Third-year Research Internship

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Arterial flow in the brain

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Summary

This internship is part of a study carried out by Sheila M. Byrd (National Lung and Heart Institute, Imperial College) looking at the influence of cardiac illnesses requiring valve surgery (especially regurgitation) on the arterial flows in the brain. Transcranial doppler (TCD) ultrasounds were used to measure intracranial blood velocities (a non-invasive technique), and data were exploited with MATLAB.

This internship aimed at finalizing the MATLAB program that will be used during the whole study and at setting up the protocol of the clinical part of the study, using measurements carried out on eight healthy patients. These measurements were used to build a program able to analyze a wide range of cerebral flows as well as to decide which parameters should be studied more closely on impaired patients. On two healthy patients, further measurements were carried out in order to build a model of the flow in the middle cerebral artery (MCA).

Ce stage s'inscrit dans le cadre d'une étude conduite par Sheila Byrd (National Lung and Heart Institute, Imperial College, London) étudiant l'influence des dysfonctionnements des valves cardiaques sur la circulation artérielle dans le cerveau, en particulier dans le cas de valves induisant un phénomène de régurgitation. Cette étude se base sur la mesure de la vitesse du sang dans les artères cérébrales par Doppler Trans-Crânien (TCD) et l'exploitation de ces mesures avec MATLAB.

Le but de ce projet est de finaliser le programme MATLAB qui sera utilisé pendant l'étude ainsi que le protocole des test cliniques, en se basant sur les mesures réalisées sur huit patients sains. Ces mesures sont utilisées comme construire un programme analysant une large gamme de profils de vitesse, ainsi que pour tirer les caractéristiques principales de l'écoulement, caractéristiques qui seront particulièrement étudiées chez les patients malades. Des mesures complémentaires ont été réalisées sur deux patients sains afin de construire un modèle de l'artère cérébrale moyenne (MCA).

Special thanks

I would like to thank Professor Kim H. Parker, who has followed my project and introduced me with this very interesting domain of study.

I would also like to thank Sheila Byrd, sonographer at Saint Mary's Hospital, whose study formed the basis of my intership. She has helped me acquire raw data for this project and provided me with all the medical and physiological information I needed. I wish her good luck for her Ph.D.

Contents

Introduction

This intership took place in the Physiological Flow Studies Group, Department of Bioengineering, Imperial College and at St Mary's Hospital, in the National Heart and Lung Institute, Imperial College.

Aim of the study

The aim of the whole study is to look to what extend illnesses requiring valve surgery (especially regurgitation problems) affect the arterial flows in the brain. It appears that the decision to operate on a sick patient is essentially based on a thorough analyze of the state of the heart and of the flow coming out of the heart, without taking into consideration the fact that the cerebral circulation could be seriously affected long before this moment.

This study aims at finding criteria based on TCD measurements to decide when it is time to operate. My internship represents the beginning of Sheila Byrd's study.

The three steps of the project

This paper contains three main parts.

First, we present elements of anatomy and physiology required to understand the study.

Second, we present the clinical protocol, the measurements, and the results obtained.

Third, we present a model of the middle cerebral artery (MCA) based on further measurements based on two healthy patients.

1 Elements of anatomy and physiology

This chapter is based primarily upon material from [3].

1.1 The anatomy of blood vessels

The peripheral circulatory system can be divided into the systemic and the pulmonary vessels ; this circulatory system and the heart are regulated to maintain sufficient blood flow to tissues. The functions of the peripheral circulation is to carry blood, exchange nutrients and gases, transport hormones, regulate blood pressure, and direct blood flow.

We can underline three main features of blood vessel structure : (1) Blood is pumped from the heart through elastic arteries, muscular arteries, and arterioles to the capillaries ; (2) Blood returns to the heart from the capillaries through venules, small veins, and large veins ; (3) Except for capillaries and venules, blood vessels have three layers : the tunica intima (endothelium, basement membrane, and connective tissue), the tunica media (smooth muscle and elastic fibers), and the outer tunica adventitia (connective tissue).

Arteries and veins supplying the same region typically lie side by side ; however, arteries and veins may be distinguished by the following characteristics :

Arteries : Large elastic arteries have many elastic fibers but little smooth muscle in their walls and carry blood from the heart to smaller arteries with little decrease in pressure : their expansion/contraction cushions the sudden rise/decrease in pressure during the cardiac cycle ; by the time blood reaches the arterioles, the pressure oscillations have almost completely disappeared.
Muscular arteries have much smooth muscle and some elastic fibers.
Arterioles are the smallest arteries and have smooth muscle cells and a few elastic fibers and undergo vasodilation and vasoconstriction to control blood flow to local areas : they are called resistance vessels

Capillaries : Capillaries consist of only endothelium and are surrounded by a basement membrane and loose connective tissue.
Fenestrated capillaries contain pores that span the endothelial lining, while continuous capillaries have a complete lining.
Nutrient and waste product exchange is the principal function of capillaries.
Blood is supplied to capillaries by arterioles. Precapillary sphincters

regulate blood flow through capillary networks.

Veins : Venules are endothelium surrounded by a basement membrane.
Small veins are venules covered with a layer of smooth muscle.
Medium-sized and large veins contain less smooth muscle and elastic fibers than arteries of the same size.
Venous valves prevent the backflow of blood in the veins, since blood pressure along a peripheral venule is only about 10% of that in ascending aorta, it is so low in medium-sized veins that it cannot oppose the force of gravity

1.2 The Heart

The heart functions are mainly generating blood pressure, routing blood through the systemic and pulmonary circulation, ensuring, thanks to its pumping action and the valves, a one-way flow of blood through the heart and blood vessels, and helping regulate blood supply to tissues.

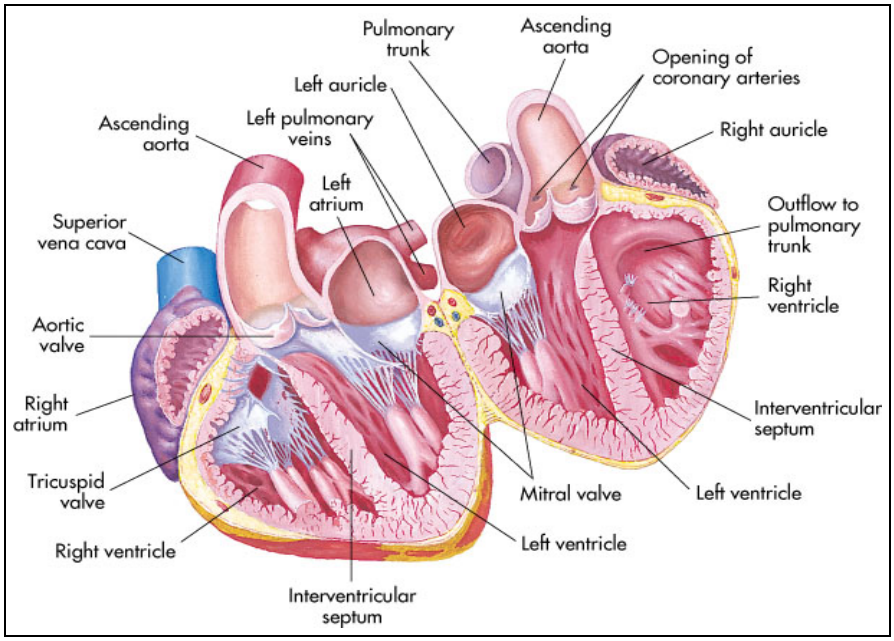

Figure 1: The heart

1.2.1 Anatomy of the Heart

There are four chambers in the heart. The left and right atria receive blood from veins, function mainly as reservoirs while contraction of the atria

completes ventricular filling.The ventricles are the main pumping chambers of the heart : the right ventricle pumps blood into the pulmonary trunk and the left ventricle, which has a thicker wall, pumps blood into the aorta.

The inferior and superior venae cavae enter the right atrium while the four pulmonary veins enter the left atrium ; the pulmonary trunk exits the right ventricle, and the aorta exits the left ventricle.

The heart valves ensure one-way flow of blood. The tricuspid valve (three cusps) separates the right atrium and right ventricle, and the bicuspid valve (two cusps) separates the left atrium and left ventricle. The aorta and pulmonary trunk are separated from the ventricles by the semilunar valves. The skeleton of the heart is a plate of fibrous connective tissue that separates the atria from the ventricles, acts as an electrical barrier between the atria and ventricles, and supports the valves of the heart.

1.2.2 Route of blood flow through the heart

The left and right sides of the heart can be considered as separate pumps ; blood flows from the systemic vessels to the right atrium and from the right atrium to the right ventricle. From the right ventricle blood flows to the pulmonary trunk and from the pulmonary trunk to the lungs. From the lungs blood flows through the pulmonary veins to the left atrium, and from the left atrium blood flows to the left ventricle. From the left ventricle blood flows into the aorta and then through the systemic vessels.

1.2.3 Cardiac Cycle

Atrial systole is contraction of the atria, and ventricular systole is contraction of the ventricles. Atrial diastole is relaxation of the atria, and ventricular diastole is relaxation of the ventricles. During atrial systole, filling of the right ventricle is completed. During ventricular systole, the tricuspid valve closes, and blood forces open the pulmonary semilunar valve ; blood flows into the pulmonary trunk. Also, the bicuspid valve closes, and blood forces open the aortic valve ; blood flows into the aorta.

1.2.4 Electrical activity of the Heart

Action potentials in the cardiac muscle are different from other action potentials : they are prolonged compared with those in skeletal muscle and have a depolarization phase, a plateau phase, and a repolarization phase. The depolarization is due mainly to opening of the voltage-gated sodium

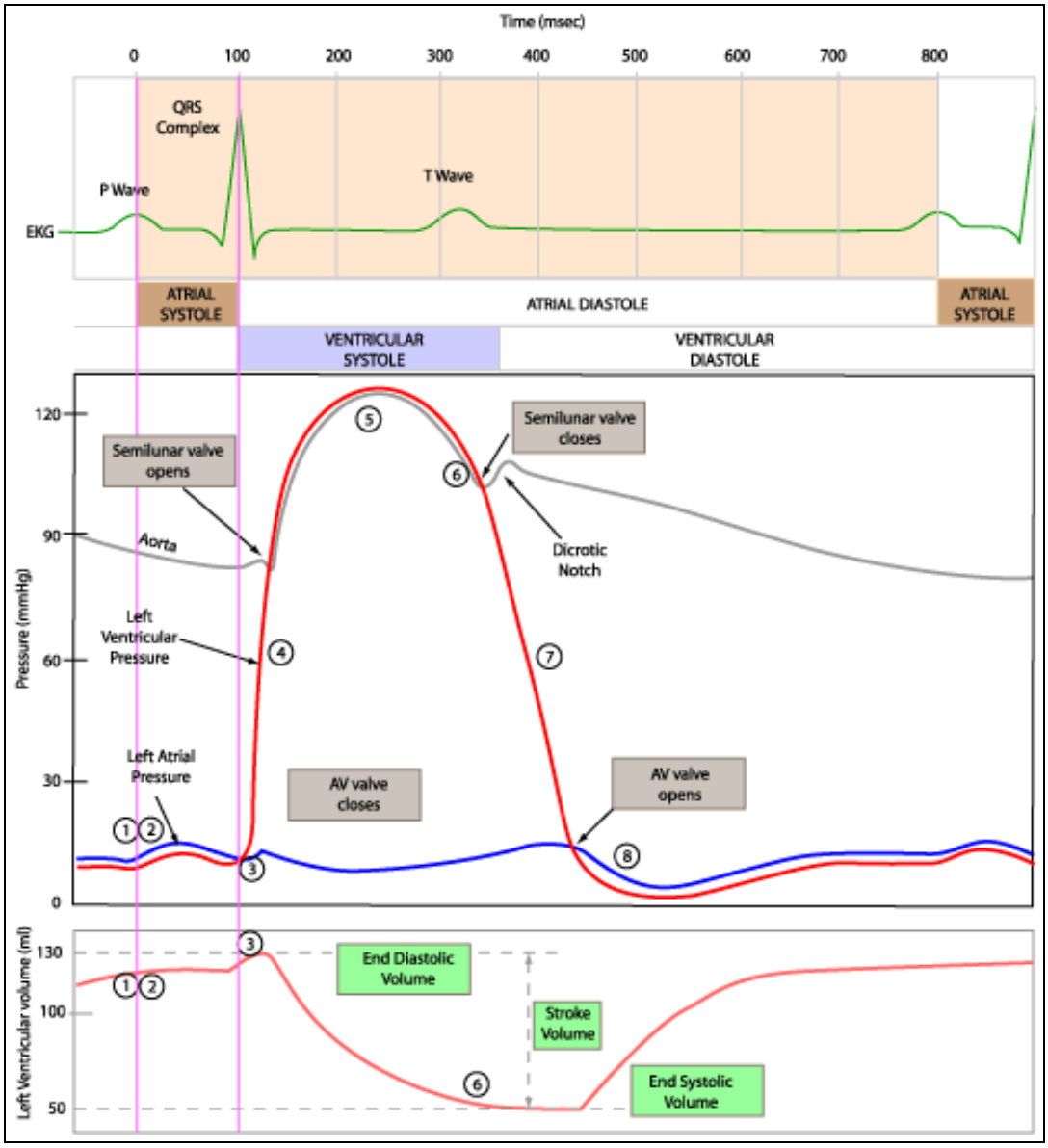

Figure 2: The cardiac cycle

ion channels, and the plateau phase is due to opened voltage-gated calcium ion channels. Repolarization at the end of the plateau phase is due to the opening of potassium ion channels for a brief period. The prolonged action potential in cardiac muscle ensures that contraction and relaxation occurs and prevents tetany in cardiac muscle.

1.2.5 Electrocardiogram

The ECG is a record of electrical events within the heart. The normal ECG consists of a P wave (atrial depolarization), a QRS complex (ventricular depolarization), and a T wave (ventricular repolarization). Atrial contraction begins contracting around 100ms after the start of the P wave, during the P-Q interval, and the ventricles contract shortly after the peak of the R wave and relax during the Q-T interval.

1.3 Blood vessels of the systemic circulation : arteries

The aorta : The aorta leaves the left ventricle to form the ascending aorta, aortic arch, and descending aorta, which consists of the thoracic and abdominal aorta ;

Arteries of the head and neck : The brachiocephalic, left common carotid, and left subclavian arteries branch from the aortic arch to supply the head and the upper limbs. The common carotid arteries and the vertebral arteries supply the head. The common carotid arteries divide to form the external carotids (which supply the face and mouth) and the internal carotids (which supply the brain).

1.4 The physiology of circulation pressure and resistance

Blood pressure fluctuates between 120 mm Hg (systolic) and 80 mm Hg (diastolic) in the aorta. If constriction of blood vessels occurs, resistance to blood flow increases, and blood flow decreases. Pulse pressure is the difference between systolic and diastolic pressure ; it increases when stroke volume increases.

1.5 The brain

The brain has a very high demand in oxygen, and it receives a substantial supply of blood. Under a variety of conditions, the blood flow to the brain remains steady at about 750mL/min, which is roughly 12 percent of

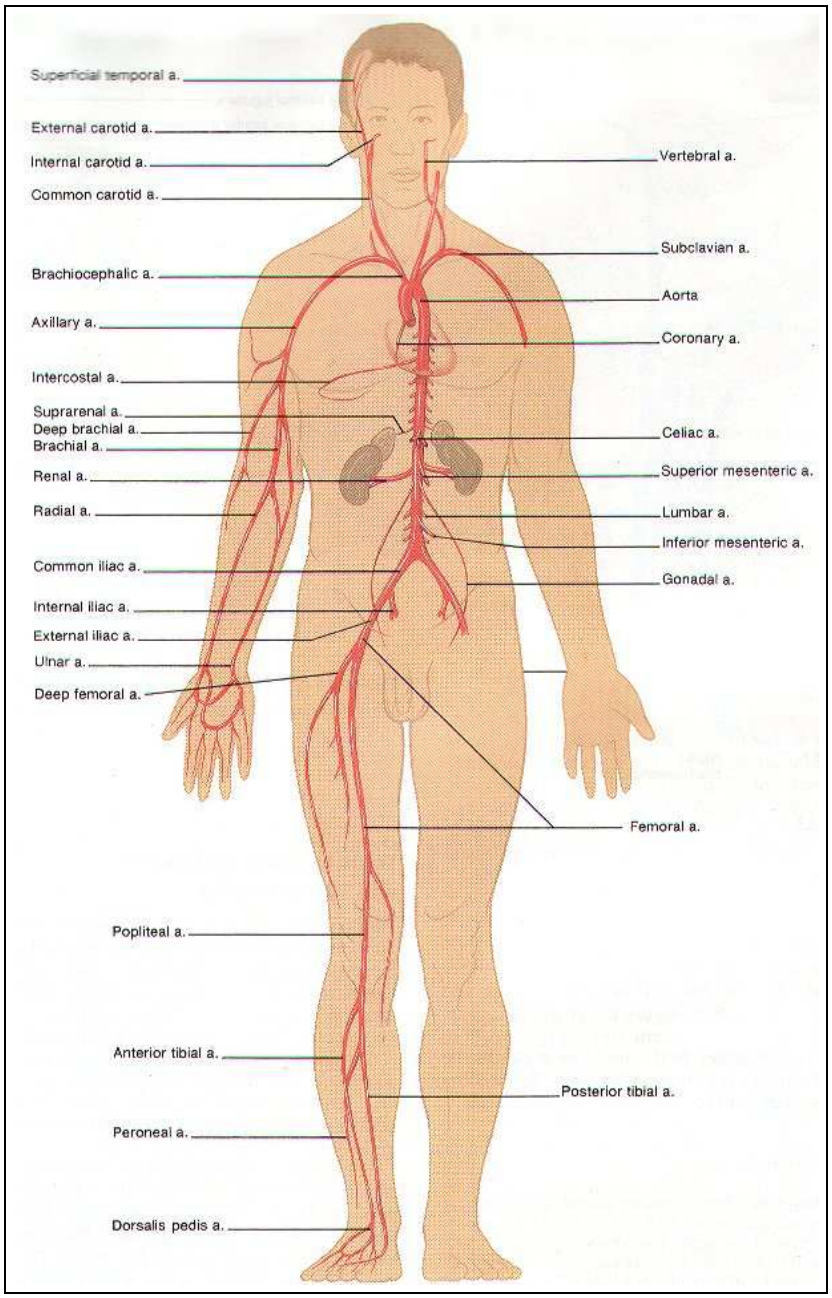

Figure 3: The major arteries

the cardiac output, delivered to an organ that represents less than 2 percent of the body weight. Neurons do not maintain significant energy reserves, and on functional terms, most of the adjustments made by the cardiovascular system treat circulation to the brain as a number one priority. Even when a circulatory crisis is under way, blood flow through the brain remains as near normal as possible. While the cardiovascular centers are calling for widespread peripheral vasoconstriction, the cerebral vessels are told to dilate.

The brain receives arterial blood via four arteries. Because these arteries form anastomoses inside the cranium, interruption of any one vessel will not compromise the circulatory supply to the brain.

The common carotid arteries ascend deep in the tissues of the neck, each divides into an external and an internal carotid artery at the carotid sinus. The external carotids supply blood to the structures of the neck, pharynx, lower jaw, and face. The internal carotids enter the skull through the carotid foramina of the temporal bones, delivering blood to the brain. The internal carotids ascend to the level of optic nerves, where each divides into three branches : (1) an ophthalmic artery, which supplies the eyes ; (2) an anterior cerebral artery, which supply the frontal and parietal lobes of the brain ; and (3) a middle cerebral artery, which supplies the mesencephalon and lateral surfaces of the cerebral hemispheres.

Blood reaches the brain through vertebral arteries as well as by way of the internals carotids. The left and right vertebral arteries arise from the subclavian arteries and ascend within the transverse foramina of the vertical vertebrae. The vertical arteries enter the cranium at the foramen magnum, where they fuse along the ventral surface of the medulla oblongata to form the basilar artery.

The internal carotids normally supply the arteries of the anterior half of the cerebrum, and the rest of the brain receives blood from the vertebral arteries. But this circulatory pattern can easily change, because the internal carotids and the basilar arteries are interconnected in a ring-shaped anastomosis, the cerebral arterial circle, or circle of Willis.

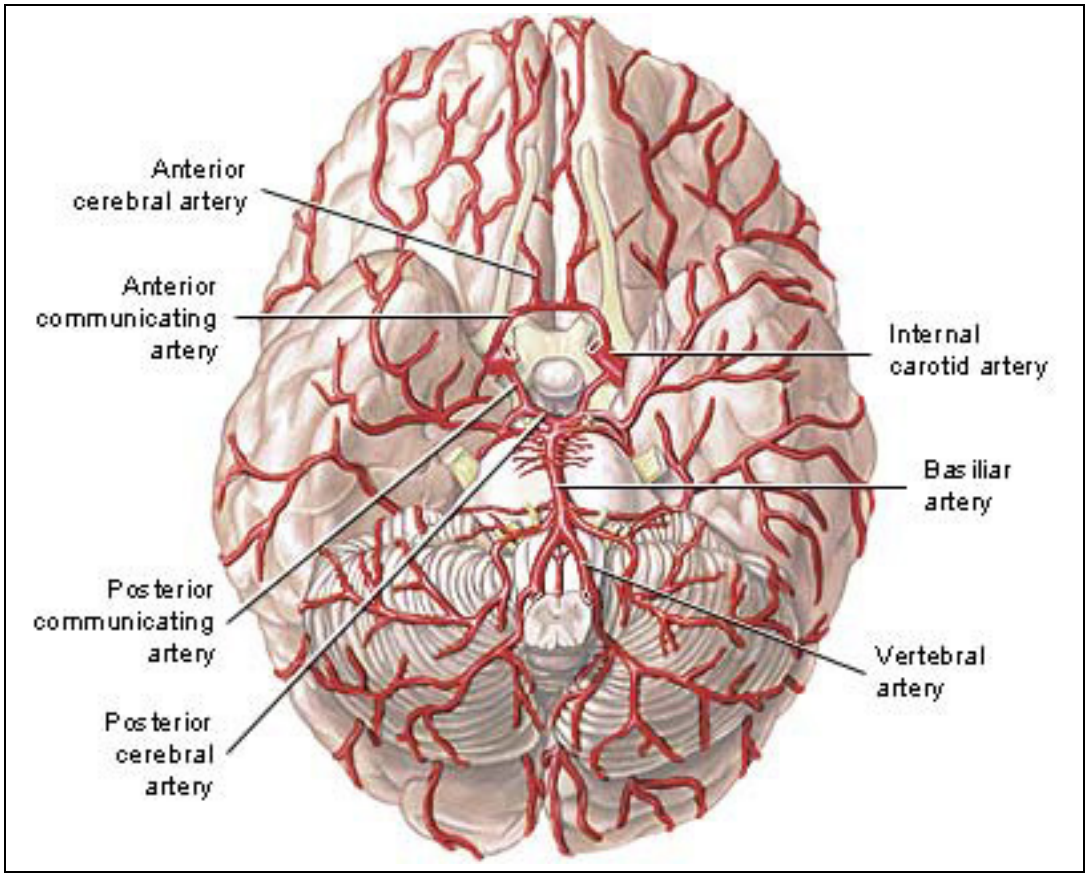

Figure 4: Arteries of the brain

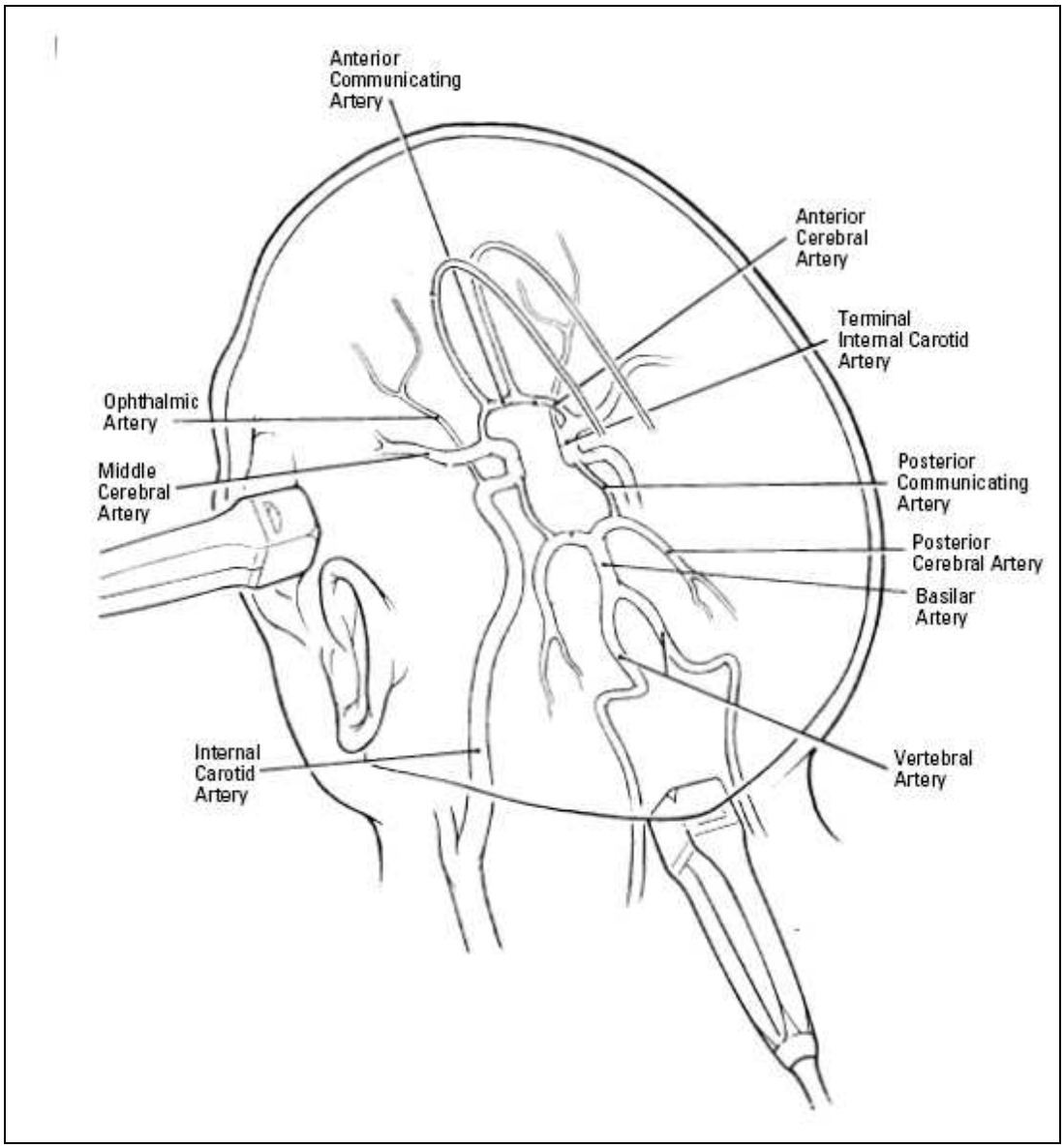

Figure 5: Cerebral arteries and the circle of Willis

2 Medical measurements

2.1 The vasoreactivity test

The clinical protocol consists in a vasoreactivity test : the patient breathes room air, or room air with 6% more CO2, or hyperventilates. Blood velocity in the middle cerebral artery (MCA) is measured with a Trans-Cranial Doppler TCD, heart rate is recorded with an ECG, and the amount of CO_2 breathed is recorded with an end-tidal CO_2 monitor.

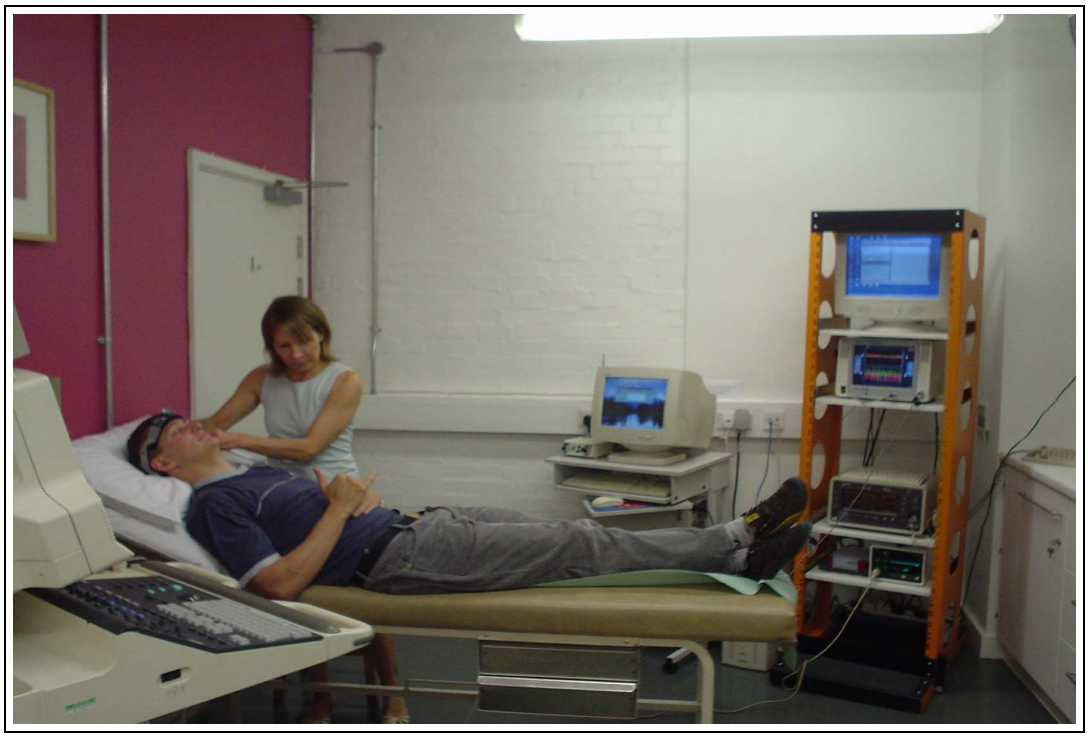

Figure 6: Ultrasound Research Laboratory

The protocol is the following :

1. Room air, 3 minutes ;
2. CO_2 (+ 6%), 3 minutes ;
3. Room air, 3 minutes ;
4. Controlled hyperventilation, 3 minutes ;
5. Room air, 3 minutes ;

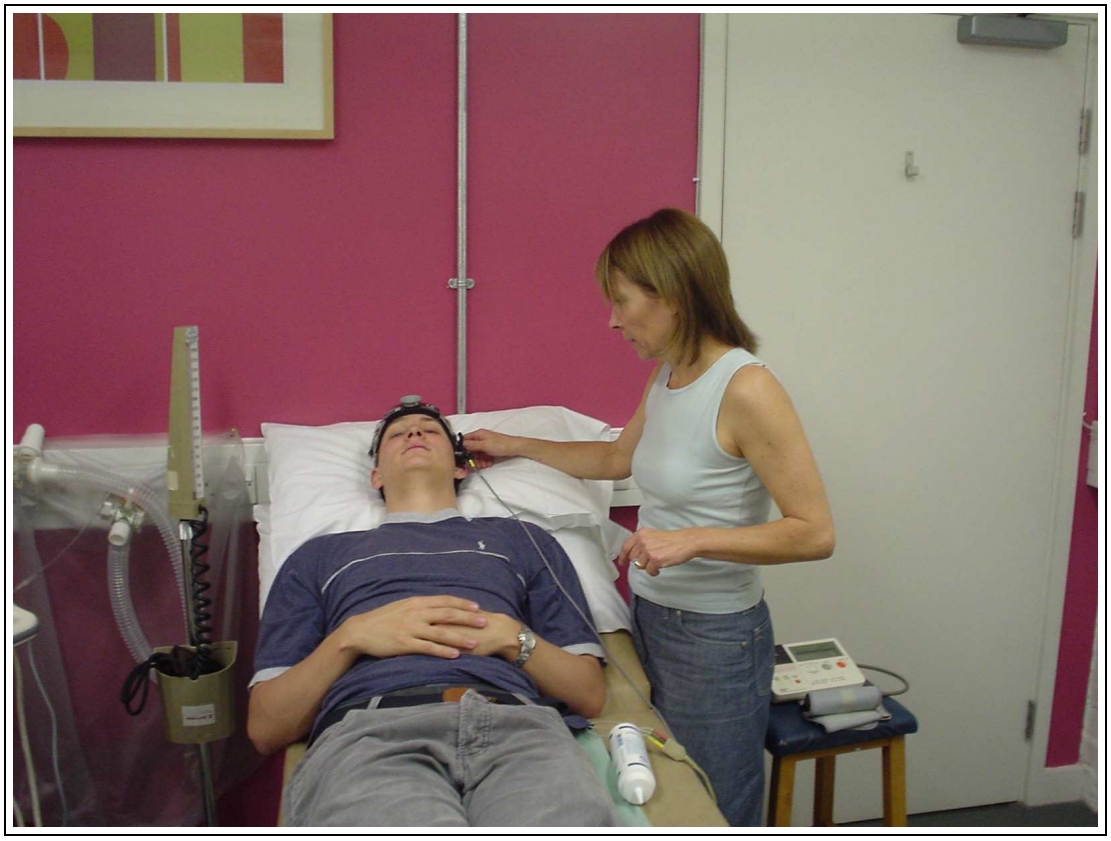

Figure 7: Setup of the TCD probe

The measurements are recorded for 16 seconds during the last 30 seconds of each phase. The overall test lasts 15 minutes and is carry out a second time another day (reproductibility). Then the data are synchronized with an auxiliary MATLAB program. This is necessary since we use two different monitors to record our measurements. After this synch, we obtain raw data which consist in vectors (time, ECG, TCD, CO_2) in five .txt files. The sampling rate of the measurements is 200 Hz (one measure every 5 ms).

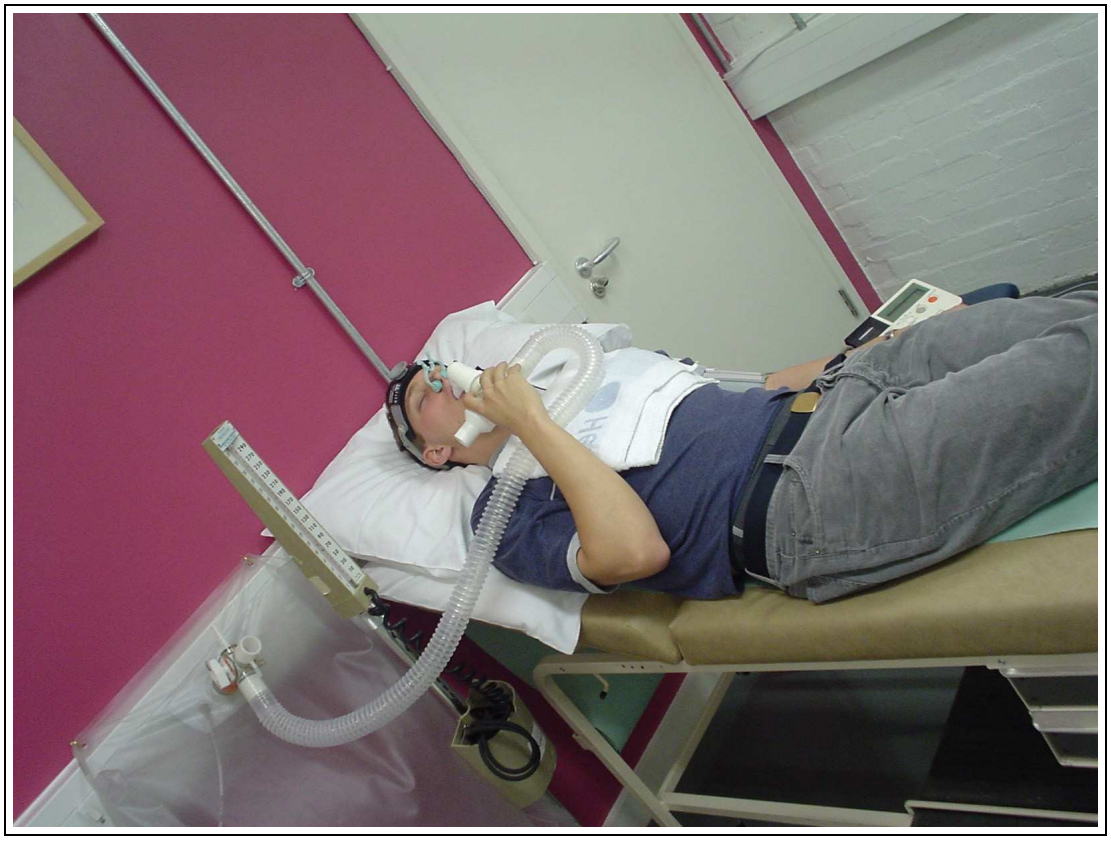

Figure 8: Patient during a vasoreactivity test

In addition, the blood pressure is measured just before the end of each phase.

2.2 Transcranial Doppler

Transcranial Doppler (TCD) is a non-invasive ultrasound technology used to assess blood flow velocity in the major basal intracranial arteries on a real

time, beat-to-beat basis. Blood flow velocity is calculated and used to make determinations about intracranial hemodynamics [5].

In 1979, Drs. William Stern and Robert Barnes first used Fast Fourier Transform (FFT) to analyze the change in frequency of the returned audio signals of ultrasound instruments. The device which carried out this analysis, the Angioscan, allowed clinicians to calculate the Doppler shift or frequency of the audio signal, resulting in reproducible and consistent quantification of blood flow velocity.

The FFT, displayed visually as a waveform, offered additional information, including direction of flow in vessel, and helped distinguish between laminar and turbulent flow. Subsequently, normal ranges of frequency values were established, and the FFT analysis of Doppler frequency became known as spectral analysis.

Ultrasound has several advantages over other diagnostic modalities, including its portability, low cost, and safety. Because ultrasound is non-invasive, studies may be performed repeatedly and without the need for contrast agents.

In 1982, Dr. Rune Aaslid discovered that it was possible to send an ultrasound beam into the brain through a thinning of the skull. He used an Angioscan to analyze a Doppler signal reflected from cerebral arteries and his discovery heralded a breakthrough in the evaluation of intracranial blood flow velocity. This technique is referred to as Transcranial Doppler (TCD).

The vessels in the circle of Willis lie at known depths in the brain. The operator selectively evaluates specific vessels by controlling the placement of the ultrasonic sample volume and the transducer's orientation. Depth of insonation, flow direction, velocity, and audio pitch assist in vessel identification. TCD signals have been extensively correlated with angiograms, and are accepted as reliable measurements of intracranial blood flow velocity.

TCD may be performed from three physical approaches, known as ultrasonic windows. The transtemporal window allows evaluation of the middle cerebral artery, internal carotid artery bifurcation, anterior cerebral artery, and posterior cerebral artery. The transorbital window allows evaluation of the ophthalmic artery and the internal carotid artery siphon (when using this window, the ultrasonic power output of the instrument should be lowered to 10 or 20%). The sub-occipital window allows serial evaluation of major por-

tions of the vertebral and basilar arteries. In some patients, tortuous anatomy may limit the portions of the basilar artery that are available for sampling.

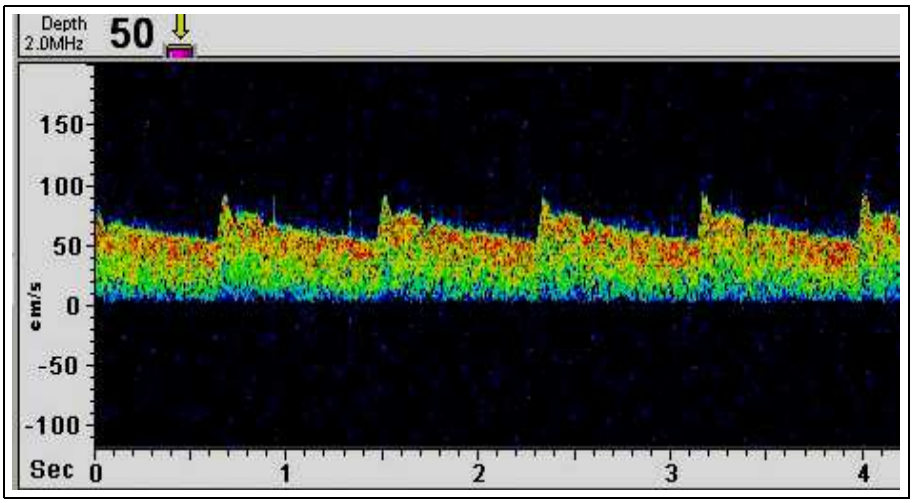

Figure 9: Screen of a TCD

To perform the examination, the operator places a 2 MHz transducer on the appropriate ultrasonic window. An ultrasound beam is sent out from the unit through the transducer directly into the vessel. The depth of penetration (or length of the beam) is controlled by the operator. The TCD instrument evaluates the difference between the signal sent (transmitted frequency) and the signal returned (reflected frequency). Spectral analysis then calculates this difference (Doppler frequency shift).

2.3 The exploitation of medical measurements

We need a programm to visualize curves, to average the velocity measured over the heart beats, and to extract important values from this mean velocity : standard deviation, local minima and maxima of the velocity, of its first derivative, etc.

The MATLAB programm `TCD` developed for this study does this all and works for the majority of the healthy patients, that is to say, for most kinds of velocity curves [2].

Its features are :
– averages the velocity over the heart beats (ensemble average) ;

- allows the user to ignore some heart beats (especially at the beginning or the end of the recording). This is really useful since one of the device records the 20 seconds following the moment you push on the "Enter" key whereas the other one records the last 20 seconds of data when you hit the "Save" button ;
- plots a three-dimension figure of the velocity during each beat to help visualize the standard deviation ;
- detects the three local minima of the velocity or, if some don't exist, find where they should be located ;
- detects the three local maxima of the absolute value of the acceleration or, if some don't exist, find where they should be located ;
- matches the slow decrease of the last part of the averaged velocity with an exponential decrease and gives the value of the time constant of this exponential decrease ;
- exports characteristic values into excel ;
- compares several TCD measurements with rescaling options ;
- works for both flow directions (towards the transducer and away from it).

The filtering part of the program is based on FFT transforms for the ECG, on the Savitsky-Golay filter for the velocity. The Savitsky-Golay provides a versatile smoothing filter by using a moving window, with an nth order polynomial least-squares fitted to the points in the window. A set of polynomial coefficients is produced for each point in the window. A by-product of the Savitsky-Golay filter approach allows first derivative filters.

The rest of the program is basic MATLAB programming implementing classic analytical analysis, graphics and input/output of data.

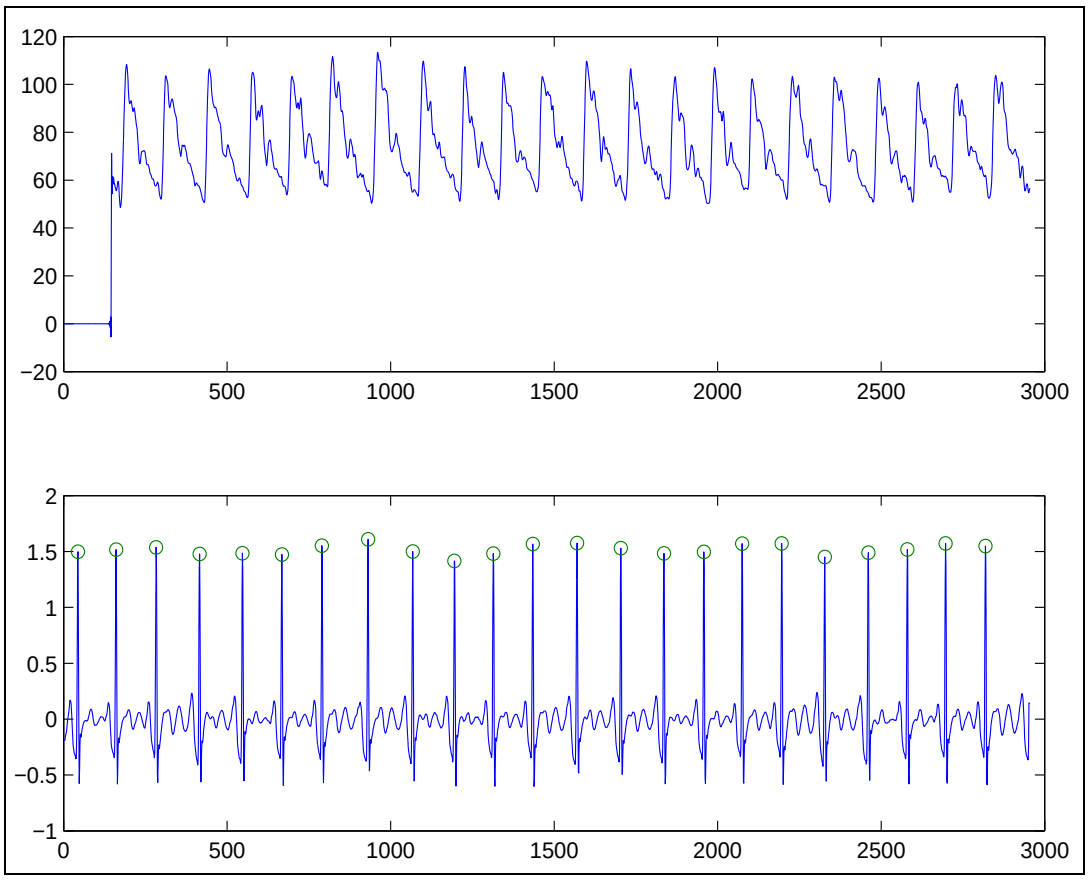

Figure 10: Raw data from the TCD (velocity in cm/s, top) and the ECG (signal in millivolts, bottom) measured with a sampling rate of 200Hz

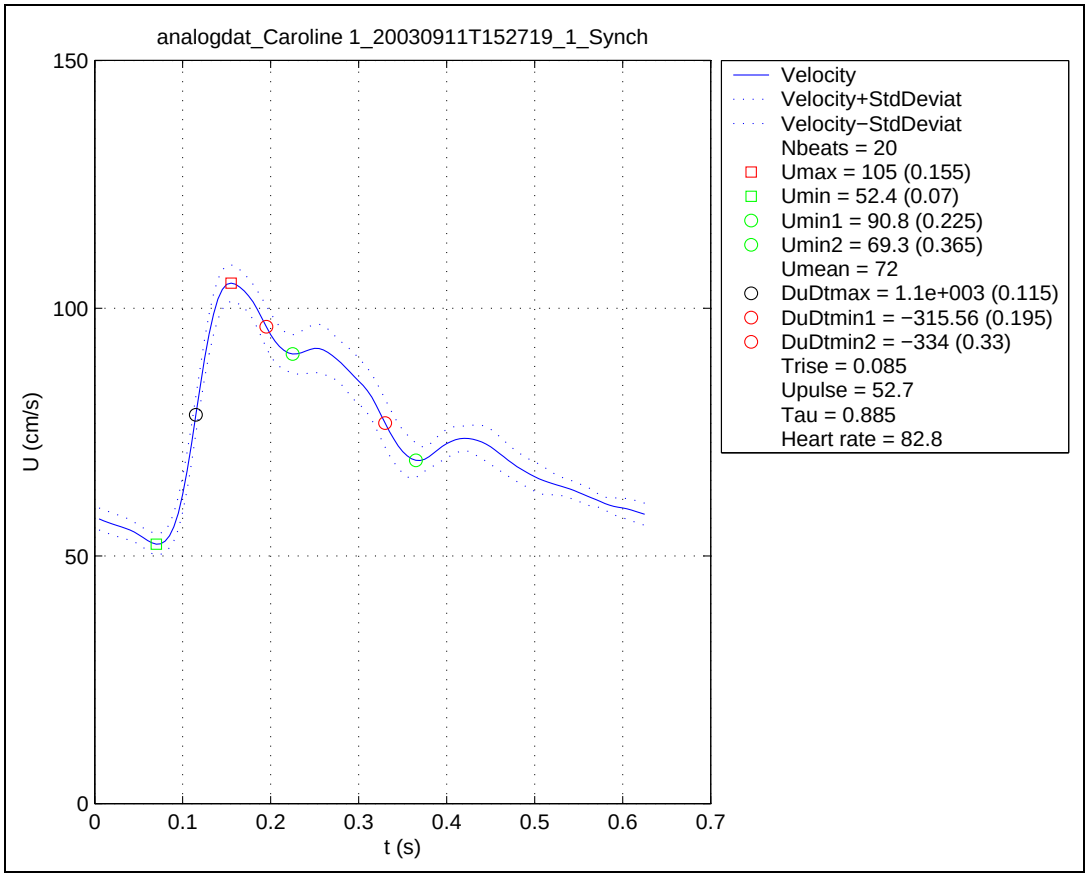

Figure 11: Average velocity and main characteristics given by the MATLAB programm `TCD` for the standard case

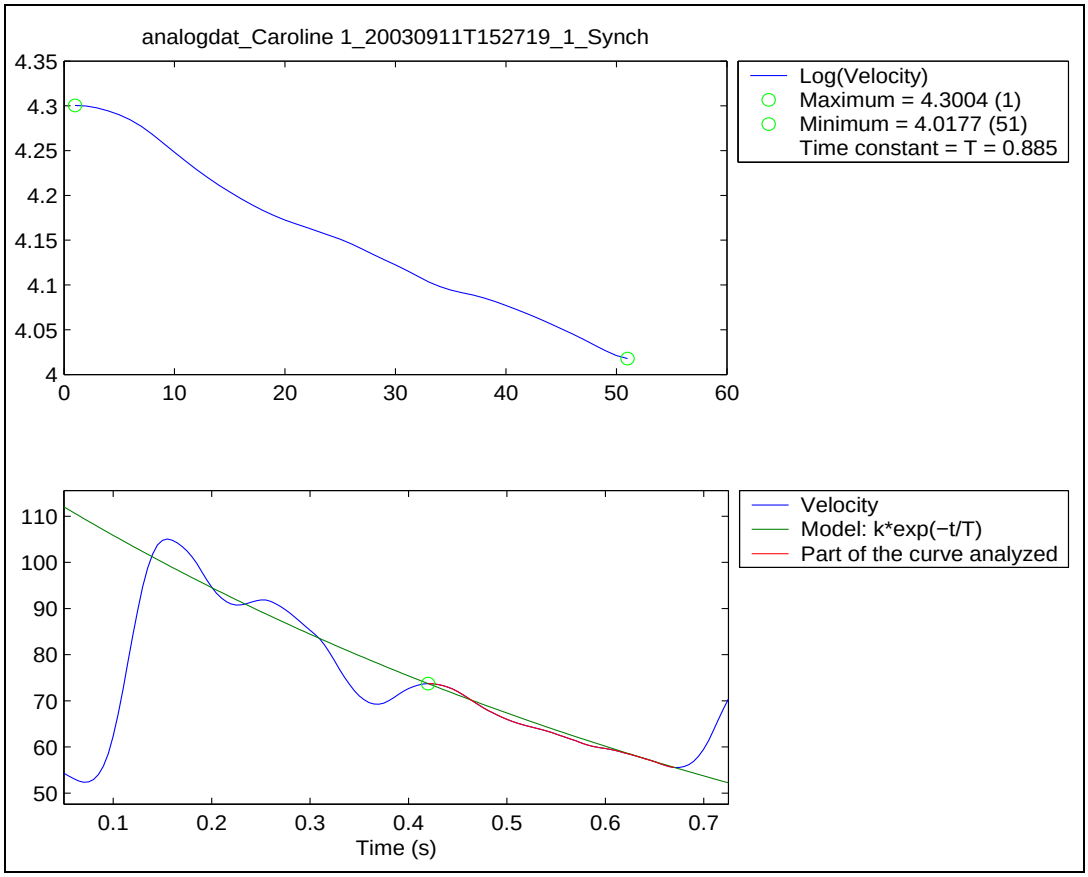

Figure 12: Value of the time constant that characterizes the exponential decrease of the last part of the velocity curve. Bottom : part of the curve analyzed (red) ; Top : Logarithm of the velocity for the red part of the curve above

2.4 Results

During my stay at the PFSG, we only measured eight healthy patients. These preliminary measures were meant to help us understand which parameters will be important to monitor during the study on patients suffering from cardiac valve malfunction, to assess the accuracy of the protocol and, more generally, to understand a little more about the cerebral circulation.

2.4.1 Preliminary remarks

To be able to understand further analysis of the velocity curves, we should first make some preliminary comment on an example. The following five curves (figure 11) have been measured and post-processed during a test following the protocol presented above (five measurements : baseline, CO2, baseline, hyperventilation, baseline, C02).

We should first comment the shape of the curve : during systole, the curve can be described by a peak in velocity followed by the two local minima (that we will call first and second plateau from now on). They can be perfectly see on figure 10.

The first plateau can be interpreted as a consequence of wave reflection : at the end of the MCA, we find a bifurcation or a trifurcation, which is probably a reflection site for the velocity wave. The backward wave (negative velocity) tends to sharpen the peak and to create a first local minimum.

The second plateau, which occurs at approximately 400ms, can be interpreted as the closure of the aortic valve : valve closure is associated with a small backflow of blood into the ventricules and a characteristic notch (incisura or dicrotic notch) in the aortic and pulmonary artery pressure tracings and, in typical arteries of the systemic circulation, with a negative blood velocity (figure 14). The main feature of cerebral circulation is that blood flow never goes backward ; however, our measurements show that the dicrotic notch can possibly be spotted on cerebral waveforms too. This assumption will be verified in the section "Recording of the sound of the aortic valve closure".

During diastole, we observe an exponential decrease of the velocity, with a fall-off time between 0.5 and 1.5 second. This can be interpreted as a consequence of the windkessel model ; the windkessel model is explained in the section "The Windkessel Model", where this supposition is tested.

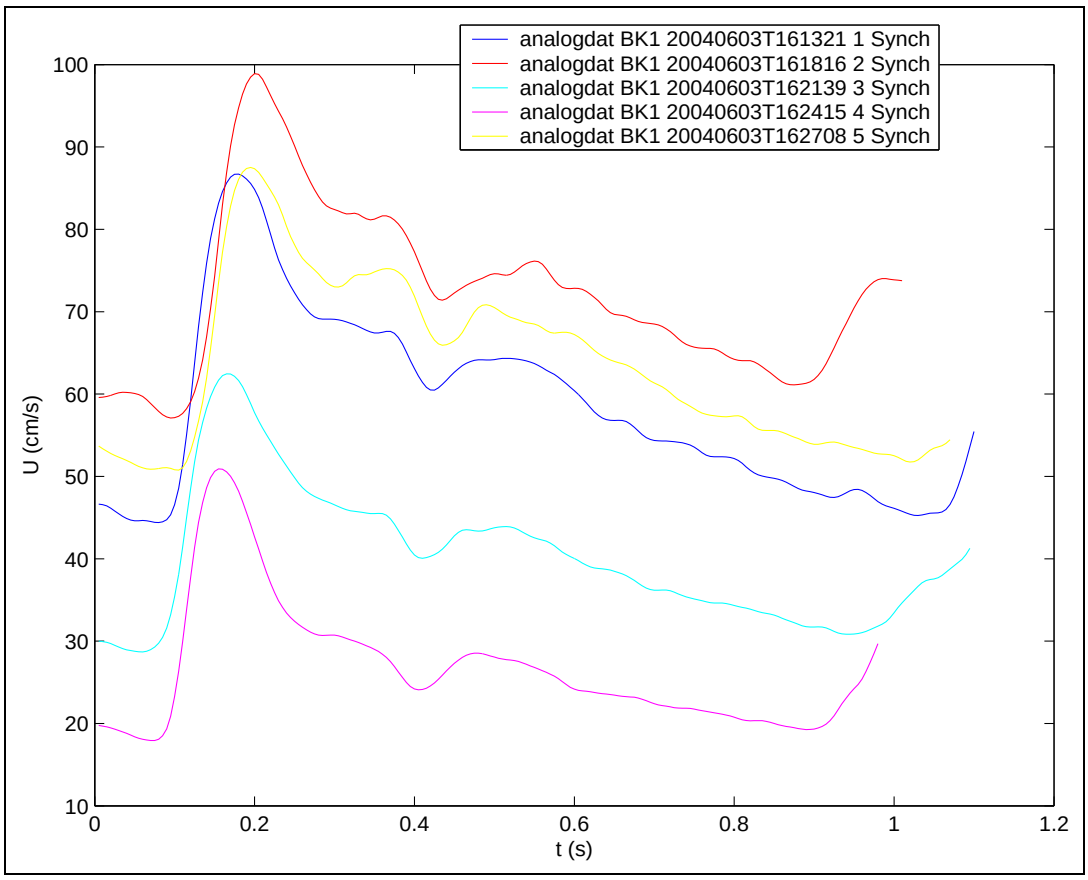

Figure 13: Measurements taken on a young patient (aged 22). Curves : baseline, CO2, baseline, hyperventilation, baseline, C02)

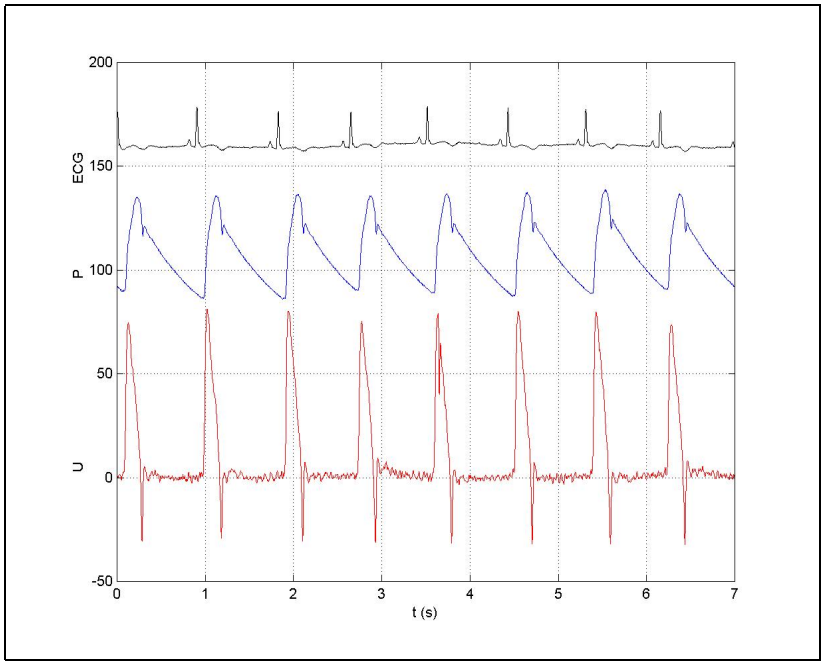

Figure 14: Example of waveforms in the systemic circulation : ECG (for reference), the pressure (P) in mmHg and the velocity (U) in cm/s in the ascending aorta. These data were measured invasively using a catheter on an healthy patient [6].

2.4.2 Reproducibility

By definition, reproducibility is the variation in average measurements obtained when two or more people measure the same parts or items using the same measuring technique.

First, in contrast to electrophysiological and spectroscopic monitoring, the information obtained with TCD measurements is highly dependent on the skill and experience of the monitorist. In this regard, Shen et al. [7] studied in 1999 the reproducibility and variability of TCD information. They found excellent (more than 90%) agreement in velocity measurements among a group of experienced ultrasonographers. However, they observed that low variance and high reproducibility required frequent practice. After an eight-week break, performance deteriorated markedly. Their conclusion was that lack of regular practice adversely affected the accuracy of measured flow velocity indices. Their recommendation was that the monitoring companies develop devices, i.e. phantom heads to facilitate training and enable efficient practice regimens. These devices could dramatically improve the clinical acceptance of this technology.

In our study, we try not to be influenced by the problem of reproducibility due to the experience of the sonographer : we didn't change the operator, we aimed at knowing whether our figures and indices were significant or too different from one measurements to the other. In order to do so, we tested the variability of two indexes and one parameter :

Shape Index 1 (SI1) : This index characterizes the first "plateau" where is located `Umin1` (see figure 9). SI1 is defined by

$$SI1 = \frac{Umin1 - Umin}{Umax - Umin}$$

This gives the level of the plateau, which seems to be a very important part of the description of the shape of the curve.

Shape Index 2 (SI2) : This is the same thing as SI1, but for the second plateau, when it exists.

Tau : This time constant characterizes the exponential fall-off of the second part of the velocity curve (figure 13).

Why would we choose these parameters ? When you know the standard shape of the velocity curve, these three parameters allow you to "redraw"

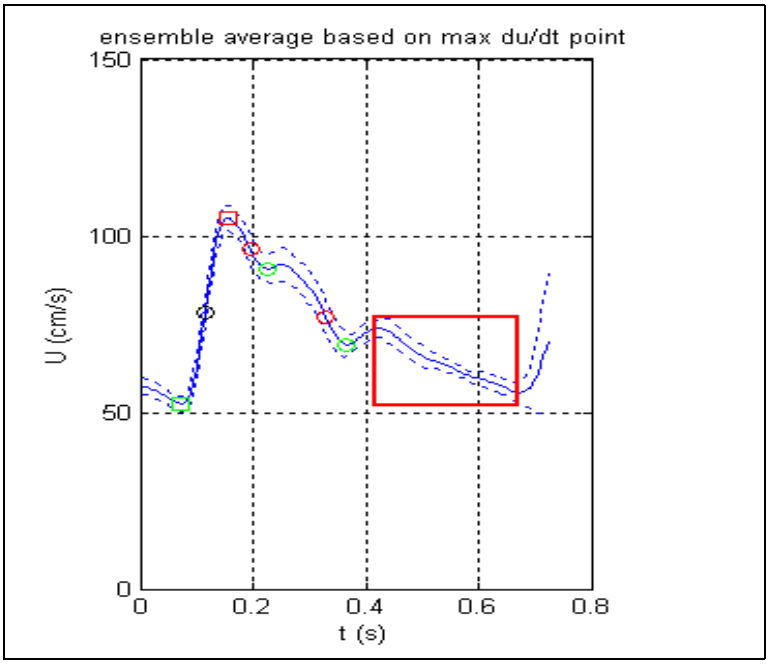

Figure 15: Part of the velocity curve characterized by the time constant tau

the curve quite accurately. If there were three parameters necessary to reconstruct the TCD velocity curve of an MCA, it would be SI1, SI2 and Tau.

At first sight, the results seem to be quite disappointing : the reproductibiliy test was carried out on seven healthy patients (five measurements for each test, two tests), and for each patient we measured the change (in %) of the index or parameter between the first test and the second test. Then these five percentage of change (one for each phase of the test) were averaged. This gave us the reproducibility rate for each patient.

	SI1	SI2	Tau
Average reproducibility (%)	21.29	25.60	21.14
Standard deviation (%)	8.68	11.18	11.82

A twenty-percent variation between two measurements in average could be surprising. Actually, since the tests were carried out on two different days for each patient, it entails a lot of physiological changes, such as heart rate changes (stress, physical activity like walking before the test), changes in the blood flow repartition (lunch, etc). In the next section, we present other

statistical results proving that our protocol doesn't fail to show the vasoreactivity of the cerebral vessels, even if these reproductibility results seem to be quite disappointing.

2.4.3 Vasoreactivity

First, we will look at the changes in mean velocity in comparison with the first baseline during the vasoreactivity test.

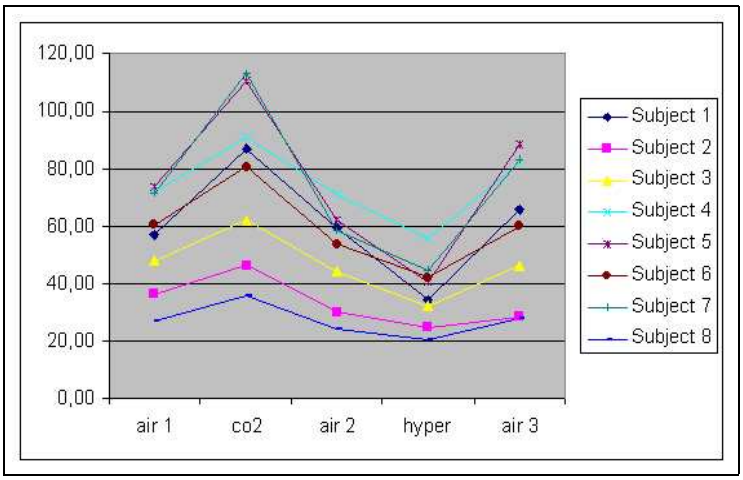

Figure 16: Mean velocity in the MCA (cm/s)

Mean velocity	CO2	Baseline 2	Hyperventil.	Baseline 3
Average change % Baseline 1	38	-9	-32	5
Standard deviation	11	6	6	11

On average, the increase / decrease due to CO2 / hyperventilation is really large (more than 30%). We have a massive response of the body, which can be explained mainly by two phenomenons. These changes in cerebral blood flow velocity are due both to changes in the diameter of the cerebral vessels (vasodilatation / constriction) and to changing cardiac output and flow velocity in the central circulation (heart rate, mean arterial pressure). Changes in heart rate are the following : an increase of 14% on average for CO_2, whereas the increase amounts to 32% during hyperventilation (see figure 17). For the mean arterial pressure (figure 18), defined by $= (P_{systolic} - P_{diastolic})/3 + P_{diastolic}$, increase of 11% and 0.6% respectively (the mean arterial pressure (or MAP) corresponds to the mean of the arterial pressure assuming a triangular waveform).

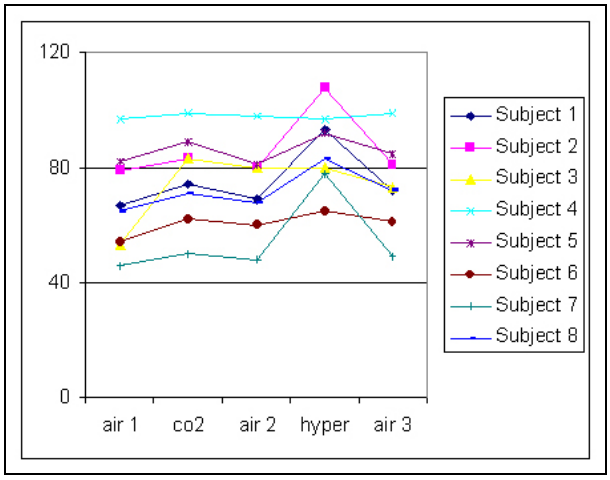

Figure 17: Heart rate (beats per minute)

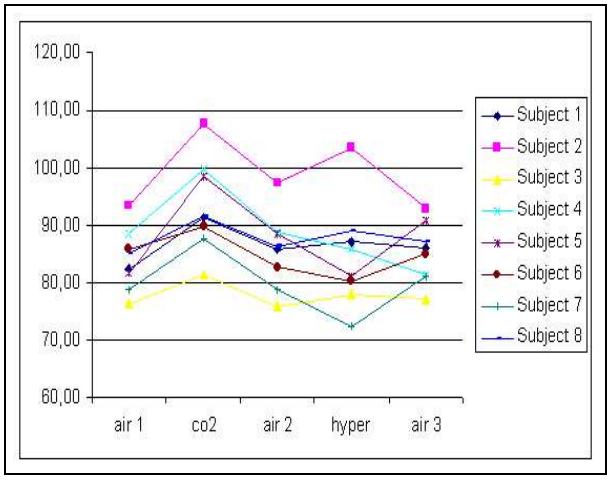

Figure 18: Mean pressure in the systemic circulation (mmHg)

To understand how the cerebral circulation responds to CO2 and hyperventilation, it is also important to look at the change of the three parameters (SI1, SI2, Tau) in comparison with their value for the first baseline.

SI1	CO2	Baseline 2	Hyperventil.	Baseline 3
Average change % Baseline 1	9	-1	-38	3
Standard deviation	27	13	14	18
SI2	CO2	Baseline 2	Hyperventil.	Baseline 3
Average change % Baseline 1	15	7	-39	3
Standard deviation	22	16	21	23
Tau	CO2	Baseline 2	Hyperventil.	Baseline 3
Average change % Baseline 1	-7	-24	-37	-19
Standard deviation	28	18	13	22

For baseline 2 and baseline 3, we can consider that, within 3 minutes, most patients have managed to go back to normal. It may be interesting to make these phases last 5 or 8 minutes and see if we can diminish the standard deviation for the 25% of patients who have a change of more than 10% between baselines.

In the CO2 test, we can notice an increase in the two plateaus, which can be interpreted as a decrease in the intensity of the backward wave. This may be linked to the fact that vasodilatation contributes to a decrease in reflection magnitude. We cannot note any significant trend with regard to the fall-off time.

In the hyperventilation test, both plateaus decrease remarkably, which, conversely, means an increase in reflection magnitude. The significant decrease in the fall-off time could mean that the arterial compliance and / or resistance decrease. However, too many physiological changes are likely to occur to draw a certain conclusion about that fact.

2.5 Recording of the sound of the aortic valve closure

Since the second plateau happens around 400ms after the beginning of the heart cycle, and since the dicrotic notch usually characterizes the aortic valve closure, we planned to record the heart sounds, mainly aortic valve movements, with a phonocardiograph. The electronic sensor is placed on the subject's chest, and one of the sound peaks with the largest amplitude is the

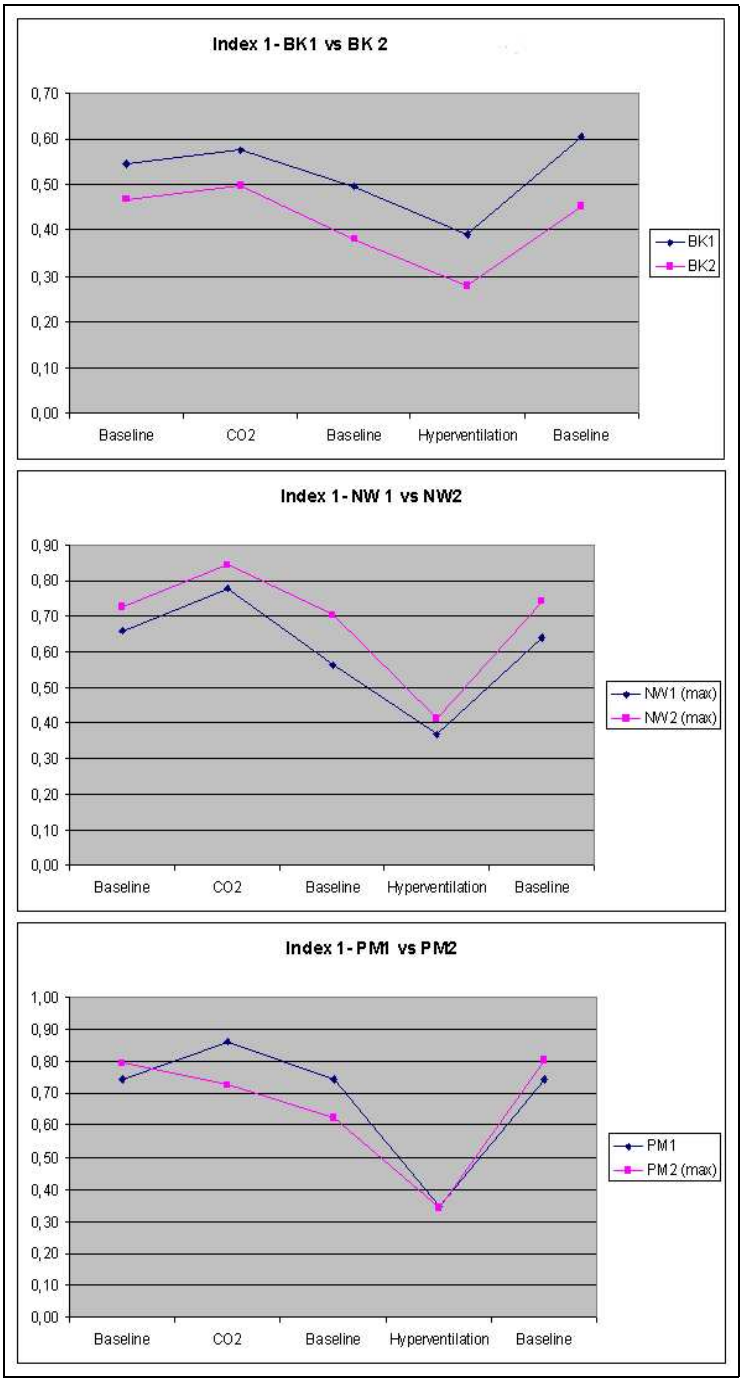

Figure 19: Changes in SI1 for three patients

aortic valve closure.

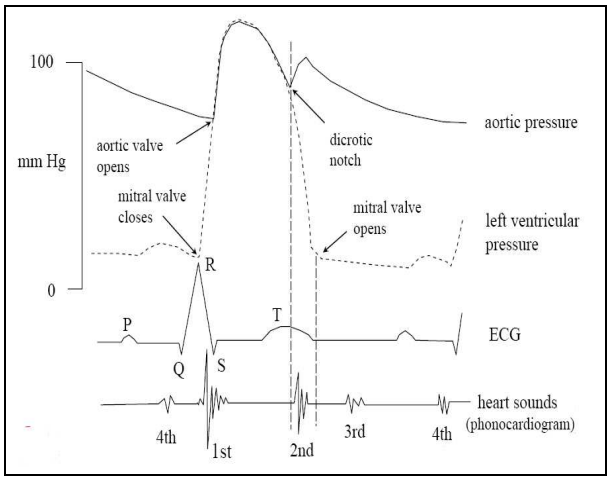

Figure 20: Phonocardiography : Measurement of Heart Sounds

However, we also wanted to record this sound in the way we did it for the ECG and end-tidal CO2, so as to be able to synch the sound with the TCD. For this reason, we build our own phonocardiograph with a computer microphone. The mic was then put into a frame to attenuate noise from the outside and linked to our acquisition system. You can see the signal obtained without filtering on figure 17.

We only checked one patient, but the results confirm that the second minimum on this velocity curve is due to valve closure.

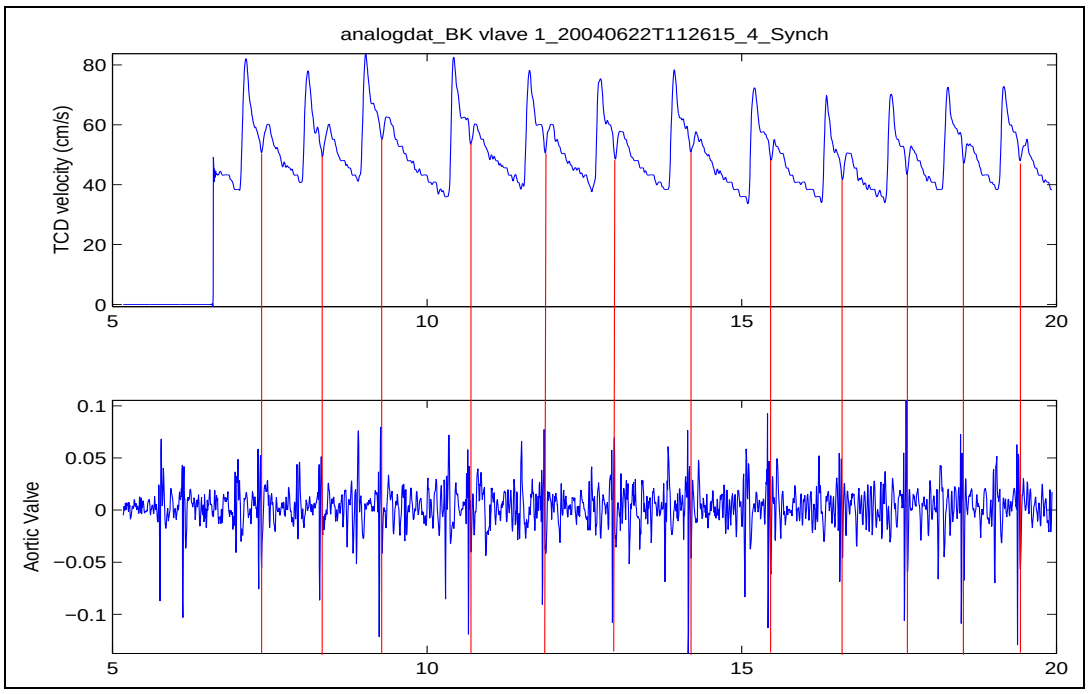

Figure 21: Measurement of the velocity (cm/s) and the heart sounds (amplitude of the signal in mV)

3 A model of the blood flow in the Middle Cerebral Artery

3.1 The Windkessel Model

The primary function of arteries is to allow the exchange of gases, nutrients and wastes, and for this function, arteries serve as conduits which bring blood to the peripheral microcirculation. But their elasticity allow them to carry out another function : a hydraulic capacitor which serves to smooth out the highly pulsatile nature of flow from the heart.

In 1898, Otto Frank compared this mechanism to the Windkessel (literally, the "air chamber") used on early fire pumps to convert the pulsatile pumping action into relatively smooth flow. The Windkessel theory considers that the whole arterial system is a single compliant compartment, and that blood flows into it from the LV during systole (flow Q_{in}), and out of it through the microcirculation (flow Q_{out}). Given the high resistance of the microcirculation, this theory also assumes that Q_{out} follows a hydraulic Ohm's law. With this assumption, it is possible to solve the model and to obtain the pressure of the arterial compartment, which leads to an exponential function increasing during systole and falling during diastole.

Unfortunetely, measurements show that this model of the arterial system is a poor description of systolic flow. Current researches tend to show that the difference between the predicted Windkessel pressure and the pressure mesured is related to the generation of arterial waves [8].

3.2 Our model of the blood flow in the MCA

3.2.1 The two part of our model

The MCA starts at the circle of Willis, has a length of approximately 7mm, can have 0, 1 or 2 branches, and ends with a bifurcation or a trifurcation.

We measured blood velocity in the MCA of two patients.

Patient 1 : Velocity of the proximal and the distal MCA. The MCA has no branch and ends with a trifurcation ;

Patient 2 : Velocity of the proximal artery and a branch. The MCA has one branch at its center and ends with a bifurcation.

We aim at calculating the velocity at the end of the MCA (distal MCA or MCA branch) U_{out} given the velocity in the proximal MCA (U_{in}) and confirm these calculations with our measurements.

Our model is based on the combination of two parts : a forward / backward wave model coupled with a Windkessel model.

Forward / backward wave model We suppose that the velocity we measure is the proximal MCA is the sum of a forward wave U_{fwd} and a backward wave $U_{bwd}(t) = r \cdot U_{fwd}(t - 2 \cdot \tau)$ where τ is the time the wave needs to reach the reflection site. Then the forward wave follows the Windkessel model, whereas the backward wave contributes to U_{out} by the factor $r \cdot U_{fwd}(t - \tau - \theta)$ where $\theta < \tau$ and r is a reflection coefficient. This assumes that there is only one main reflection site.

Windkessel model We suppose that U_{fwd} is the input of a Windkessel circuit. This model can be derived from electrical circuit analogies where current represents arterial blood flow and voltage represents arterial pressure, here a RC-circuit with one resistor and one capacitor. The calculation is presented is the next subsection.

3.2.2 The Windkessel part

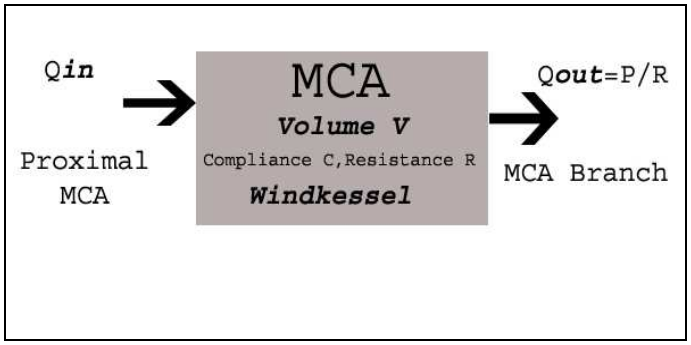

Figure 22: Windkessel model

We note Q_{in} the flow entering the circuit, Q_{out} the flow exiting, R the resistance and C the compliance of the system, and V its volume.

$$\begin{cases} Q_{in} &= A_{in} \cdot U_{fxd} \\ Q_{out} &= \frac{P - P_\infty}{R} \\ \frac{dV}{dt} &= Q_{in} - Q_{out} \end{cases}$$

where P_∞ is the asymptotic pressure of the diastolic exponential decay and A is the diameter of the artery.

Since $\frac{dV}{dP} = C$ by definition,

$$C\frac{dP}{dt} = \frac{dV}{dt} = A_{in}U_{fwd} - \frac{P - P_\infty}{R}$$

And with $\hat{P} = P - P_\infty$ and $\xi = \frac{t}{RC}$,

$$\frac{d\hat{P}}{d\xi} + \hat{P} = R \;\; A_{in} \; U_{fwd}$$

Since C can be very small, we will look for an asymptotic solution. We write $\sigma = \epsilon \cdot \xi = o(1)$ where $\epsilon \ll 1$. We obtain

$$\epsilon\frac{d\hat{P}}{d\sigma} + \hat{P} = R \; U_{fwd}(\sigma)$$

Assume $\hat{P} = P_0 + \epsilon P_1 + \epsilon^2 P_2 + \ldots$ If we separate orders, we obtain :

$$\left\{ \begin{array}{lll} o(1) & P_0 & = \quad R \; A_{in} \; U_{fwd} \\ o(\epsilon) & P_1 & = \quad -\frac{dP_0}{d\sigma} = -R \; A_{in} \; \frac{dU}{d\sigma} \\ o(\epsilon^2) & P_2 & = \quad -\frac{dP_1}{d\sigma} = R \; A_{in} \; \frac{d^2U}{d\sigma^2} \\ & & \ldots \end{array} \right.$$

Then $Q_{out} = \frac{P - P_\infty}{R}$ and, since there are three output branches at the end of the system (bifurcation plus branch or trifurcation), $U_{windkessel} = \frac{Q_{out}}{3 \cdot A_{out}}$ where A_{out} is the diameter of the branch.

3.3 Simulation

The aim of the simulation is to calculate U_{out} given U_{in} with MATLAB. U_{in} is an array (velocity versus time) of approximately 150 points, obtained with the same protocol as the vasoreactivity test (measurements then averaging).

Forward / backward wave model : Since we have $U_{in} = U_{fwd} + U_{bwd}(t) = U_{fwd} + r \cdot U_{fwd}(t - 2 \cdot \tau)$, we calculate U_{fwd} and U_{bwd} by using a Fast Fourier Transform (FFT). This is a classic technique for equation with dephasing.

Windkessel model : The simulation presents no difficulty since the use of Savitsky-Golay filters in the programm `TCD9` provides us with the first and second derivatives of the velocity.

Parameters : All in all, we have 8 parameters.

A_{in}	A_{out}	C	R	P_∞	r	τ	θ
diameter	diameter	compliance	resistance	asympt. pressure	reflect. coeff.	delay time	delay time

3.4 Numerical results

3.4.1 First patient

The best results were obtained with the following parameters :

A_{in}	A_{out}	C	R	P_∞	r	τ	θ
0.3	0.428/3	0.3	0.01	60	0.4	15 ms	15 ms

The velocity curve we obtain is the following :

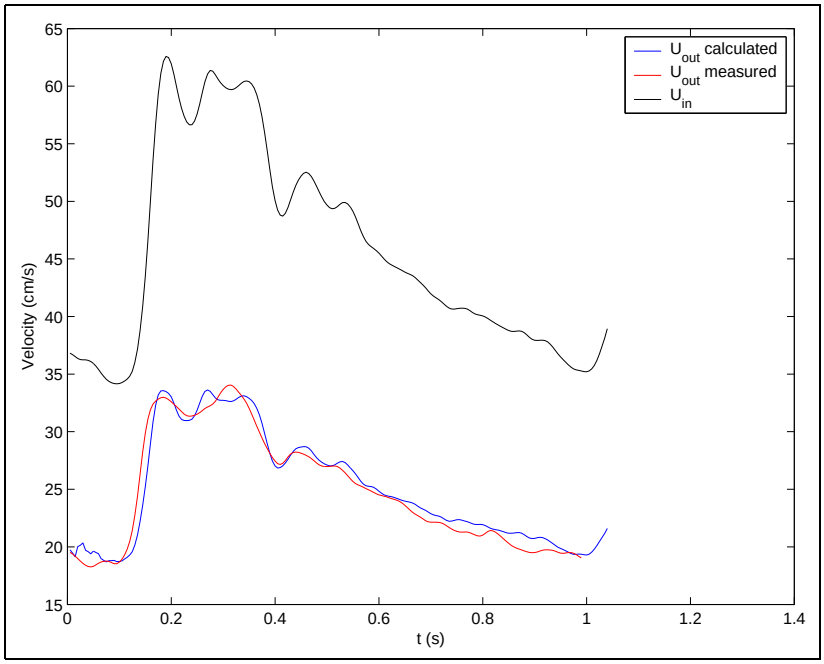

Figure 23: Comparison of the velocity measured and calculated in the distal MCA (patient 1)

3.4.2 Second patient

The best results were obtained with the following parameters :

A_{in}	A_{out}	C	R	P_∞	r	τ	θ
0.3	0.425/3	0.3	0.01	60	0.4	15 ms	15 ms

The velocity curve we obtain is the following :

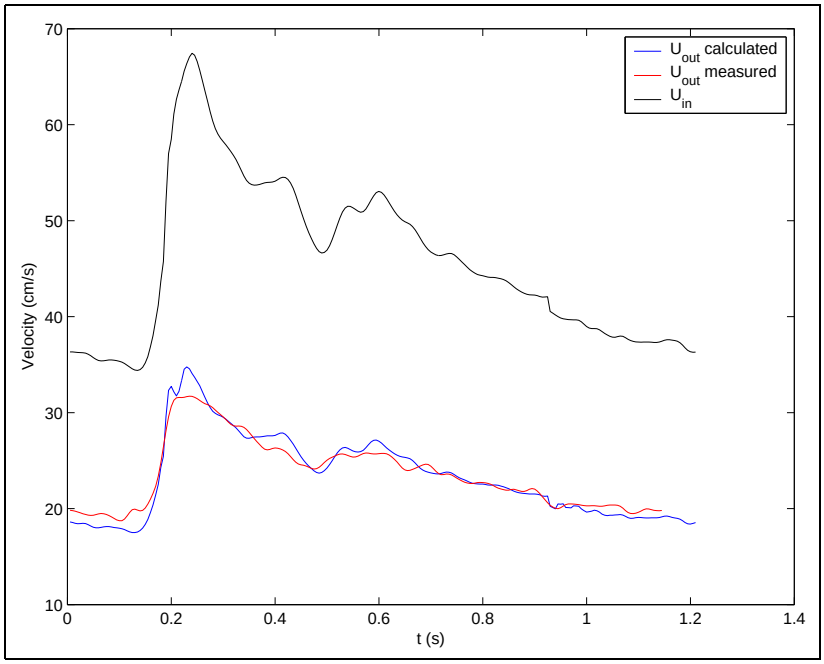

Figure 24: Comparison of the velocity measured and calculated in the MCA branch (patient 2)

3.5 Discussion

3.5.1 Values of the parameters

A_{in} and A_{out} : These values are coherent with the standard diameter of the MCA.

C : Arteries are, typically, 20 times less compliant than veins. The order of magnitude of the compliance of a systemic artery is 1 ml/mmHg ; it means that moving 1 ml of blood into the veins from the arterial circulation results in a pressure decrease of 1 mmHg. For the MCA, we found that the compliance is 10 times smaller. This is consistant with the idea that, when you go down the arterial tree, the vessels' compliance diminishes : compliance is decreased by movement outward in the arterial tree toward the arterioles, as their relatively thicker and more muscular walls resist stretch more effectively.

R **:** The effective resistance of the peripheral systemic circulation should be between 0.1 and 1 $mmHg \cdot s/cm^3$. Our value is really too low. This is the worst result of our model. However, high-resistance vessels are arterioles, so it is possible that the MCA is a low -resistance vessel.

P_∞ **:** This value only changes the level of the pressure curve; we cannot deduce something from it.

r **:** This large reflection seems to indicate an important reflection site down the arterial tree.

τ **and** θ **:** These two values show us two things : first, the fact that $\tau = \theta$ shows that this part of the model is quite coherent since the MCA measures 3 cm and our minimum dephasing value is 5 ms (due to the sampling rate of the TCD). Second, if we suppose that the wave speed is equal to the pulse wave velocity (which is approximately ten times that of flow velocity, several meters per second rather than centimeters per second), it follows that the reflection site is located $15 \cdot 10^{-3} s \cdot 10\ m/s = 15\ cm$ down the circle of Willis.

3.5.2 Limits of the model

First and foremost, our model gives us a value of $R \cdot C$ of $3 \cdot 10^{-3}$s, while our measurements gave us a fall-off time between 0.6 and 1 second for each measurement. The Windkessel part of our model is based on the observation of an exponential fall-off in the velocity curve, and the fall-off time of our RC-circuit should have matched the time constant of the measured exponential fall-off. This could mean that the MCA doesn't really acccount for the exponential fall-off.

Actually, as the pulse wave travels toward smaller arteries, we observe a damping of pulses : pulse waves are progressively damped in smaller vessels The reasons for pulse damping are the vascular resistance to blood flow (flow must distend the vessel ahead of it) and the compliance of vessels (the more compliance, the more volume is needed to raise pressure). So the damping is directly proportional to $R \cdot C$. In arteries, we have a high R and a high C (especially in the arterioles), whereas in capillaries we have a low R and low C (since their main function is exchange).

This mean that one reason for our problem, $R \cdot C \ll 1$, is that the MCA doesn't play a role in the damping of the pulse pressure wave.

Second, our model has been built with a disputable outflow condition for

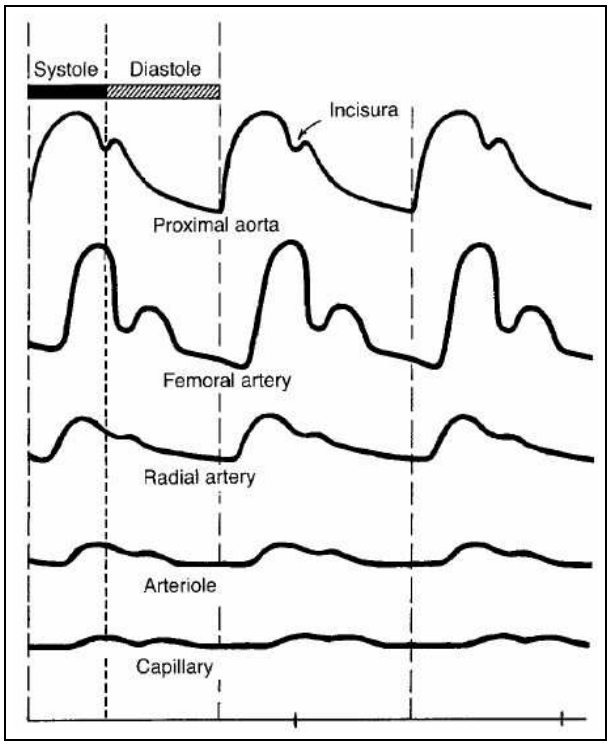

Figure 25: Changes in pulse pressure contour as the pulse wave travels toward smaller arteries ("damping of pulses") [4].

the blood flow, which states that the outflow only depends on the diameter of the distal arteries and is indifferent of outflow resistance. Unfortunately, it is very likely to be false, since the flow in the distal MCA can be expected to depend on the terminal branches of the arterial tree. This is the central problem in modelling the blood flow, and it would be better to determine a physiologically based boundary condition.

This modelization may be the reason why our time constant, $R \cdot C$, is too low : high downstream resistance has not been taken into account.

Third, the Windkessel model could be improved with the use of a CLR-circuit instead of a RC-circuit : then we would have two different time constants, $\sqrt{L \cdot C}$ and $\frac{L}{R}$. This may add a parameter of freedom allowing us to improve our model.

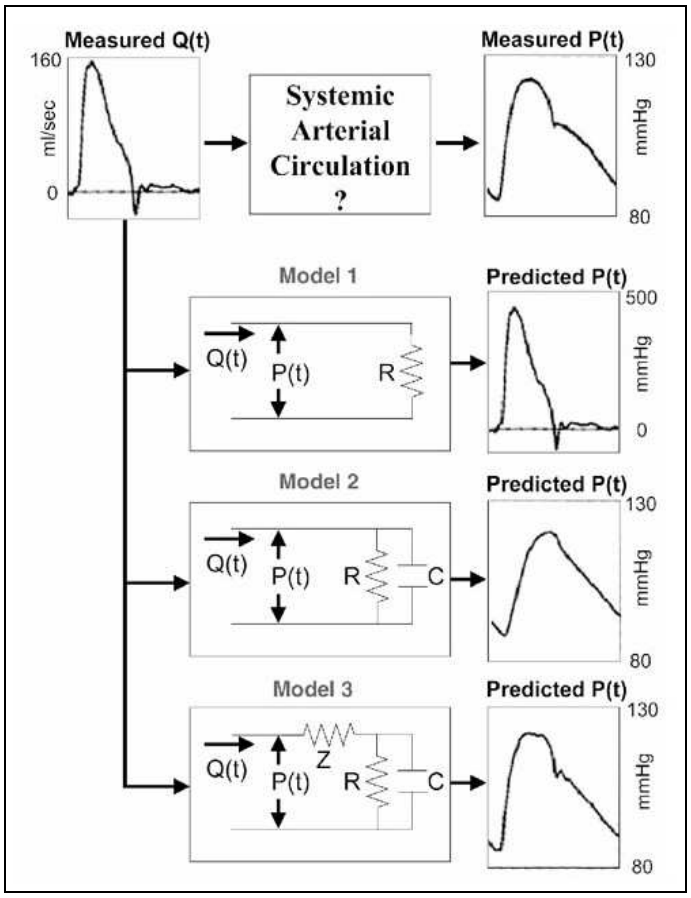

Figure 26: Various Windkessel models. Systemic circulation [1].

Conclusion

During this three-month period, the analysis of cerebral flows has shown mainly two things.

First, the use of TCD is a very efficient low-cost non-invasive way to analyze arterial problems, as long as the operator is sufficiently trained. We still need to understand the various characteristics of the velocity curve, but the results look promising. For example, we measured the blood velocity of the posterior carotid artery (PCA) during 20 seconds on a patient who closed his eyes during half of the time of the recording and opened it during the other half (figure 27).

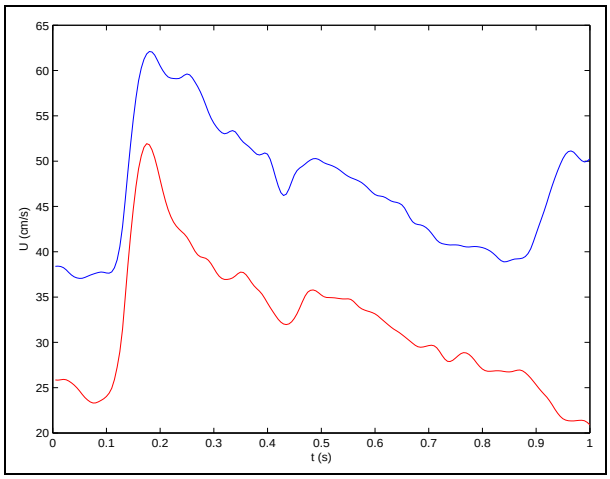

Figure 27: Velocity in the PCA (average) : red curve=eyes closed, blue curve=eyes opened.

This shows the sensibility of TCD measurements in some particular arteries, and suggests that TCD could be used for a wide range of applications, with the advantage of its non-invasiveness. However, our reproducibility study also demonstrates the sensitivity of TCD measurements to environmental and physiological changes, which must be taken into account when measurements are carry out, and outlines the need of extracting physiological explications out of velocity curves rather than relying on raw values.

Second, since it is too dangerous to place catheters in the blood vessels of the brain, simulations of flow in the brain require us to make strong hypothesis, which is what Prof. Parker called "making something out of nothing".

The hypothesis that the cerebral flow is, mainly, based on a Windkessel effect and reflection wave seems to be a good one, but we lack measurements to take other effects into account and to simulate the whole arterial circulation. For example, is a backward running wave a reflection or a forward wave from another artery going around the circle of Willis and propagating backward in the measurement artery ? Since there is direct communication of the waves in the cerebral arteries, it is much more difficult to interpret the experimental findings. Added to this is the impossibility of measuring pressure directly, and these are the reasons why, despite being one of the most important circulatory systems in the body, the cerebral circulation is one of the least understood.

The ability to predict blood flow and pressure at any position along the larger arteries of a patient could lead to a better understanding of the arterial function. Wave shapes of arterial pressure are strongly influenced by the wave reflections resulting from tapering of the vessels, bifurcations, changes in the arterial distensibility, and a high resistance in the arterioles (high downstream peripheral resistance). For example, the dicrotic wave is diminished in some patients suffering from diabetes or vascular diseases such as atherosclerosis. Therefore, comparison of velocity and pressure profiles at different positions could possibly be used for diagnostic purposes : to locate stenosis, certainly, and maybe, to detect cardiac valve malfunctions.

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