ANIMAL STUDIES USING AN OXYGEN-TENSION SENSOR FOR TISSUE VIABILITY MONITORING

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Abstract: Leakage at the site of an anastomosis is the main, yet unsolved reason for mortality in abdominal surgery. Every year, a large number of patients die due to anastomotic leakage after surgery. An objective aid to monitor the anastomotic site pre- and postoperatively and detect leakage at an early stage, is needed. Therefore, a miniature, wireless measurement system to detect tissue viability during and after colon surgery (continuously for 7 days) is being developed. The complete sensor chip should include an oxygen-saturation sensor (sO_2), an oxygen-tension sensor (pO_2), a carbon-dioxide tension sensor (pCO_2) and a temperature sensor. The present work focuses on the use of the oxygen-tension and temperature sensors for animal studies. Initial in-vivo measurements were carried out on the small and large intestines of male wistar rats. The main goal was to measure the distribution of pO_2 on the colon around the anastomosis and to determine the changes in pO_2 during repetitive ischemia-and-reperfusion experiments on the small intestine. The paper presents the obtained measurement results.

1 INTRODUCTION

An anastomosis is the surgical connection of two tubular segments to restore continuity (Figure 1). Leakage of a colorectal anastomosis is a complication in which intestinal content leaks into the abdominal cavity due to a "defect" in the anastomosis. This defect can be caused by a reduced oxygen supply and it can lead to cell death and necrosis of the anastomosis. As a result, leakage can occur and as a consequence, peritonitis may develop and can lead further to sepsis, multiple-organ failure

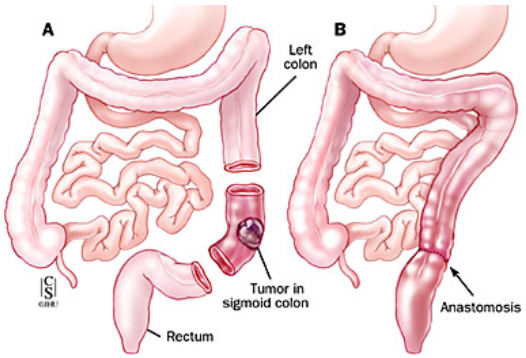

Figure 1: A colon anastomosis.

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and ultimately death. Therefore, anastomotic leakage of a colorectal anastomosis is considered a potentially lethal complication.

The reported incidence varies between 10 % and 13 % (Kanellos, 2004; Guenaga, 2003; Peeters, 2005), with a mortality rate that can be as high as 32 % (Choi, 2006). To date, no peroperative methods to avoid or predict anastomotic leakage, or any validated, objective parameters for detection of anastomotic leakage in an early postoperative phase, exist. Current diagnostic methods include observation of clinical signs and symptoms (fever and pain), while confirmation is obtained by imaging. These methods are faced with several disadvantages. When anastomotic leakage has progressed to a state of clinical manifestation, the patient is already ill and treatment needs to be initiated. Imaging modalities, more specifically abdominal CT-scans and/with contrast enemas, are normally used to confirm a clinical diagnosis of anastomotic leakage, meaning the patient is already ill (Eckmann, 2004).

At present, clinically relevant anastomotic leakage is usually diagnosed approximately 6 to 8 days after surgery (Kanellos, 2004; Alves 1999). Some studies report an even longer interval (12 days) between operation and diagnosis of anastomotic leakage (Hymann, 2007). The long intervals between the construction of the anastomosis and the diagnosis of anastomotic leakage are detrimental for the prognosis, increasing mortality rates (Macarthur, 1998).

Therefore, a biomarker reflecting the viability of the anastomosis, could be a fast and objective diagnostic tool in addition to current methods, allowing diagnosis of anastomotic leakage before its clinical presentation.

In this respect, the main goal of this research is to develop a miniature, wireless sensor system to monitor tissue viability pre- and postoperative, continuously for 7 days. The complete sensor chip should include an oxygen-saturation sensor (sO_2), an oxygen-tension sensor (pO_2), a carbon-dioxide tension sensor (pCO_2) and a temperature sensor (Figure 2).

The present work focuses on the use of the oxygen-tension and temperature sensors for animal studies.

2 MEASUREMENT SETUP

The measurement setup for the animal studies is shown in Figure 3. It consists of the pO_2 and temperature sensor block and a notebook for reading and processing the data from the sensors. The investigations were performed in the Erasmus Medical Centre in Rotterdam, using male wistar rats, 12 weeks old. They were prepared for surgery by shaving their abdomen and disinfecting it with 70% alcohol.

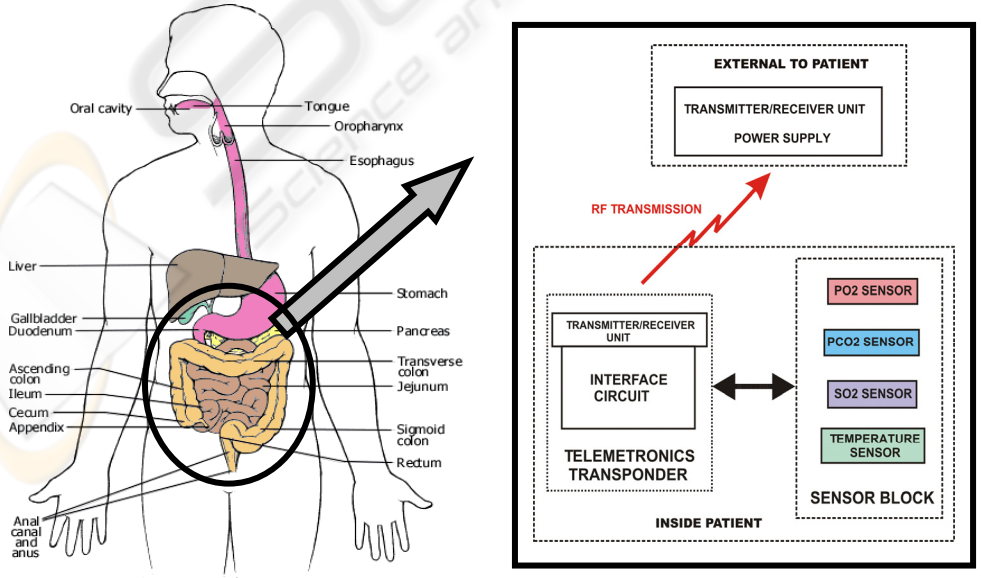

Figure 2: Schematic of the complete sensor system for tissue viability monitoring.

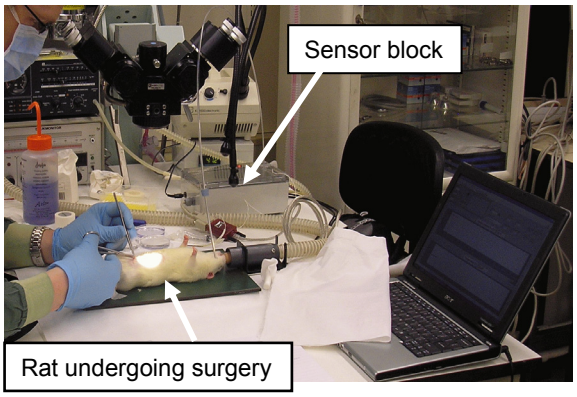

Figure 3: Measurement setup at Erasmus Medical Centre in Rotterdam comprising the sensor block and the notebook for data processing.

Afterwards, the animal undergoing surgery was placed on a hot plate and anesthetised throughout the intervention by administering a mixture of isoflurane, oxygen and air (the fraction of inspired oxygen, FiO_2=66 %). Access to the internal anatomical structures of the animals was gained by laparotomy (surgical incision into the abdominal wall) with an incision length of 4 cm. After opening the abdomen and exposing the ascending colon, the oxygen-tension and temperature sensors were fixed together and placed at pre-defined locations along the ascending colon, laterally (with respect to the peritoneal membrane) and antimesenterial (opposed to the peritoneal membrane).

The sensors were fabricated at TNO Quality of Life, The Netherlands (Draaijer, 1999) and they have been tested in a previous study (Tanase, 2007). The block diagram of the sensors is shown in Figure 4. The pO_2 sensor consists of a coating at the tip of an optical fibre (3 mm diameter) and works on the principle of dynamic quenching by oxygen of fluorescent particles immobilized in a gas permeable polymer. In our case, the fluorescent particle is ruthenium, which enters an excited state caused by the LED excitation with a wavelength of 470 nm. The excited state of ruthenium is deactivated by the collision process with oxygen, the particles emitting light with a wavelength of 600 nm. The emitted signals are detected by a photodiode (PD) and converted to a digital signal using an on-board analogue-to-digital (ADC) converter. The oxygen concentration is determined by measuring the fluorescence lifetime. In addition to the pO_2 sensor, the sensor block contains the temperature sensor (NTC type, *Farnell*), whose output is also converted via an ADC. The total sequence of data sent to the computer (via a serial connection RS 232) is BG, I1, I2 and T (the background, the two intensities at successive times and the temperature). From these data, the software (LabView, *National Instruments*) computes the oxygen tension and indicates the temperature.

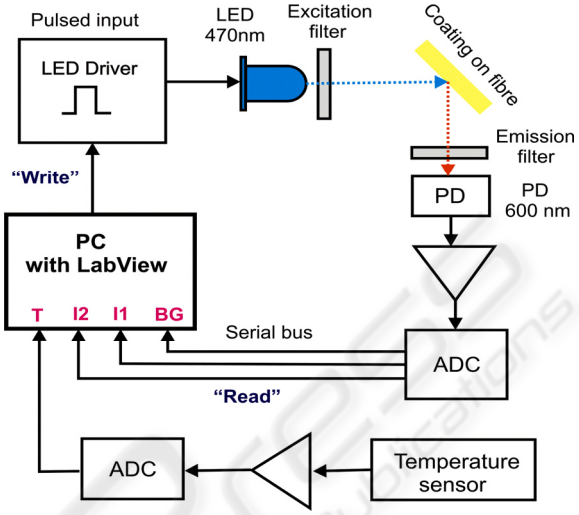

Figure 4: Schematic of the sensors with the LED driver circuit, the read-out of the photodiode and of the temperature sensor.

Figure 5 presents a photograph of the sensor block with the two sensors and a magnified view of the fibre tip with the oxygen-sensitive coating.

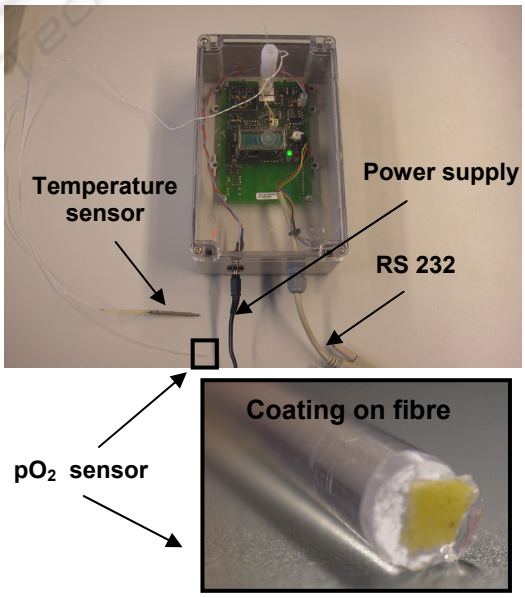

Figure 5: Photograph of the sensor block with the two sensors and a magnified view of the fibre tip showing the oxygen sensitive coating.

3 MEASUREMENT RESULTS

Initial tests were performed by placing the sensors on the colon after the construction of the anastomosis. Figure 6 shows the sensors at a distance of 1 cm away from the anastomosis, while Figure 7 presents the table and graph with the measurement results, for different sensor locations around the anastomosis. The sensors were placed radial (lateral and antimesenterial) and longitudinal, at ten different locations on both sides of the anastomosis, as indicated in Figure 7.

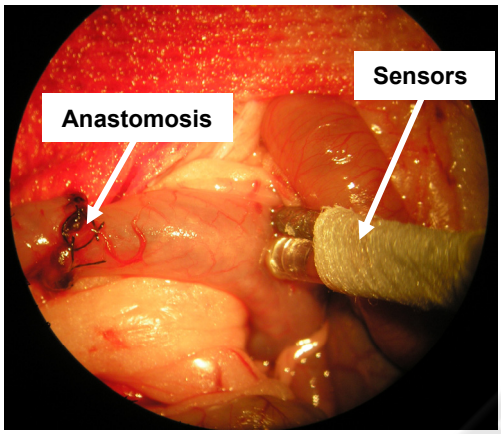

Figure 6: Photograph showing the sensors on the colon, 1 cm away from the anastomosis.

The lowest oxygen-tension values are obtained on the anastomosis (part 3 and part 8 in Figure 7). This is an expected effect - due to local cell death, tissue oxygenation at the site of the anastomosis is reduced. The farther from the anastomosis we measure, the better the oxygenation, and the higher the oxygen-tension values. The spikes on the graph are artefacts visible only at the moments when the sensors are moved from one tissue location to another, because then, for a short period of time, the fibre is in air. The temperature changes corresponding to tissue and air are visible on the temperature graph.

Another series of measurements were performed with the sensors on the small intestine (Figure 8). In this case, the blood supply to the central part of the small intestine was obstructed by two strings that were fastened for ischemia and released for reperfusion. The measurement results during the ischemia-reperfusion experiment are shown in Figure 9.

At the beginning of the test, the sensors were placed on the small intestine and by fastening the strings, the intestine was made ischemic (part 1). The values readily decreased to 4 mmHg, indicating total ischemia. Once the strings were released, an overshoot was noted, showing a maximum at 202 mmHg. Two other cycles were repeated to test the correctness of the measurement. Also in this case, the results of the tests met our expectations.

In addition to these measurements, other tests were performed by changing the levels of inspired oxygen (33.4 %, 42.8 %, 66.7 % and 91 %). We noted that the local pO_2 changed accordingly to the inspired oxygen. For an even better characterisation, a new series of tests is currently performed, during which the animals are intubated. In this way, the inspired oxygen can be accurately controlled, while the rats are being continuously monitored.

4 CONCLUSIONS

The paper has presented the initial measurements and results with an optical oxygen-tension sensor and a temperature sensor. The performed tests have shown that the principle of optical sensing is suitable for tissue measurements.

The first series of measurements has shown a significant decrease (approximately 40 mmHg) in pO_2 on the anastomosis as compared to the other measurement sites on the colon. It was also shown that on two points (lateral and antimesentery) of the anastomosis, the values for the pO_2 were approximately the same.

The ischemia and reperfusion experiments have shown that the sensor system reacted as expected to the local changes on the small intestine. When the intestine was made ischemic, the pO_2 decreased and when the obstruction was removed, the pO_2 increased significantly, with an overshoot.

This cycle was repeated three times to test the correctness and repeatability of the measurement.

LATERAL				ANTIMESENTERY			
#	Location [cm]	Start time [sec]	pO_2 [mmHg]	#	Location [cm]	Start time [sec]	pO_2 [mmHg]
1	1	100	152->126	**6**	1	4900	122->209
2	0.5	1600	126->112	**7**	0.5	5600	209->125
3	**On anastomosis**	**2050**	**112->43**	**8**	**On anastomosis**	**6400**	**125->38**
4	0.5	2900	43->85	**9**	0.5	7500	38->100
5	1	4000	85->122	**10**	1	8200	100->100

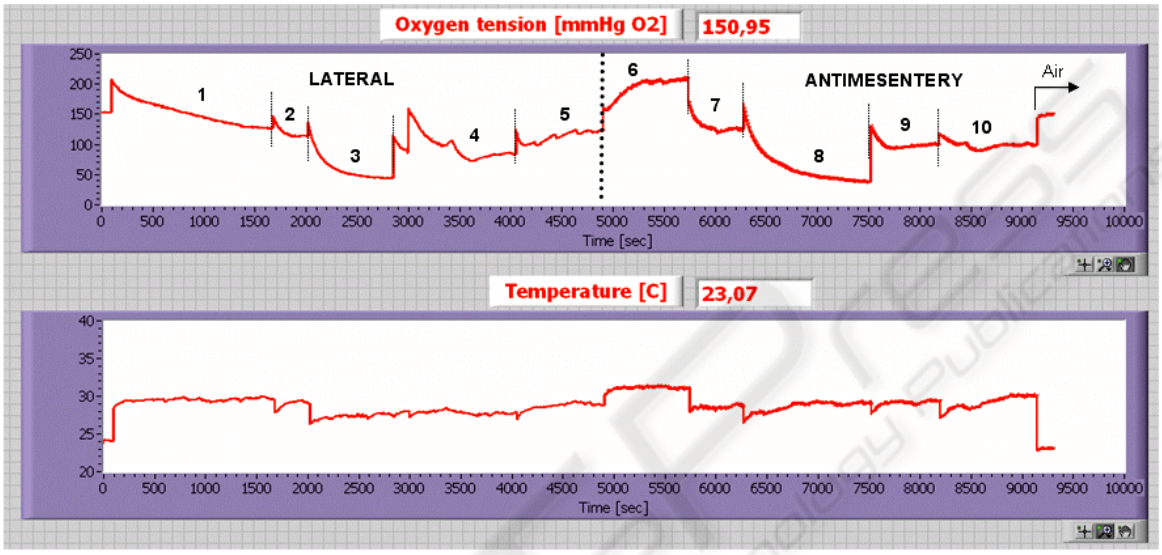

Figure 7: The numeric results and the graphical representation of the tests performed on the colon, to determine the distribution of the oxygen radially and longitudinally with respect to the anastomosis, at different locations.

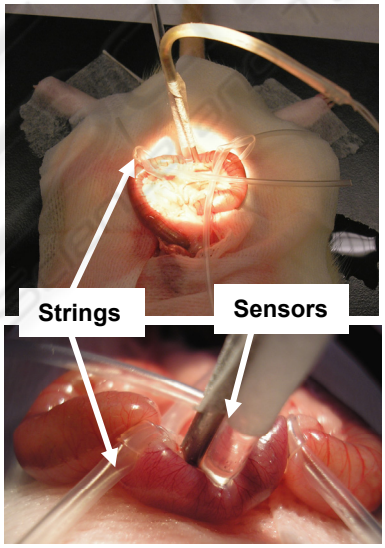

Figure 8: An overall view and a close-up of the small intestine showing the strings (used to obstruct the blood flow) and the sensors.

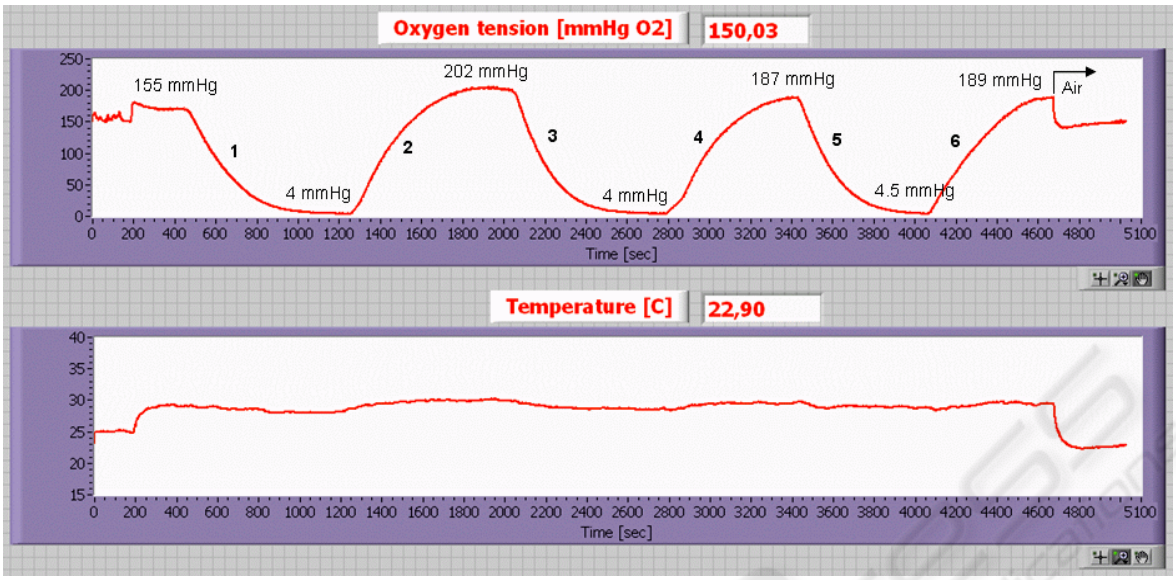

Figure 9: The graphical representation of the ischemia-reperfusion experiment on the small intestine.

Although not presented in this paper, the first steps towards an integrated sensor system have been taken. The sensor-system design is currently underway and issues regarding device sterilisation and packaging are already taken into account.

A new study is currently planned for more detailed investigations, considering also the aspects of biocompatibility.

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