Examining the effects of blood/material interactions on the performance of implanted glucose sensors

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Introduction: Contemporary implantable glucose sensing paradigms are only approved by the FDA for up to one week. An increasing body of research has suggested that interaction between the implanted tissue and the sensor is the main culprit in short sensor life [1]. Such early interactions between the sensor and the tissue are mediated by contact between the sensor surface and blood. To assess how this interface affects sensor performance, glucose sensors were immersed in both whole blood and blood constituents *in vitro*. Whole blood was found to attenuate sensor signals relative to platelet rich and platelet poor plasma, suggesting that protein adsorption has little effect on sensor attenuation. It was further shown that transport limits were not responsible for attenuation in whole blood, suggesting another route by which blood affects sensor response.

Methods: MiniMed implantable glucose sensors were graciously donated by the Medtronic Corporation for testing. Sensors were placed in a PBS solution spiked with a known solution of glucose at 37°C to gather a baseline sensor signal for two hours. Sensors were then moved into one of three different blood treatment categories: (1) whole blood, (2) platelet rich plasma (PRP) or (3) platelet poor plasma (PPP). All blood treatments had the same concentration of glucose as the PBS bath used for pre-treatment tests to ensure that any decrease in response is not due to an initial depleted supply of glucose in the blood. Heparin was added to all treatment types at a concentration of 5 units/mL to avoid thrombus formation and allow for long term monitoring. Sensors remained in these treatments for 16 hours to gather data and were then transferred back to the buffered glucose solution to see if a baseline pre-treatment signal could be restored.

An experiment was then performed to assess whether the decrease in sensor function was due to transport limitations, such as provisional matrix formation, or steric effects of cellular presence. Two sensors were submerged in a buffered glucose solution to gather a baseline signal for two hours. One sensor was then submerged for sixteen hours in whole blood with the same glucose concentration as the buffered solution. After sixteen hours, the blood submerged sensor was moved to the buffered solution and the buffer submerged sensor was moved to the blood. If the baseline signal could be restored on the blood submerged sensor, then the clot on the sensor surface would be shown to have no effect on glucose transport.

Results/Discussion: Figure 1 is a trace of glucose sensor values that have been submerged in whole blood, PRP and PPP. When normalized to pre-treatment values, sensor currents were found to only decrease in the case of whole blood immersion. Additionally, submersion of a sensor in PPP had no effect on sensor response. As PPP is composed mainly of blood borne proteins and small molecules, this finding would suggest that the protein layer formed around the implant via biofouling has little effect on retarding glucose transport.

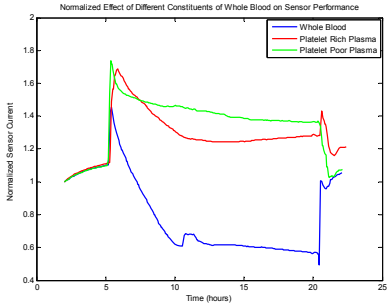

Figure 1: Plot of sensor attenuation for different blood constituent treatments. Treatment data are from 5-21 hours on the abscissa. All other data are from sensors submerged in buffered glucose solutions.

As Figure 1 clearly shows the effect of whole blood on sensor performance, Figure 2 further seeks to describe how blood affects sensor performance by either merely slowing diffusion or via local depletion of glucose.

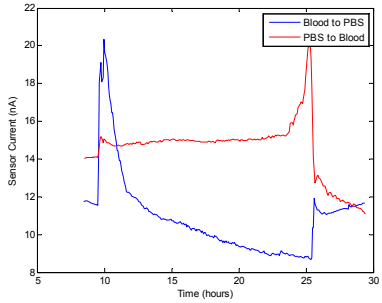

Figure 2: Plot of sensor attenuation for sensors in blood versus buffered glucose solutions.

When the sensor in the red trace is moved from buffered glucose to blood at 25 hours, its signal immediately declines, denoting that there has been a depletion of glucose in the sample. Conversely, when the sensor in the blue trace is moved from blood to buffered glucose at 25 hours, pre-treatment sensor function is restored. This finding demonstrates that the clot which forms on the sensor surface after 25 hours does not impede the transport of glucose, further pointing towards the culprit of local depletion of glucose. As cells are the only bodies in blood that can consume glucose, we hypothesize that mononuclear cells like monocytes and macrophages must be consuming glucose proximal to the sensor, contributing to the early decrease in sensor function.

Summary: Whole blood has been shown to decrease the response of glucose sensors relative to other blood constituents. Additionally, we posit that cellular consumption of glucose could be responsible for the initial decrease in sensor function. By understanding the modes by which sensors fail soon after implantation, sensor surfaces may be modified to account for these effects.

References: [1]. Wisniewski, N. Colloids and Surfaces B. Biointerfaces 2000 18: 197-219.