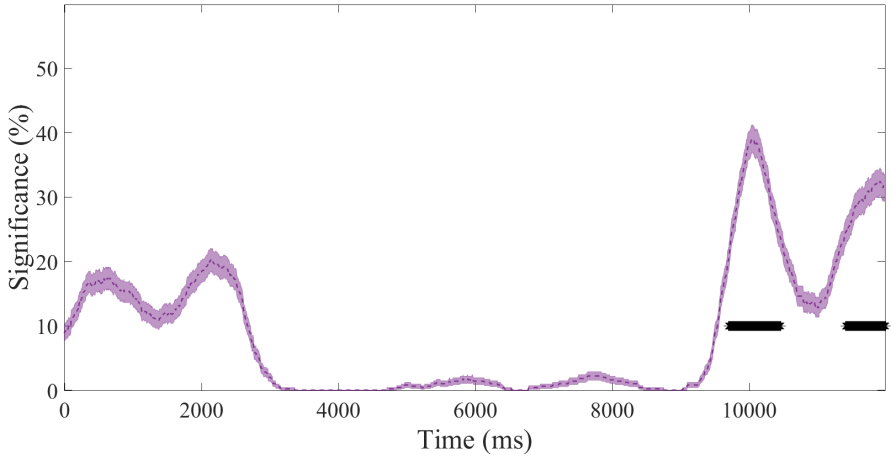

Figure 4.12: Percentage of times that the t-test comparing the cardiac responses in correct and incorrect trials was statistically significant at each time point after running 500 repetitions of the test. In the x-axis, zero is locked with the auditory cue.

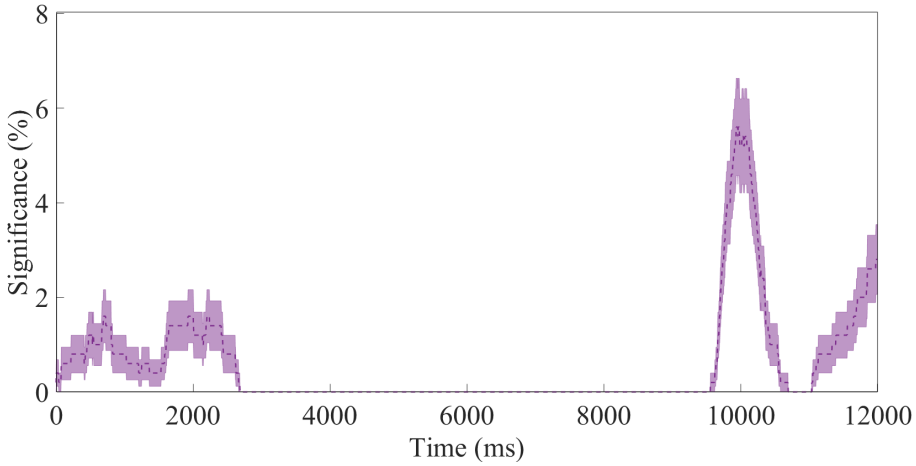

Figure 4.13: Percentage of times that the t-test comparing the cardiac responses in correct and incorrect trials was statistically significant at each time point after correction for multiple comparisons. In the x-axis, zero is locked with the auditory cue.

After running 500 times, we measured the percentage of times that the difference between correct and the incorrect trials was significant using the same number of correct trials to the incorrect ones (purple lines in figs. 4.12 and 4.13). We also ran the same statistical tests between all correct trials and incorrect trials and plotted the locations were the correct trials were significant different from the incorrect ones (black thick line in fig. 4.12).

When we performed the t-test analysis (fig. 4.12), when we compared all the trials (black thick line), we saw significant differences near the end of the trial.

When we compared the same number of correct trials to the incorrect ones, we saw significant differences in a small percentage of repetitions not only in the end of the trial but also in the immediately 2 s after the presentation of the auditory cue (purple lines in fig. 4.12). When we controlled for multiple comparisons (fig. 4.13) this percentage was even smaller. Also the significant differences between all correct and incorrect trials (thick black lines in fig. 4.12) disappeared (no thick black line in fig. 4.13).

4.2.3 Relationship between the Cue-Stimulus Interval and task accuracy

It is possible that the random time interval between the auditory cue and the visual stimulus (cue-stimulus interval) may influence the accuracy of the participants, i.e., the participant may not be prepared to visualize the stimulus.

To study that, we measured, for each subject, the average cue-stimulus interval in correct and incorrect trials and compared across conditions using a paired t-test. This statistical analysis revealed that there is no significant difference between the timing of the visual stimuli in correct and incorrect trials ($t_{16} = 1.6323$ $p = 0.1221$).

Below in fig. 4.14, the time intervals in the two conditions are not statistically different, but we can note that we have a higher dispersion in the times of the incorrect trials when compared it with correct ones.

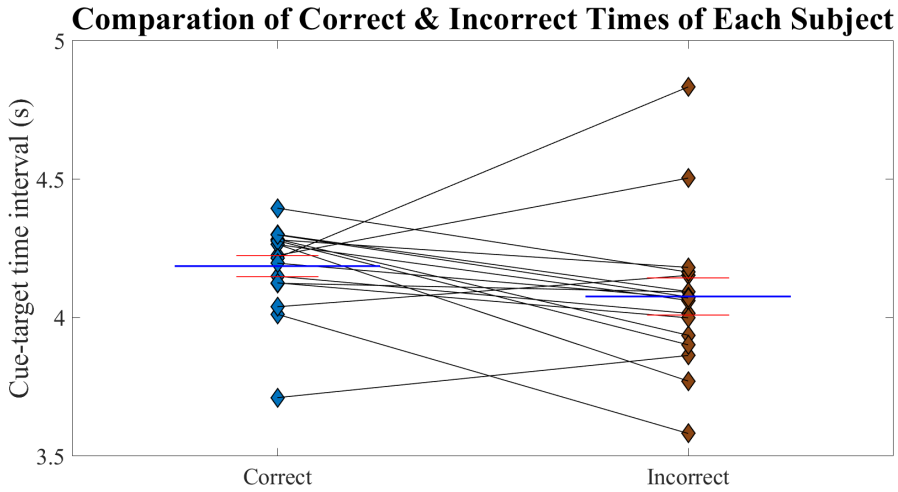

Figure 4.14: Relation between cue-stimulus time interval of correct trials (blue) and incorrect ones (brown). The blue line is the average time interval, and the red lines represent ± 1 standard error.

4.2.4 Relation between the Accuracy in Diastole and in Systole

In this analysis, we wanted to test the hypothesis that the presentation of the visual stimulus during diastole led to higher accuracies when compared to the presentation of the stimulus in systole, as it is shown in [9].

As it is reported in section 4.1.6, we measured the accuracy when the stimulus was presented in systole and when it was presented in diastole. After making the mean of each accuracy of each participant, participants got the correct answer when the stimulus was presented in systole is 81.72 ± 2.21% of the trials and 81.28 ± 2.33 % of the trials when it was presented in diastole. As fig. 4.15 shows and also the paired T-test ($t_{16} = 0.4048$; $p = 0.6913$), there is no significant difference between the accuracies of the participants when the stimulus was presented on systole and the accuracies when it was presented on diastole.

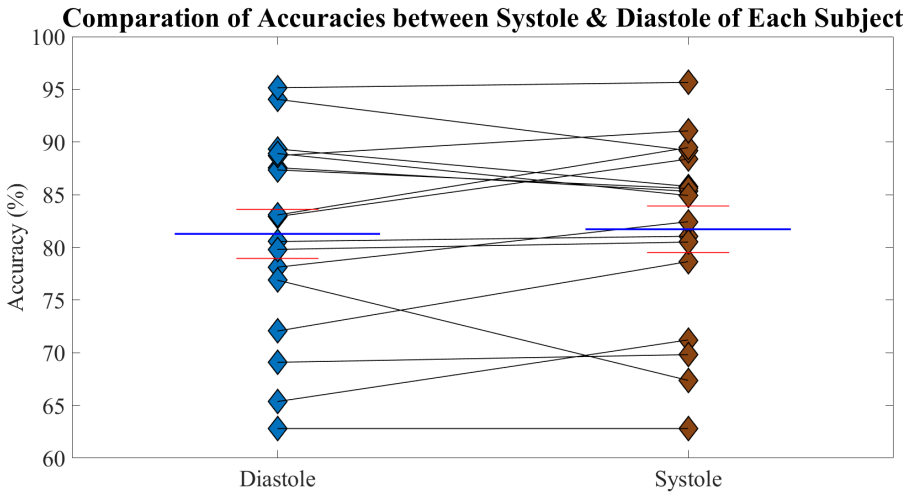

Figure 4.15: Comparison between the accuracies (%) when the visual stimulus is presented in systole (brown) and when it is presented in diastole (blue).

4.2.5 Changes in Systole and Diastole Duration Evoked by the Auditory Cue

In section 4.2.1, it is shown that the average across participants demonstrates a cardiac deceleration right after the auditory cue. This analysis is an alternative of what was seen on 4.2.1 only seen from the perspective of the cardiac cycle events.

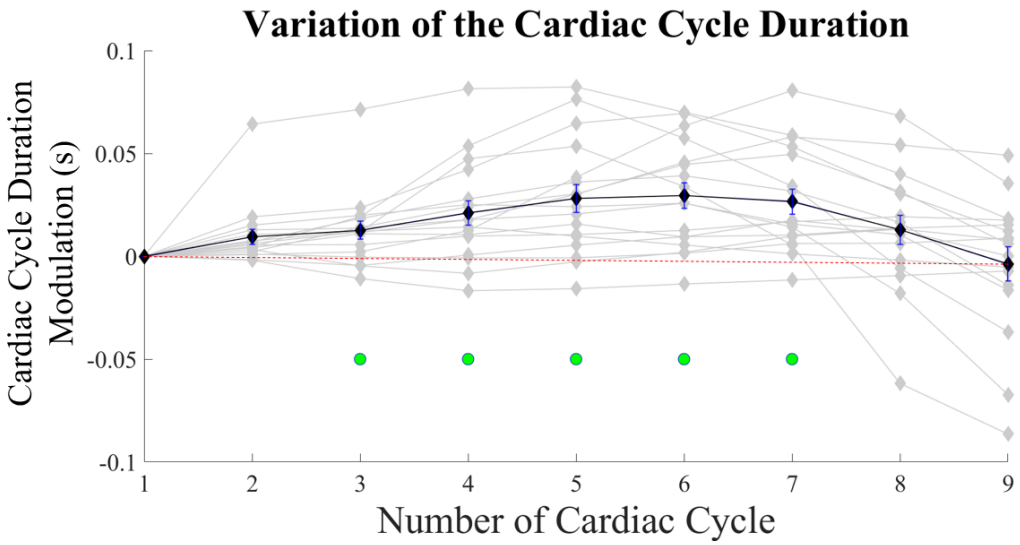

Figure 4.16: Variation of cardiac cycle duration in the 8 cycles after presentation of the auditory cue. The 1 on the x-axis represents the cardiac cycle that contains the auditory cue. The points in green are the cycles where this duration significantly differs from zero ($p < 0.05$).

As it is shown in fig. 4.16, we compared the cardiac cycle duration (time between the S peak and the T offset) in the 8 cardiac cycles after the auditory cue. It is important to note that our x = 1 is the cycle that the auditory cue is presented and we subtracted that duration from each of the eight cycle to study the variation.

We can see that we have an increasing cardiac cycle duration, which confirms that cardiac deceleration seen in section 4.2.1. Also the statistical analysis showed that the modulation in cardiac cycle's duration was significantly different from 0 between the 3rd cycle and the 7th one after the presentation of the auditory cue.

In this part of the analysis we wanted to study if the percentage of time that the heart spends in systole or diastole is modulated after the auditory cue.

We clearly see, in fig. 4.18, an increase in the percentage of the cardiac cycle dedicated to the diastole when compared to the percentage of the systole (fig. 4.17), which leads to a decrease in the percentage of the cardiac cycle dedicated to the systole. The statistical analysis reported in 4.1.7 also shows that the cue-evoked modulation in the percentages of systole and diastole were significantly different from 0 between the 3rd cycle and the 7th one after the presentation of the auditory cue.

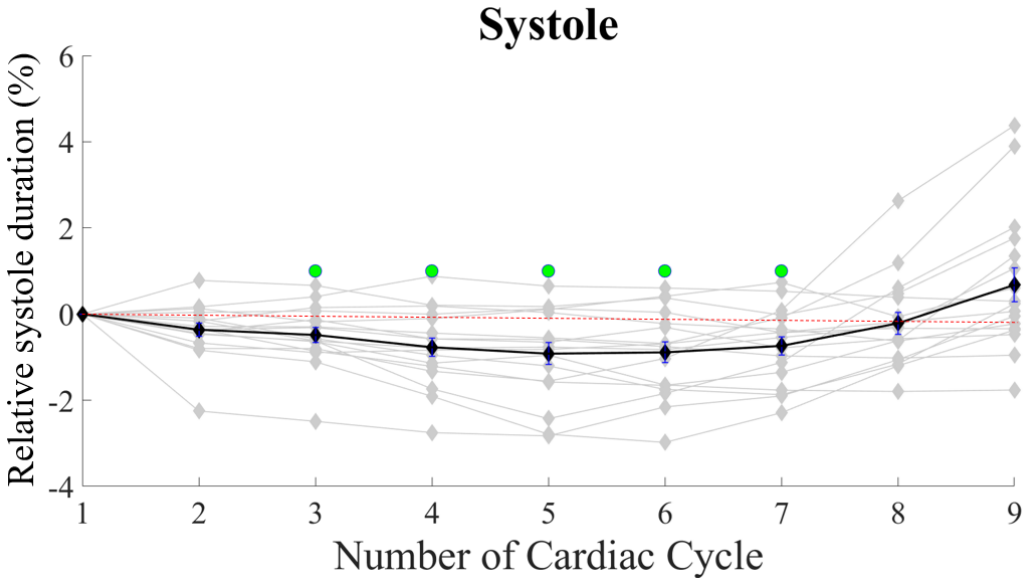

Figure 4.17: Variation of the percentage of systole duration in the cardiac cycle over 8 cycles after presentation of the auditory cue. The 1 on the x-axis is the cardiac cycle where the auditory cue was presented. The points in green are the cycles where the modulation of the duration of the systole was significantly different from zero ($p < 0.05$).

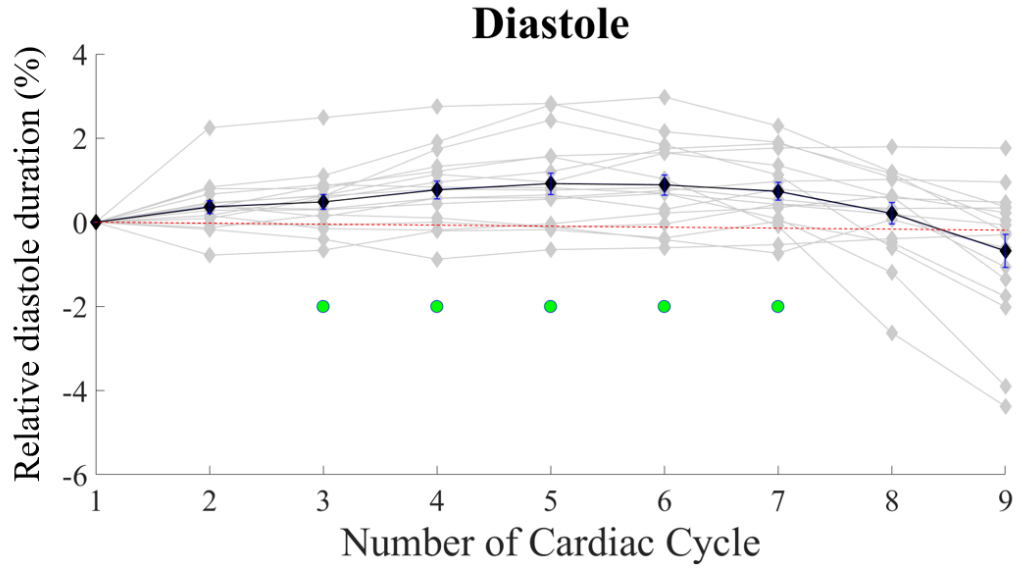

Figure 4.18: Variation of the percentage of diastole duration in the cardiac cycle over 8 cycles after presentation of the auditory cue. The 1 on the x-axis is the cardiac cycle where the auditory cue was presented. The points in green are the cycles where the modulation of the duration of the diastole was significantly different from zero ($p < 0.05$).

4.3 Discussion

In this chapter, we studied the influence of the cardiac cycle on visual perception. We investigated the modulation of heart rate during a visual discrimination task. We also studied the accuracy of participants in that visual discrimination task as a function of heart rate modulation and when the stimulus was presented during systole and when it was presented during diastole.

When we plotted the heart rate variation across the visual task, we noted a cardiac deceleration right after the auditory cue (presented on x = 0 in across participants' average plot fig. 4.8). This deceleration is related to an attentive preparatory state that is triggered by the auditory cue, as it is reported in [32, 33], but when we plotted the heart rate variation in each participant, in 23.50 % of participants we observed an acceleration right after the auditory cue followed by a long period of deceleration. In accordance to Graham et al.([8]), this could be a "defense" mechanism to the auditory cue or even a heart rate response to acoustic stimuli.

Surprisingly our results suggested that there is no correlation between heart rate deceleration during the preparatory period and visual discrimination task accuracy.

Accordingly, with the lack of correlation between heart rate deceleration and task accuracy, we could not see a clear difference between the heart rate variance in correct trials when compared to the incorrect trials. When we compared correct and incorrect trials by randomly selecting the same number of correct and incorrect trials and repeated this selection 500 times, there were a small number of tests where we could observe significant differences shortly after the auditory cue, suggesting that maybe with a larger dataset, differences between correct and incorrect trials might become evident.

We also conclude that the random time interval between the auditory cue and the visual stimuli does not influence in the accuracy of subjects (fig. 4.14) which means that the preparation time does not influence the performance of the participant.

In our study, when we compared the different phases of the cardiac cycle in the accuracy of the visual task, we hypothesized that, as had previously been observed for somatosensory stimuli [9], also visual perception might be modulated by cardiac phase. However, we concluded that when the stimulus was presented in diastole, the accuracy was similar to the one verified when the stimulus was presented in systole.

With this observation we can hypothesize two justifications:

- The effect of the cardiac cycle only happens to somatosensory stimuli and not for visual stimuli;
- The usage of the backward masking was not the best model to investigate the heart rate modulation (maybe does not reach the threshold needed to observe an effect).

As Kunzendorf et al. ([43]) mention, the percentage of diastole in the cardiac cycle increases with the cardiac deceleration, so we investigated the variation of the duration of the cardiac cycle and the percentage of systole and diastole in the cardiac cycle along the visual discrimination task. We saw that the duration of the cardiac cycle increases after the presentation of the auditory cue, which is an effect of the heart deceleration shown on fig. 4.8. When we studied the percentage of each cardiac phase, the effect reported in [43] was visualized, i.e., we saw an increase in the percentage of the diastole and a decrease in the percentage of the systole in the cardiac cycle duration.

5

Conclusion

5.1 General Conclusions

In this master's thesis, we proposed to investigate how the cardiac cycle modulates visual perception. Since we needed to define the cardiac cycle we showed that systole can be defined with precision, using the ECG. To verify the precision we compared electrical systole events from the ECG with the mechanical systole aortic valve events given by the echocardiography. We concluded that the electrical event which is approximately related to the aortic valve opening (beginning of systole) was the S peak and the one that fits with the closure of the valve (ending of the systole) was the T offset.

We also measured the effect of the exercise and the effect of cardiovascular disease on those time differences and we saw that the exercise increased the time difference between the ECG events and the aortic valve events. This suggested that estimating systole in participants after exercise is not as accurate as it was to participants in rest. Also systole can be estimated basically in participants with cardiovascular disease as the same way as it was in rest individuals, since we saw no significant differences between the time differences between the electrical heart events and mechanical aortic valve events. We also concluded that the electrical systole duration was higher than the mechanical one suggesting that we might be considering the onset of diastole when we use the electrical systole definition.

We also investigated if the heart rate was associated with the time interval measured between the electrical systole and mechanical in healthy (rest and post-exercise acquisitions) and in participants with cardiovascular disease. We concluded that for the within-participant analysis, we could relate the heart beat with the time interval in healthy participants (rest and post-exercise acquisitions) in the analysis

related to the offset of systole and in healthy participants (rest acquisition) in the analysis related to the onset of systole. For the opening of the valve (onset of systole), we concluded that periods of higher heart rate were related to earlier opening of the aortic valve and to the closing of the valve (offset of systole) higher heart rates resulted in larger time intervals between the T offset and the closure of the valve. We also made a between-participants analysis, but we found that some changes of the analysis in each participants were inverted and other were not even preserved. Actually we were comparing different things. For example in within-subject rest healthy analysis we were studying the heart beat fluctuations at rest inside the subject, whereas to between-subjects analysis we were comparing, in average, these fluctuations along each subject, in average.

Next, we studied, on a different dataset, the modulation of the heart response to a visual discrimination task. We concluded that an auditory cue evoked a state of attention in preparation for the response to the visual stimulus. This state of attention evoked a cardiac deceleration and this deceleration did not affect the participants accuracies. After that, we studied if the cue-target time interval had influence in the accuracy of the participants, which resulted in a non-influence.

Next, we used the systole definition resulted from the first study to investigate the accuracy of participants when the stimulus was applied in systole and the accuracy of participants when the stimulus was applied in diastole. To our surprise, we concluded that the difference between the accuracy when the stimulus was presented in diastole and the accuracy when it was present in systole was not significant. Perhaps the facilitation of perception in diastole only happens for somatosensory stimuli [9] and not for visual stimuli: maybe the heart only affects the tactile response and not the visual response.

Also, we studied the percentage of time that participants stayed on diastole and systole during the visual discrimination task. We concluded that, during the visual task, the percentage of diastole in the cardiac cycle increased after the presentation of the auditory cue. Also, we saw that the duration of the cardiac cycle increased right after the auditory cue, proving the heart deceleration previously reported.

After all those analysis, we can conclude that there was not a relation between the performance and the cardiac phase. Maybe the discrimination task was not the better one to study the effect of the heart phase in the visual perception, or perhaps the heart response only affects somatosensory perception.

5.2 Future Perspectives

As mentioned before, this conclusions could be more clear if we had more data. The main future milestone is to acquire more data to further substantiate our conclusions and publish a scientific report regarding this study. Also, we can prepare other visual discrimination tasks to test whether the problem of not verifying a relationship between cardiac phase and participants' accuracy was related to the task used in this dissertation.

Another possible milestone in future studies is to investigate the modulation of the heart rate on mental problems, for example anxiety. Some studies point to the fact that we can modulate fear for example thought heart rate. This fact is very promising because it can lead to future therapies regarding anxiety (a mental condition related to fear), for example [55–57].

A

All Participants Plots

A.1 All Healthy Participants Time Differences Distribution

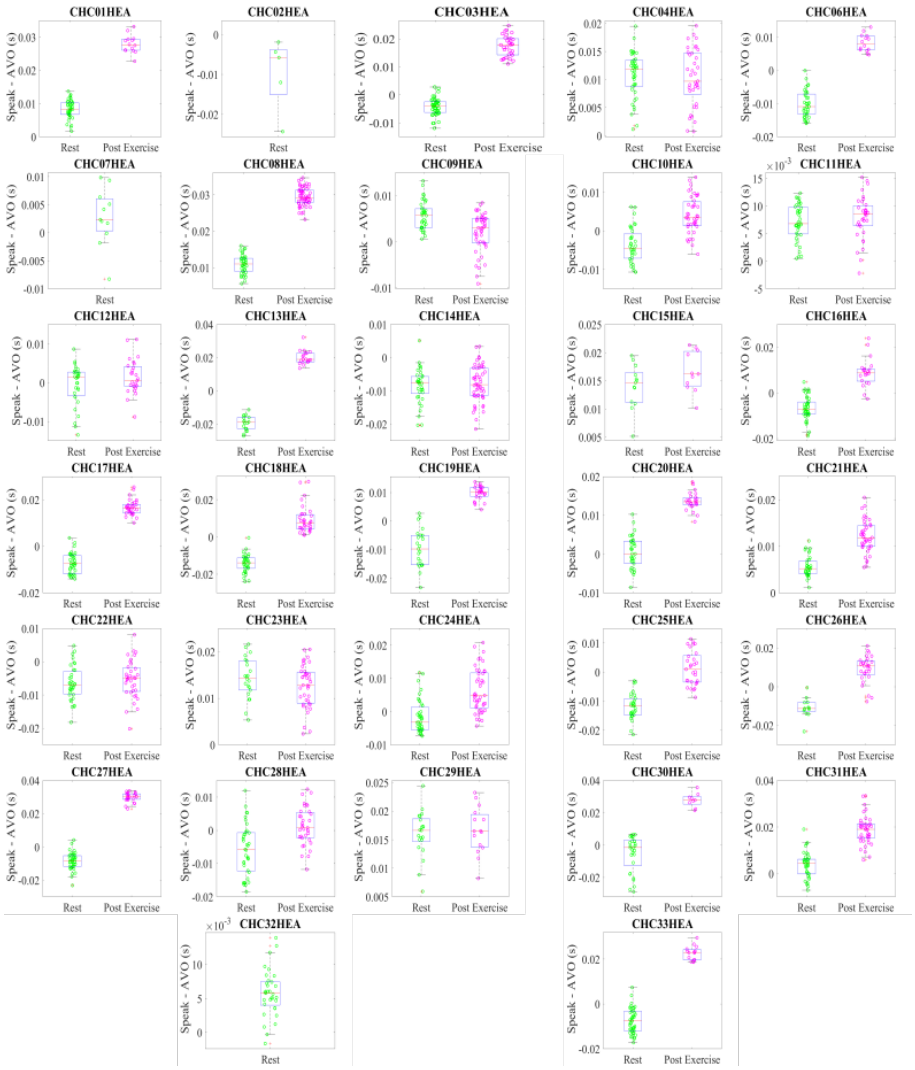

Figure A.1: Box-plots that show the distribution of the difference between the S peak and the Aortic Valve Opening (AVO) of all healthy participants. In green is the resting state and in magenta is the post exercise state.

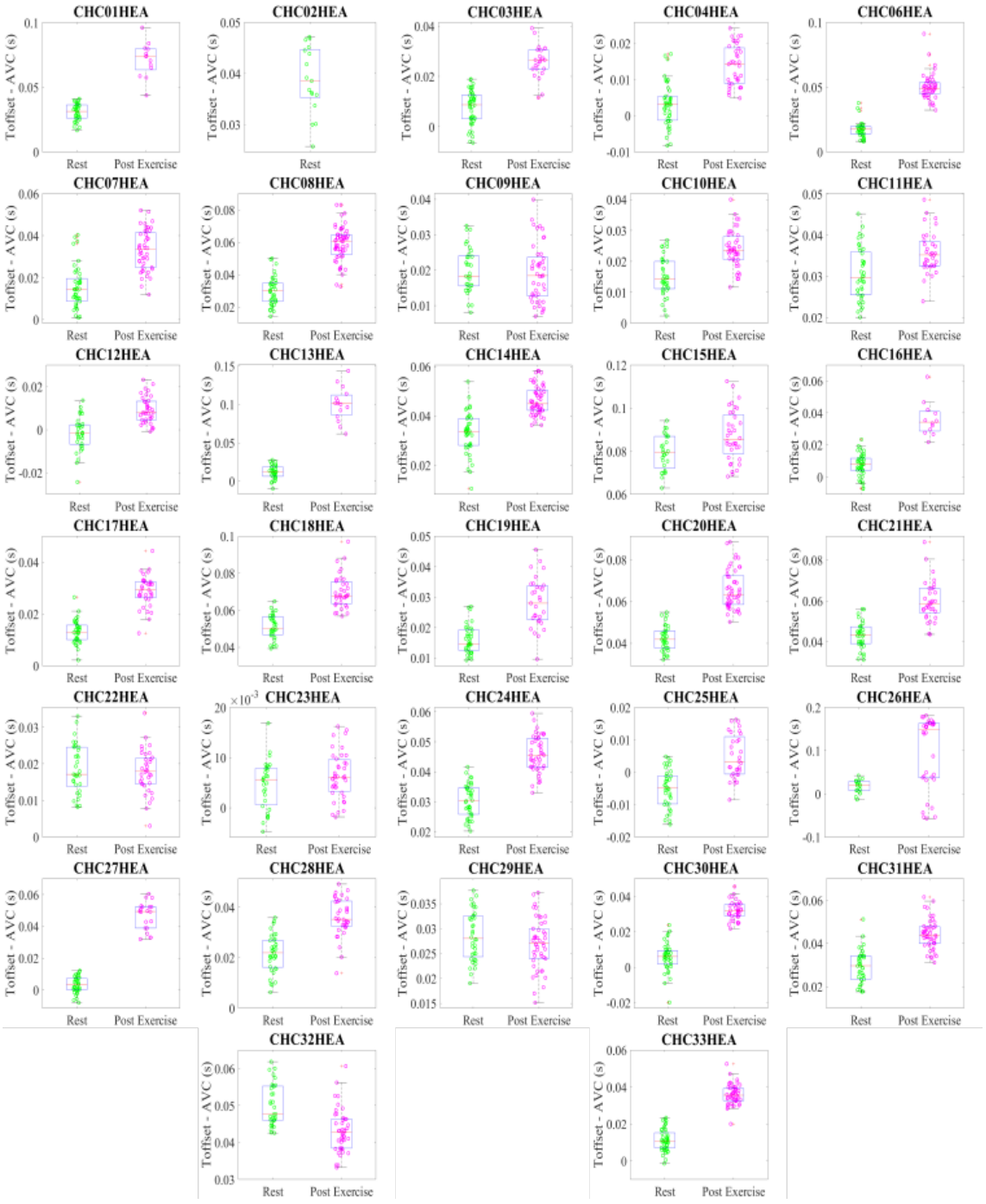

Figure A.2: Box-plots that show the distribution of the difference between the T offset and the Aortic Valve Closure (AVC) of all healthy participants. In green is the resting state and in magenta is the post exercise state.

A.2 All Participants with Cardiovascular Disease Participants Time Differences Distribution

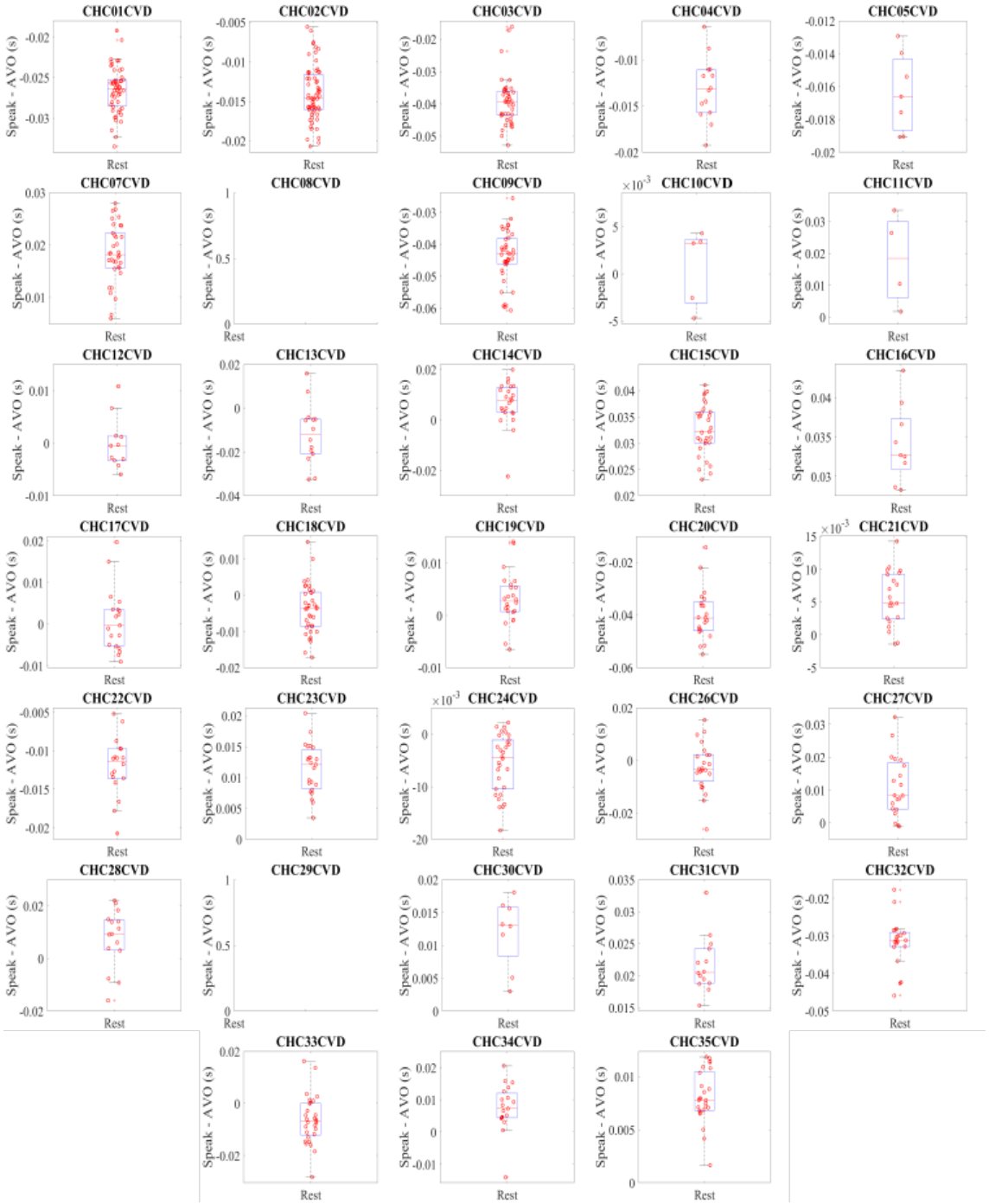

Figure A.3: Box-plots that show the distribution of the difference between the S peak and the Aortic Valve Opening (AVO) of all cardiovascular diseased participants.

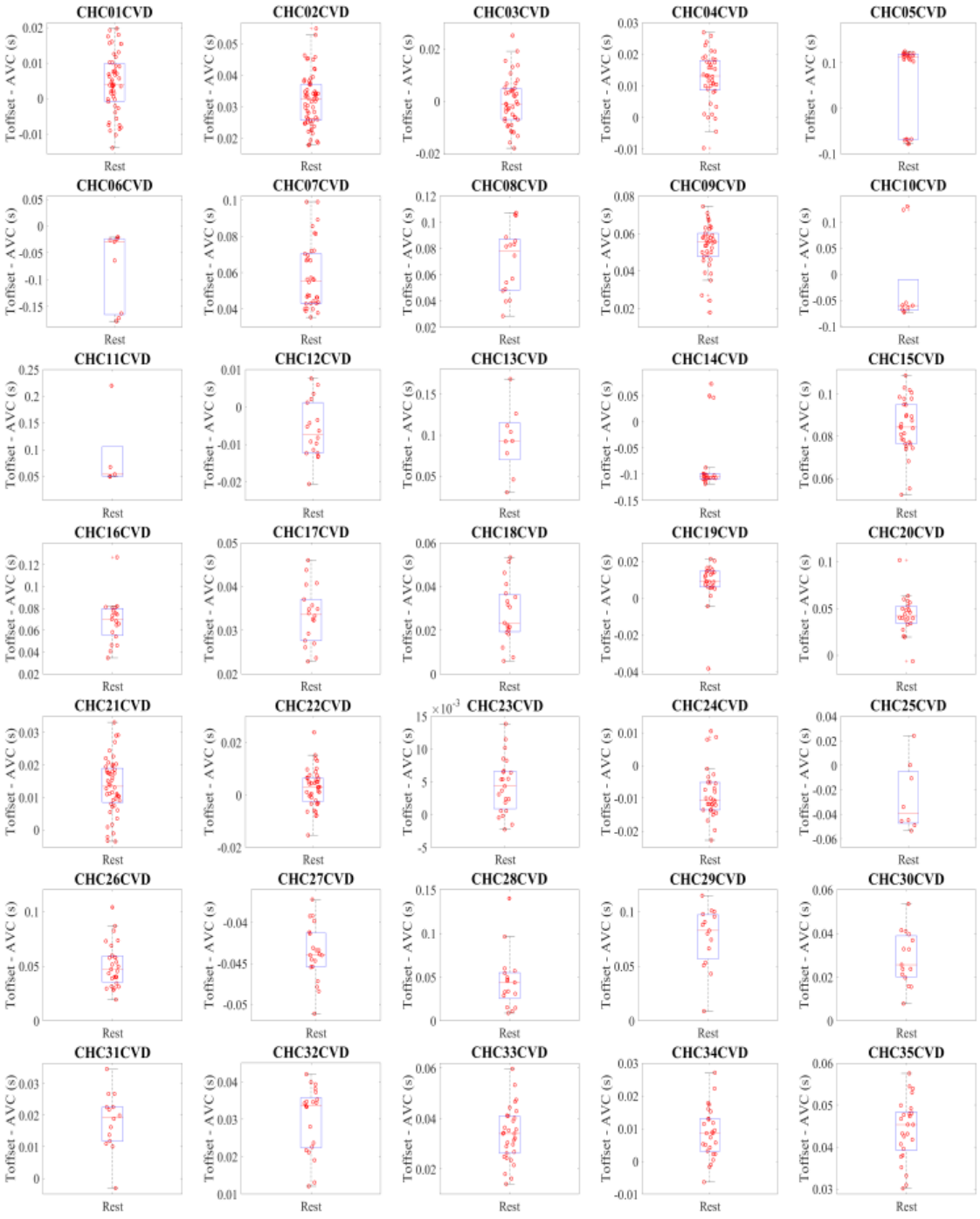

Figure A.4: Box-plots that show the distribution of the difference between the T offset and the Aortic Valve Closure (AVC) of all participants with cardiovascular disease.

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