PRELIMINARY STUDY OF THE HEART RATE VARIABILITY AS A INDICATOR OF THE INTERACTION BETWEEN THE GLYCAEMIA REGULATION SYSTEM AND THE AUTONOMOUS NERVOUS SYSTEM

Pablo F. Viñas*, Lázaro Gorostiaga Cánepa*,
Enrique Baeyens Lázaro, Javier. Pérez Turiel** and José R. Perán González****

* *Biomedical Engineering Division of CARTIF. Valladolid, SPAIN*
(pabvin@cartif.es)
** *Department of Systems Engineering and Automatic Control*
Universidad de Valladolid. SPAIN

Abstract: There have been numerous improvements to optimize the insulin treatment of patients with Diabetes Mellitus during the last years. Several model-based algorithms to regulate the insulin flow from a pump, given a sensor measurement, have been developed. Our opinion is that this kind of algorithms can be improved with information about the state of the autonomous nervous system and in this way we could improve the treatment of these patients. A scheme of glycaemia regulation considering the influence of the Neuro-Endocrine system is proposed here. The results of a preliminary experiment designed to study the relationships between both systems is presented.

Keywords: Biomedical systems, Physiological models, Data acquisition, Feedback systems, Signal processing

1. INTRODUCTION

The metabolism includes all the physical and chemical processes of the body that generate and use energy.

The glucose is the more elementary and essential carbohydrate for life, because it is the initial component or the result of the main routes of metabolism.

The glucose is degraded when arrives to the cells, with the aid of oxygen, in the glucolysis process. The glucose is oxidized resulting in water (that could be eliminated or reused) and carbonic anhydride (that is exhaled by the breathing) as products of this reaction (Williams et al., 1984).

The body obtains energy in this way in order to perform all the activities that it requires. Under lack of this glucid, the essential proteins are metabolised to obtain energy and to avoid short term irreparable damages. Although if the cells are unable to catch glucose in the medium term, they will suffer serious consequences.

The concentration of glucose in the blood (glycaemia) is strictly regulated by a set of hormones that conform a complex regulatory system.

The insulin plays a fundamental role in this regulatory system due to the fact that it is the only hormone that facilitates the absorption of the glucose in certain tissues as the muscular and fatty ones. Since the insulin is the most important anabolic hormone of storage, it is not surprising that its secretion is controlled carefully in the organism. In this regulatory process there are a lot of substrates and hormones, as it has been shown on "in vivo" studies. The relation among each one of the controlling components and the insulin secretion is a complex phenomenon. In the first place, the duration of the stimulus, as well as its amount, determines the rate of the insulin secretion. In addition, a stimulus of fixed duration but variable intensity, gives a curve, dose-response, of liberation of the insulin of sigmoid morphology.

Diabetes mellitus includes a set of ***metabolic diseases***, characterized by the presence of elevated glucose levels in blood, that can be produced by:

- deficient insulin secretion
- resistance to the action of the insulin
- a mix of both phenomenons.

The treatment that is administered to the patients with type 1 diabetes mellitus (DM1)—associated with the deficient insulin secretion—and many of the patients with type 2 diabetes mellitus (DM2)—associated with the resistance to the action of insulin—consists of the

intensive administration of insulin (multiple doses each day). In this way the physician tries to maintain the glycaemic profiles in a narrow margin trying to mimic those of a normal person.

According to the Diabetes Control and Complications Trial (DCCT) Research Group (1993; 1996), most of the long-term complications associated with diabetes, such as nephropathy and retinopathy, result from sustained hyperglycemia (blood glucose exceeding 120 mg/dL). Hypoglycemia (defined as the condition of blood glucose concentrations less than 60 mg/dL, which is consistent with the DCCT range for low blood sugar) is a short-term concern because it starves the body cells of fuel. This condition is typically caused by the over-delivery of insulin and can lead to insulin shock as well as death.

There have been numerous improvements from the technical and technological point of view to optimize the treatment with insulin of patients with DM, as shown in the works presented by (Bellazzi et. al, 2001) and (Viñas et al., 2004), among others.

The most promising results are those related to the development of a closed-loop device capable of maintaining normoglycemia over extended periods of time, that could dramatically improve the quality of life for diabetic patients, see Fig. 1. A device of this type would contain three primary components: (i) a mechanical pump; (ii) an in vivo glucose sensor; and (iii) a mathematical algorithm to regulate the pump flow given a sensor measurement. Extracorporeal and implantable insulin pumps have been in service for over 15 years, and recent advances have made available programmable and variable-rate infusion pumps. (Parker et al. 2001)

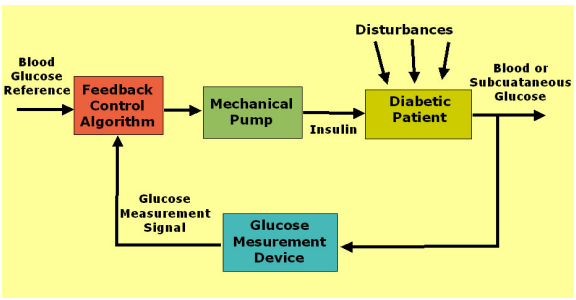

Fig. 1. Closed-loop device of glycaemia regulation system

In (Parker et al. 2001), an excellent compendium has appeared in addition to simulation results of an adaptation mechanism that updates the controller internal model. The result of the variability between the predicted glucose concentration and the measured patient glucose concentration is incorporated into the MPC with state estimation (MPCSE), and a MPC with state and parameter estimation (MPCSPE) algorithm updates selected model parameters through a Kalman filter at each time step.

Our opinion is that this kind of algorithms, that are based on models of the glycaemia regulation system, can be improved with information about the state of the autonomous nervous system and in this way we could improve the treatment of these patients. The rest of the paper is structured as follows: we begin presenting a revision of different works that studied the neurologic influence on the endocrine pancreas. Then, we will analyze a scheme of glycaemic regulation, explaining the physiological bases of the HRV (Heart Rate Variability) to relate both mentioned systems. Next, we will present a preliminary experiment that we have designed to study the relationships between both systems. Finally we will show the results that we have obtained.

2. NEUROGENIC INFLUENCE OVER THE ENDOCRINE PANCREAS

Since a major function of the endocrine pancreas is to control the levels and rate of utilization of various fuels in the body, it is reasonable to expect that any reflex secretions of the gland will be triggered by excesses, deficiencies, or rapid changes of these parameters.

(Woods and Porte, 1974) reviewed several works and concluded that several categories of reflexly elicited insulin secretion are mediated via the nervous system. In one of these, insulin is secreted when the brain detects an increase of glucose relative to the periphery. In another one, the presentation of food-associated stimuli (sight, taste, time of day, etc.) elicits insulin secretion even in the absence of a caloric challenge to the body. Finally, neurally elicited insulin secretion can be brought under stimulus control through learning.

More recently (Ahrén, 2000), studied the autonomic regulation of islet hormone secretion and explained that insulin secretion is stimulated by parasympathetic nerves or their neurotransmitters and inhibited by sympathetic nerves or their neurotransmitters. The islet autonomic nerves seem to be of physiological importance in mediating the cephalic phase of insulin secretion, in synchronising the islets to function as a unit allowing oscillations of islet hormone secretion, and in optimising islet hormone secretion during metabolic stress, *e.g.* hypoglycaemia and neuroglycopenia.

He also explained that there are four different neuro-transmitters localised into islet parasympathetic nerves (acetylcholine, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating polypeptide and gastrin realeasing peptide), which are all released by activation of the vagus nerve and that stimulate insulin and glucagon secretion. Therefore, all of them could contribute to vagally induced stimulation of insulin and glucagon secretion. The four potential parasympathetic neurotransmitters activate islet signalling mechanisms which are partially different. The relative contribution of the four neurotransmitters to the islet hormone responses to vagal nerve activation is not known and needs to be established.

The Sympathetic nerves innervate the islets. Three are the neurotransmitter candidates localised into these nerves and released on their activation (noradrenaline, galanin and the neuropeptide Y). Activation of the sympathetic nerves inhibits basal and glucose-stimulated insulin secretion. Although mediation of this effect by noradrenaline has been established, mediation of the inhibited basal insulin secretion is still not established. Furthermore, the relative contribution of galanin and the

neuropeptide Y to islet effects of the sympathetic nerves is also still to be established.

In (Ahrén and Holst, 2001) another study is presented. This paper showed that the autonomic nerves are essential for the majority of the preabsorptive insulin response to meal ingestion in humans, explaining 70% of the initial 10-min. response, and that this effect involves both cholinergic and noncholinergic mechanisms. They conclude that the autonomic nerves are of major importance for the early islet hormone secretion after food ingestion and for the preservation of glucose tolerance in humans through both cholinergic and noncholinergic mechanisms. Based on this finding, they suggested that a failure of islet innervation might contribute to the development of glucose intolerance, and finally proposed that augmentation of neural-induced insulin secretion might be a target for treatment of islet dysfunction in diabetes.

3. NATURAL STRUCTURE OF REGULATION OF THE BLOOD GLUCOSE CONCENTRATION

Insulin is the primary regulator of glucose homeostasis. It is secreted by pancreatic B-cells into the portal vein in response to a rise in glucose concentration. Before reaching the systemic circulation, it passes through the liver, where a consistent fraction, approximately 50%, is degraded. The residual insulin reaches the target organ or tissues, such as muscle and adipose tissue, where it exerts its hypoglycaemic action—before being eliminated by the liver and other organs, such as the kidney. Insulin action depends on insulin concentration in proximity of the insulin-sensitive cells. This is the result of three processes: pancreatic secretion, hepatic extraction, and insulin kinetics (Carson and Cobelli 2001)

Mechanics of glucose control on B-cell secretion are complex and involve a number of events at the molecular level.

The model of insulin secretion presented in the book of Carson and Cobelli (2001) was developed by Licko. It is based on the theory of the threshold secretory mechanism. Two assumptions underlie this theory: 1) a threshold control of glucose on insulin secretion, meaning that glucose concentration is able to stimulate insulin secretion only if it exceeds a given threshold; and 2) the existence of populations of B-cells (packets) having different sensitivity to the glucose stimulus, or different glucose thresholds. This theory has emerged from the analysis of experimental data obtained in the isolated perfused rat pancreas, in absence of any feed-back effect of insulin on glucose (open-loop condition). In these experiments, glucose concentration was varied at the inflow to reproduce specific glucose patterns like a step, a staircase, and a ramp. Insulin, which was not present at the inflow, was present at the outflow because of the pancreatic secretion stimulated by glucose.

(Sorensen, 1985) analyses the sympathetic and parasympathetic nervous system. He explained that both branches may play important roles in the modulation of insulin release. The islets of Langerhans are enervated by sympathetic fibres from the greater and lesser splanchnic nerves.

Based in the previously mentioned works we propose a scheme of the glycaemia regulation considering the influence of the Neuro-Endocrine System, see Fig 2.

The main components of the regulatory scheme are the Neuro-Endocrine System, the Pancreas and Circulatory System.

We consider that, given its structure, the glycaemia regulatory system resembles a Distributed Control System (DCS).

Another consideration done was that the pancreas is similar to a Split-Range-Controller, which from the measurement of glycaemia generates the control signal on the subsystems of Insulin and Glucagon.

Also we suppose the existence of a feedback control with a fixed reference who acts upon the insulin and glucagon secretion in inverse form.

Finally we consider that the Neuro-Endocrine System has a feedforward action on the glycaemia regulation that diminish the effects of the disturbances, in order to keep the levels in a narrow rank.

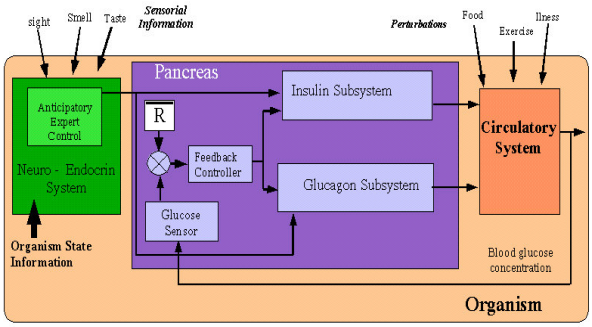

Fig. 2. Diagram of regulation of the blood glucose concentration

4. PHYSIOLOGIC BASIS OF HEART RATE VARIABILITY (HRV)

Blood circulation is a periodic process, caused by a cyclic activity of the heart. Its unit of measurement is one heart cycle. A heart period (**HP**) is a length of the heart cycle. Heart rate (**HR**) is inversely proportional to the heart period. Both indexes are the fundamental characteristics of blood circulation.

Although cardiac automatism is intrinsic to various pacemaker tissues, the heart rate and rhythm are largely under the control of the autonomic nervous system

Efferent sympathetic and vagal activities directed to the sinus node are characterized by a discharge that is largely synchronous with each cardiac cycle and that can be modulated by central (vasomotor and respiratory centres) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators. These oscillators generate rhythmic fluctuations in efferent neural discharge that manifest as short- and long-term oscillation in the heart period, they are known as High Frequency (HF) and Low Frequency (LF), respectively. Analysis of these rhythms may permit inferences on the

state and function of (a) the central oscillators, (b) the sympathetic and vagal efferent activity, (c) humoral factors, and (d) the sinus node.

An understanding of the modulatory effects of neural mechanisms on the sinus node has been enhanced by spectral analysis of HRV. The efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic manoeuvres such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. More controversial is the interpretation of the LF component, which is considered by some as a marker of sympathetic modulation (especially when expressed in normalized units) and by others as a parameter that includes both sympathetic and vagal influences. This discrepancy is due to the fact that in some conditions associated with sympathetic excitation, a decrease in the absolute power of the LF component is observed. It is important to note that during sympathetic activation the resulting tachycardia is usually accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation.

5. STUDY OF THE HRV DURING BREAKFAST

1.1 Methodology.

We recruited 13 individuals, of which 8 were women and 5 were men. All individuals were between 25 and 34 years old. Each one was invited to have breakfast in our laboratory for three days. They were instructed to arrive each morning without having eaten in order to have breakfast.

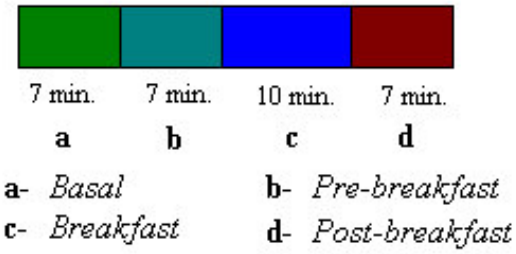

Fig. 3. The 4 stages of each experiment

Each experiment was divided in 4 stages, as can be shown in Fig. 3.

- The *Basal* stage serves to establish the initial state of each individual.
- The Pre-breakfast stage during which the food is presented to the individuals, so they can see and smell it but not to ingest the food.
- The Breakfast stage during which the individual ingests the food.
- The Post-breakfast stage serves to establish the final state of the individual.

For each one of these 4 stages the electric activity of the heart (ECG) of each individual was recorded in derivation II, using a data acquisition system (Biopac System, model MP100).

The sampling rate was chosen equal to 2 Khz and the higher frequency of the pass band filter was selected to 500 hz.

The AcqKnowledge 3.7.3 software included with the Biopac System was used for the detection of R events of the ECG signal, This signal was stored in digital format. This registry was processed off-line with a software (HRV Spectral Analyzer) developed under Matlab 5.3.

The HRV Spectral Analyzer calculates the spectral indices that were presented in the work of the (Task Force, 1996) and is based on the recommendations made by (Garcia, 1998) and the work of (Fumis and Viñas, 2002).

Table 1 **Selected frequency domain measures of HRV Analysis of short-term recordings (5 min)**

Variable	Description	Frequency range
5 min total power	The variance of RR intervals over the temporal segment	Approximately≤ 0.4 Hz
VLF	Power in very low frequency range	0·04 Hz
LF	Power in low frequency range	0·04–0·15 Hz
LFnorm	LF power in normalised units LF/(Total Power–VLF) *100	
HF	Power in high frequency range	0·15–0·4 Hz
HFnorm	HF power in normalised units HF/(Total Power–VLF)*100	
LF/HF	Ratio LF [ms2]/HF [ms2]	

1.2 Results

The Spectrogram of the RR signal for the 4 stages during the first breakfasts for the individual Nº 10 is shown in Fig. 4.

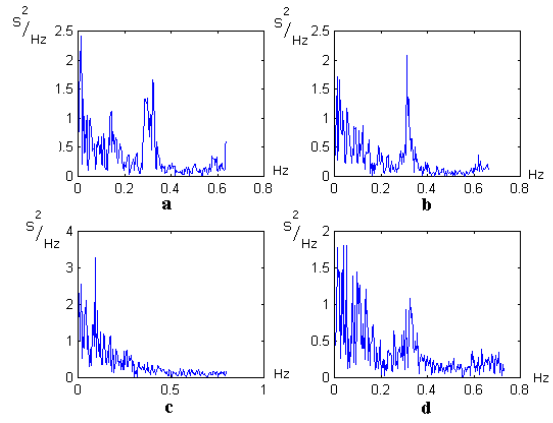

Fig. 4. Spectrogram of signal RR for the 4 stages during the first breakfast

For each patient the average RR and the indexes of the spectral analysis were calculated at each stage, then the average of all the values was computed. These results are presented in Table 2.

Table 2 **Average value of the: average RR, the relation LF/HF, value Lfu and value Hfu of all the individuals and standard deviation**

	Basal	***Pre-breakfast***	***Breakfast***	***Post-Breakfast***
Mean of RR [s]	0.8777	0.8652	0.7539	0.8142
Standard deviation	0.1811	0.1746	0.1280	0.1458
LF/HF	1.0119	1.0468	1.2393	1.1252
Standard deviation	0.3990	0.3892	0.3294	0.3554
LFnorm	0.4807	0.4918	0.5396	0.5105
Standard deviation	0.1084	0.0924	0.0652	0.0888
HFnorm	0.5138	0.5019	0.4526	0.4808
Standard deviation	0.1058	0.0918	0.0686	0.0909

The values of the table in graphical form are showed in figures 5 to 8.

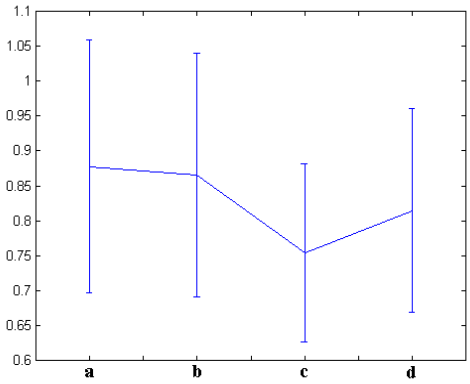

Fig. 5. RR mean value for the whole 13 individuals. Vertical segment shows the Standard deviation

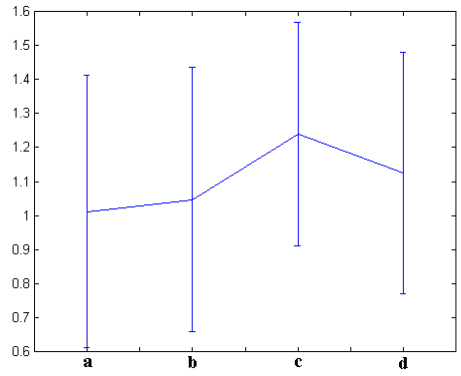

Fig. 6. LF/HF mean value for the whole 13 individuals. Vertical segment shows the Standard deviation

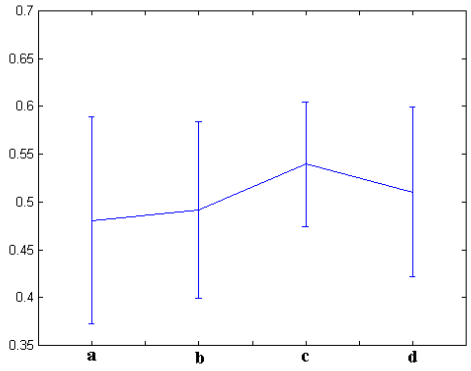

Fig. 7. LFnorm mean value for the whole 13 individuals. Vertical segment shows the Standard deviation

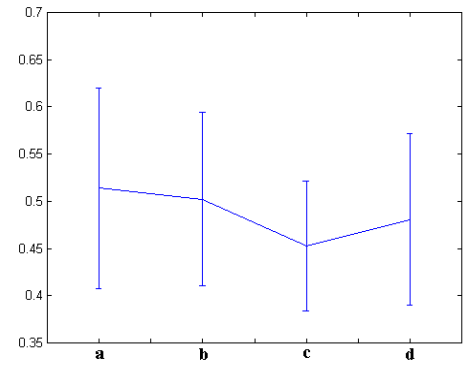

Fig. 8. HFnorm mean value for the whole 13 individuals. Vertical segment shows the Standard deviation

By taking into account the values of the indexes (mean of RR, LF/HF, Lfnorm, Hfnorm) obtained for each one of the stages as "matched samples", it is posible to calculate the significance indexes for the null hypothesis.

A value of 0.01 was defined as limit for rejection of the null hypothesis. These values are presented underlined in tables 3, 4, 5 and 6.

Table 3 **Significance indexes (P) for the Mean of RR**

P	***Basal***	***Pre-Breakfast***	***Breakfast***	***Post-Breakfast***
Basal		5,740E-02	2,893E-12	4,000E-08
Pre-Breakfast			6,179E-12	3,13E-006
Breakfast				2,340E-11
Post-Breakfast				

Table 4 **Significance indexes (P) for the LF/HF**

P	*Basal*	*Pre-Breakfast*	*Breakfast*	*Post-Breakfast*
Basal		2,399E-01	4,246E-04	8,700E-03
Pre-Breakfast			3,693E-04	5,520E-02
Breakfast				3,690E-02
Post-Breakfast				

Table 5 **Significance indexes (P) for the LFnorm**

P	*Basal*	*Pre-Breakfast*	*Breakfast*	*Post-Breakfast*
Basal		3,375E-01	1,700E-03	2,820E-02
Pre-Breakfast			8,657E-04	1,074E-01
Breakfast				3,290E-02
Post-Breakfast				

Table 6 **Significance indexes (P) for the HFnorm**

P	*Basal*	*Pre-Breakfast*	*Breakfast*	*Post-Breakfast*
Basal		2,399E-01	4,246E-04	8,700E-03
Pre-Breakfast			3,693E-04	5,52E-002
Breakfast				3,690E-02
Post-Breakfast				

6. CONCLUDING REMARKS

The influence of the SNA on the regulation of glycaemia is still not totally clarified. New results who help to clarify these relationships can have much importance in the improvement of the diagnosis and treatment of individuals with alterations in the metabolism.

In the results of the experiment a remarkable diminution of the HF band on the spectrogram of the stage, Fig. 4 c, can be observed. Also, it can be noted the inverse variation of the LFnorm index and HFnorm index during the experience.

Through a view point of the "simpatic-vagal" balance, at the moment of the ingestion it can be observed an increase of the simpatic activity and a depression in the vagal activity.

It would be interesting to study the variations of the indexes in relation to the insulin and glucose blood concentrations.

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