DIABETES COMPLICATIONS
Development of a New Tool for Obliterating Arteriopathy of the Lower Limbs Detection

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Abstract: Obliterating arteriopathy of the lower limbs (OALL) is a common complication in diabetes. This vasculopathy, which is associated with mild injury and with the diabetic neuropathy, is the source of diabetic foot ulcers which precede approximately 85% of amputations. Simple measures may avoid this dreaded complication if it is identified in time. OALL detection is currently undertaken by measuring ankle systolic pressure. The latter could be evaluated with microcirculatory technique but these techniques have a number of limitations: time consumption and cost. OALL detection is therefore limited to a small number of specialized units. In order to allow detection of OALL in ambulatory medicine, we propose a simple system based on photoplethysmography. The idea is to apply a pre-set "warning" pressure to the patient's toe and to optically check if arterial pulsation still exists. If not, the patient is directed to the adequate hospital unit for full diagnosis. This "warning" system which can easily be used at the general practitioner's office is meant to help detecting the OALL at an early stage, hence reducing the number of amputations. In this position paper, we present the system, some early results and we propose a discussion concerning the screening of OALL.

1 INTRODUCTION

Obliterating arteriopathy of the lower limbs (OALL) is a common complication in diabetes (between 17 and 21% of the diabetic population between 50 and 75 years old) (HAS, 2006). This vasculopathy, which is associated with mild injury and with the diabetic neuropathy, is the source of diabetic foot ulcers which precede approximately 85% of amputations (VALMI, 2008). The prevalence of amputations would be 1.3% of diabetic patients. Simple measures may avoid this dreaded complication if it is identified in time (Boccalon, 2004 – Girach, 2006), and one of the five-year objectives fixed by the Saint Vincent European Declaration is to reduce the rate of foot amputations among diabetic patients by 40%.

Given the extent of this issue and the objectives fixed, Alfediam, followed by HAS (French Health High Authority), recommend OALL screening among patients over 40 years old or having suffered from diabetes for over 20 years.

This detection is currently made by measuring ankle Systolic Pressure Index (SPI). This examination consists in measuring the humeral systolic pressure and the ankle systolic pressure. The SPI is simply given by the ratio of these two measurements.

These ankle examinations, however, are easily disturbed due to the common existence of mediacalcosis among diabetic patients (prevalence

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between 17 and 24% of diabetics). SPI could be evaluated with microcirculatory techniques (TcPO2 and Laser Doppler) which usually offer a reliable insight into the quality of distal vascularisation (Becker, 1989 – De Graff, 2003). But, these techniques have a number of limitations: time limits (45 mins) undervalue (15.01 euros) requiring a considerable initial investment (42000 € for a PERIMED brand microcirculation unit), precise interpretation requiring specialist expertise, and numerous limitations in the process itself (infection, oedema, general haemodynamic, etc). This situation has confined its use to rare specialist centres which are almost entirely based in hospitals, while these examinations have become essential for classifying and managing arteriopathy in diabetic patients.

Ankle SPI can be extremely perturbed by the presence of a mediacalcosis which leads to an over estimation of the SPI. In this case toe SPI can be used together with a clinical and Doppler examination (Moe, 2002 – Kröger, 2003 – Carter, 1996). The PERIMED system can be used for SPI measurement. However, due to its cost, its use is limited to a small number of specialized centres. Recently, the SysToe® system has been launched by Atys Medical. This equipment, based on photoplethysmography, is much more affordable (2500 €) but still too expensive for being used on a routine basis in the physicians office. Indeed, we recall that the number of amputations could drastically be reduced with a large scale screening of OALL.

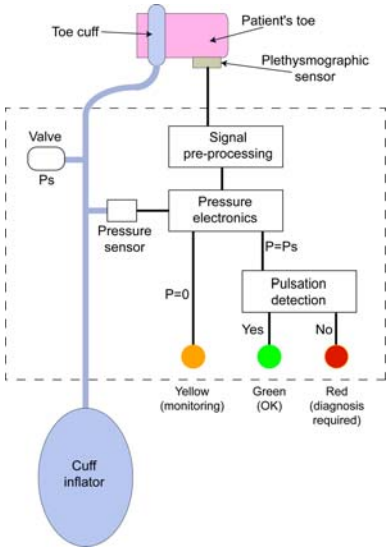

Figure 1: Description of the device.

In order to allow detection of OALL in ambulatory medicine, we propose a simple system based on photoplethysmography. The new concept consists in applying a pre-set "warning" pressure to the patient's toe and to optically check whether arterial blood circulation is observed or not. If not, the patient is directed to the adequate hospital unit in order to undergo specialized diagnosis. This "warning" system which can easily be used at the general practitioner's office is meant to help detecting the OALL at an early stage, hence reducing the number of amputations.

2 DESCRIPTION OF THE DEVICE

We recall that our system is a "warning" system used to screen the possible existence of an OALL. The principle consists in applying a "warning pressure" to the patient's toe and to check whether or not an arterial circulation is detected. A schematic description of the device is shown in figure 1. It consists of a pneumatic and an electronic part that are connected together *via* a pressure sensor. First of all, the physician places the toe cuff and the photoplethysmographic sensor onto the patient's toe. The signal delivered by the optical sensor is pre-processed in the pre-processing unit (see next section).

At that moment, the cuff inflator has not yet been used and the pressure in the pneumatic circuit is zero. When the pressure is zero, only the driving of the yellow LED is enabled. It pulsates at the patient's heart rate and acts as a sensor position monitor. Indeed, when the yellow LED is pulsating the physician knows whether the sensor is correctly installed or not.

Now that the optical sensor is correctly installed, the physician uses the cuff inflator in order to reach the "warning pressure" value. Let us call it Ps. A calibrated valve is used to adjust the pressure to the "warning" value. When the pressure Ps is reached, the pressure electronics disables the yellow LED and enables the pulsation detection unit. (Arterial pulsation is detected by comparing the signal to a threshold value that has been determined with healthy volunteers.) Now, if an arterial pulsation is detected, the green LED is switched on; everything is alright with the patient. Conversely, if no pulsation is detected, the red LED is switched on and the patient is addressed to a specialized hospital unit for further diagnosis.

Note that for the moment, and according to the very little literature, the "warning" pressure is set to

70 mmHg (Boccalon, 2004 – De Graff, 2003 – Johanson, 2002). The actual value will have to be confirmed with clinical trials we are setting up at the moment.

3 EXPERIMENTAL RESULTS

3.1 Signal Pre-processing and Pulsation Detection

3.1.1 Signal Preprocessing

While reading the above mentioned description one could think that everything is trivial in this system. However, photopletysmographic sensors are used to measure absorption of light into the tissue. In order to detect arterial pulsation, we must be able to measure the small absorption variation due to arterial blood only. Therefore, the signal to noise ratio at the direct output of the optical sensor is quite low. Furthermore, the optical sensor also detects variations of light that can be due to patient's movements or changes in the ambient light.

A signal pre-processing is therefore required. In what follows, we briefly describe the signal processing we used. The rest of the electronic circuitry is somehow more conventional and the description of it may lengthen this paper.

Figure 2 shows the signal pre-processing we developed.

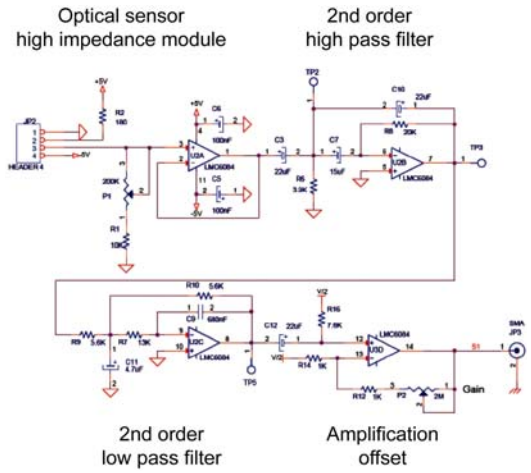

Figure 2: Signal pre-processing.

Right after the optical sensor head, we use a high impedance follower in order to reduce the influence of noise. The signal obtained at the output of this stage is shown in figure 3(a).

At that stage, the signal exhibits a slowly varying offset due to patient's movements and variations in the ambient light. A second order high pass filter (cut-off @ 1 Hz) is used to cancel this varying offset. The result is shown in figure 3(b).

Here, the signal is somehow independent of external perturbations but is still quite noisy. The noise is now rejected by means of the second order low pass filter (cut-off @ 10 Hz).

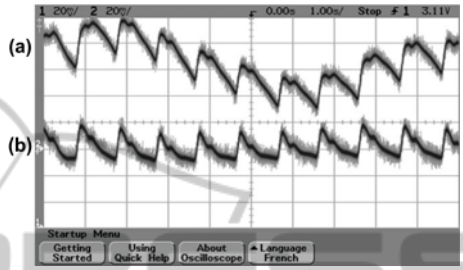

Figure 3: Detail of the signal pre-processing. (a) at the optical sensor and follower output. (b) at the high pass filter output.

Finally, a ×100 gain amplifier is used and an offset is added in order to centre the signal around 6 Volts, a value compatible with the rest of the electronic circuit. Figure 4 summarizes the signal pre-processing. Figure 4(a) shows the signal after the follower while figure 4(b) shows the signal after pre-processing. It can be noted that the signal issued from the optical sensor looks different between figure 3(a) and 4(a). This difference arises because the sensor is not placed exactly the same way between the two measurements. This is not a problem because signal filtering changes the signal shape (frequency filtering). At the end, the signal always looks like figure 4(b) after signal processing. This shows that the device is independent not only of unwanted movements or light variations, but also of placement inaccuracies.

A last amplification (not shown in the figure) is used in order to set the signal to an amplitude compatible with the rest of the electronic circuit.

3.1.2 Pulsation Detection

Pulsation detection consists in comparing the pre-processed signal with a reference voltage. This reference voltage was determined after tests conducted with healthy volunteers. In figure 5(a), a pressure of 60 mmHg was applied to the toe. With this pressure, arterial pulsation still exists. In particular, maxima of the signal are greater than the reference voltage. In this case, the green LED is switched on. Conversely, when the pressure is 100

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mmHg, the signal is lower than the reference voltage. Here, the red LED is switched on.

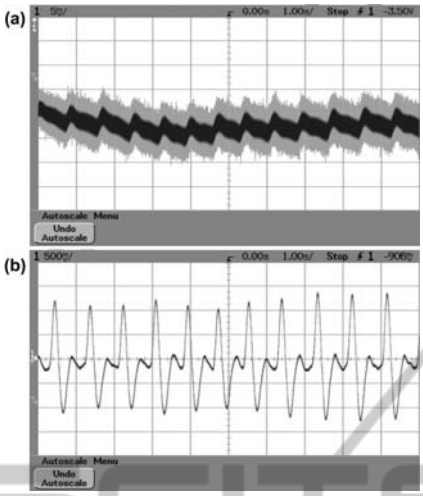

Figure 4: Comparison between the signal issued from the sensor (a), and the signal obtained after pre-processing (b).

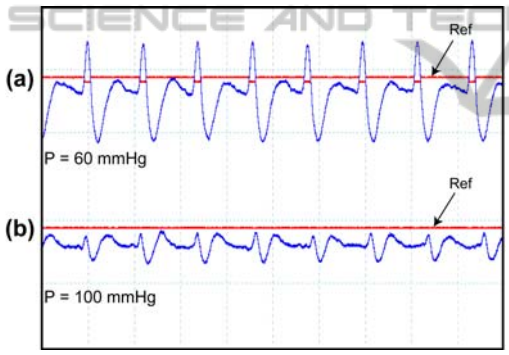

Figure 5: LEDs driving. (a) Pressure=60 mmHg, signal crossing the reference voltage, green LED is switched on. (b) Pressure=100 mmHg, the signal not crossing the reference voltage, red LED is switched on.

3.2 Experimental Device

The device is shown in figure 6.

Toe cuff, optical sensor and cuff inflator are not shown in the figure. These three elements were purchased from Hokanson:

- Infra-red photoplethysmographic sensor: COPPHO
- Toe cuff: UPC2.5
- Cuff inflator: DS400

All the electronic circuits were made using surface mounted components in order to reduce the size of the device.

On figure 6, we can see that we used an external power supply. Of course, this device is not the final one. In the last version, batteries will be used instead of the external power supply. Also, for this intermediate version, SMA connectors have been included in order to monitor different signals at strategic points of the electronic circuit. These measurements were used to define the reference voltage mentioned above and to tune the offsets and the gain of the amplifier to an appropriate value.

The device can be operated in two ways for clinical trial purposes. We mentioned above that the monitoring yellow LED is driven only when the pressure is zero. Conversely, when the "warning" pressure is applied, only the red and green LEDs are driven. This configuration corresponds to the normal used in ambulatory medicine.

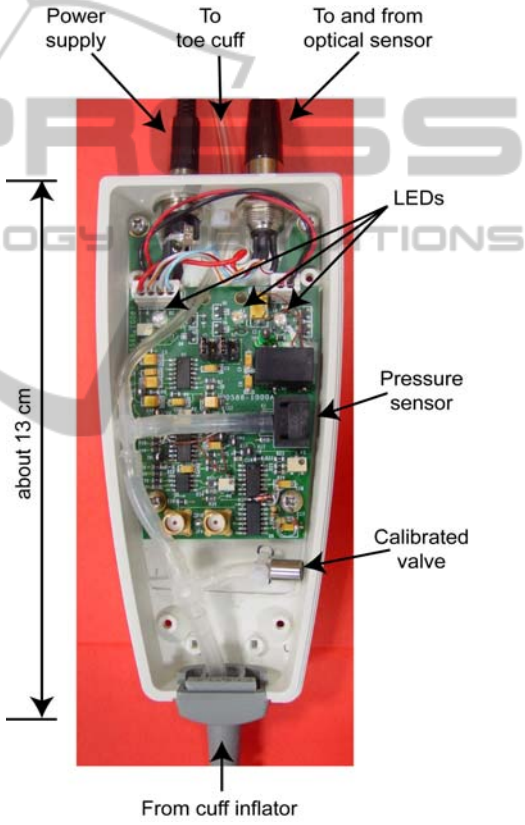

Figure 6: Experimental device.

However, clinical trials imply various experimental configurations. For the first clinical trial (to be described in the next section) the pressure sensor must be disconnected. Therefore, we also design the electronic circuit so that this configuration can be used. In this case, the three LEDs are driven simultaneously.

3.3 First Clinical Trials

Clinical trials for this device can be separated in

three parts.

In a first time, we have to check whether or not the measurements made with our new device are consistent with what is observed with the gold standard technique. In a second time, the intra-operator and inter-operator stability of our system will be evaluated. These two first trials are conducted at the Besançon University Hospital, with the assistance of the cardio-vascular surgery unit and the diabetology unit. These trials are performed with patients suffering of various grade of OALL. Finally, clinical trials in physician's office with any kind of patients will be done and the screening result will be compared with diagnosis made at the hospital.

Up to now, only the first step has been passed. Patients were first tested with conventional Doppler technique. Their toe systolic pressure was recorded for both toes.

Then, they were tested with the new device. For this, discrete pressure values were applied to their toe according to the systolic pressure measured before. The pressures ranged from 50 mmHg above the systolic pressure down to 50 mmHg below with 10 mmHg steps. To do this, the pressure sensor in our device was disabled as explained above. In order to control the pressure values, we used the Hokanson compressor (ref. AG101) and the corresponding pressure regulator (ref. E20). Some results are summarized in figure 7.

	Patient N°	12		16	
	Side	Right	Left	Right	Left
Toe pressure (Doppler)		102	106	53	47
New device measurements	170				
	160		OK		
	150	OK	OK		
	140	OK	OK		
	130	OK	OK		
	120	OK	OK		
	110	OK	OK		
	100	OK	OK	OK	OK
	90	OK	OK	OK	OK
	80	OK	OK	OK	OK
	70	OK	OK	OK	OK
	60	OK	OK	NNNNN	OK
	50	OK		OK	OK
	40			OK	OK
	30			OK	OK
	20			OK	OK
	10			OK	OK
	0			OK	OK

Figure 7: Some examples of measurements made during the first clinical trial step.

The colours of the cells correspond to the colour of the LED lighting during the test. For example, for patient 12 right toe, the red LED was on from 150 to 110 mmHg and the green was on from 100 to 50 mmHg. If we compare to the systolic pressure measured by means of the Doppler equipment, we see that the behaviour of our device is correct because the LEDs switch from red to green when the pressure steps from 110 to 100 mmHg. This is indicated by the "OK" appearing in the cells. The same behaviour is observed with the left toe when the pressure steps from 110 to 100 mmHg.

However, discrepancies are sometimes observed. This is illustrated with patient 16 right toe were the LED should have been red for 60 mmHg. This discrepancy is indicated by the "NNNNN" in the cell. Up to now, we are still analysing the complete set of data (new device and Doppler records) in order to fully understand this aspect.

4 SHORT DISCUSSION

We still have to finish the clinical trials before deciding of the benefit of this method. Questions or problems to be solved are:

- understanding the discrepancies that occur sometimes
- investigating the possibility to use digital electronics instead of analog technique
- defining an actual "warning pressure"
- investigating the intra or inter operability
- conducting the final clinical trials.

In the case of success with these aspects, EC labelling is foreseen before any commercialization.

However, we recall that up to now, there is no means of screening OALL. The only devices commercially available concern the measurement of the systolic pressure index (SPI) which is more a diagnosis than a screening technique. Furthermore, the price of these systems restricts their use in specialized centres.

We think that detecting the presence or the absence of arterial pulsation when a "warning pressure" is applied to the patient is a potential alternative to the current cost effective and time consuming techniques. The market study we ordered shows that a device price of about 250 € would be accepted by most of the possible users. It is very likely that the device we propose can be sold at this low price, as long as it is fabricated at a scale large enough.

5 CONCLUSIONS

In this position paper, we proposed a new device

that could be used to screen OALL in ambulatory medicine. It is meant to be used by general practitioners but also by podiatrists. These professionals have been identified by a market study we recently ordered.

The principle is not to measure the systolic pressure index (SPI), as it is commonly done in specialized centres that can afford the expensive equipment required. The new concept simply consists in applying a “warning pressure” to the patient’s toe and to check whether an arterial pulsation is detected or not. If not, the patient is directed to a specialized centre for complete diagnosis.

First clinical trials show that our screening device is consistent with what is observed with conventional diagnosis techniques. However, full clinical trial programme should be concluded before deciding of the benefit of our method.

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