Noninvasive In Vivo Millimeter-Wave Measurements of Glucose: First Results in Human Subjects

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***Abstract*— We present initial data on noninvasive millimeter-wave tracking of glucose levels in human subjects. Measurements were made using three separate test systems, all giving similar results: (1) a K-band (WR42) rectangular waveguide clamp coupled to a direct detector to measure transmission magnitude through the upper ear between 15 and 25 GHz; (2) a K-band waveguide clamp connected to a vector network analyzer to measure magnitude and phase of transmitted power through the ear lobe; and (3) a Ka-band rectangular waveguide clamp operating from 26-36 GHz also recording complex transmission coefficients through the ear lobe. A novel compact CMOS heterodyne transceiver operating at 19-21 GHz was also tested, but failed to show sufficient antenna-to-antenna power coupling to produce useful results. Data was collected during a standard oral glucose tolerance test (OGTT) in one healthy volunteer and correlated with blood glucose measurements using a commercial glucometer. Preliminary results show good correlation between blood glucose measurements (invasive) and both magnitude and phase of millimeter-wave transmission (non-invasive) through the skin, and are in accordance with our earlier animal experiments conducted on anesthetized rats.**

I. INTRODUCTION

NONINVASIVE tracking of glucose in humans has been a long term goal of the medical device industry for more than five decades [1]. This paper discusses initial human in vivo measurements of glucose levels in the skin using continuous active microwave and millimeter-wave transmission (MMT) monitoring. The MMT techniques presented have been developed over the past three years [2], and are being tested in a human subject for the first time. These measurements confirm and extend our earlier work in anesthetized rats [3], indicating that the proposed MMT technique can be successfully employed in awake human subjects. Both the MMT magnitude and phase at all frequencies tested track changes in blood glucose levels measured with an invasive finger pricking procedure and commercial test strip glucometer. An observed delay of 30-45 minutes in the peak MMT levels through the tissue, versus peak glucose readings in the blood, supports our prior observations in animals [3] and agrees qualitatively with published data from implanted subcutaneous glucometers [4] and iontophoresis measurements in skin [5].

II. METHODS

The noninvasive tracking of glucose changes in tissue is based on MMT techniques first explored by the authors [2]. In the present human study, the upper ear and the ear lobe were utilized for measurement. A custom clamping system was employed to secure the tissue between rectangular waveguide flanges which were gapped to a "comfortable" spacing (Fig. 1. insert photo).

For the first set of measurements, a 4.5 mm gapped K-band waveguide was employed: aperture=10.7x4.3mm, nominal frequency range 18-26.5 GHz, but used down to 15 GHz. The subject was connected to an RF generator via a coaxial cable during measurements and remained seated. An HP83620A synthesizer was used to generate up to 70mW of power at the input waveguide port between 15 and 25 GHz (unleveled), and an HP8474 square-law diode detector was attached to the output waveguide-to-coax transition to record the available RF passing through the tissue [3]. Clamping the waveguides on the upper ear or the ear lobe resulted in a typical transmission-plus-reflection loss of 40-50dB – hence the need for 70mW of incident power when the direct detector was used without a lock-in amplifier. Only transmission magnitude can be detected with this set up. Incident and measured power at each frequency varies with synthesizer output, cable loss, connector and transition mismatch and tissue absorption and reflection coefficients. Only relative changes with time at each frequency are used to correlate with glucose readings in the blood.

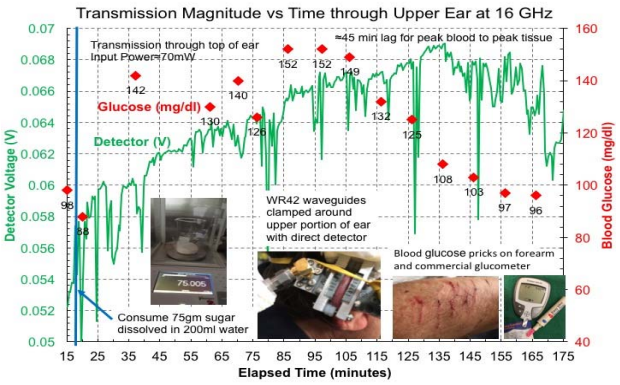

Fig.1. OGTT test with blood glucose concentration (red) and MMT magnitude data (green) at one representative frequency.

An oral glucose tolerance test (OGTT) was administered after overnight fasting (consumption of 75 g sucrose diluted in 200 ml water – Fig. 1. left insert), while continuous MMT recordings were made over a three-hour period. Blood samples from the forearm were taken at roughly 10 minute intervals and blood glucose concentrations were obtained with a Bayer Contour NEXT glucometer and chemical test strips (Fig. 1. right insert photos). A typical plot showing MMT against blood glucose readings over time at one frequency (16 GHz – the highest available transmitted power) is shown in the plot of Fig. 1. Note that the presence of glucose in the blood (and presumably, in the tissue) *reduces* the millimeter-wave dielectric absorption coefficient [6],[7], and results in *increased* detector voltage. The time lag of 45 minutes between peak glucose level in the

978-1-5090-6050-4/17/$31.00 ©2017 IEEE

blood and peak MMT (and presumed peak glucose in the tissue) is consistent with our earlier results on anesthetized rats [3] and published results using subcutaneous glucometers and iontophoresis measurements in skin [4], [5].

In order to decrease the required incident power for the measurements, and to add phase information (better correlated with changes in the real part of the dielectric constant), a second arrangement was employed that substituted the RF generator and direct detector with a more sensitive vector network analyzer, as originally described in [2]. The same K-band waveguide clamp system was used on the ear lobe during the OGTT. A typical plot of MMT phase versus time is shown in Fig. 2 at 20 GHz (measurements were performed from 15-25 GHz and all showed similar behavior). For easier comparison on the plot, the MMT phase data has been inverted. Note that the *phase delay* through a fixed distance of tissue *decreases* as the *glucose* concentration *increases* because the real part of the dielectric constant is going down (see Fig. 15 in [6]). Incident power was less than 1mW for these measurements.

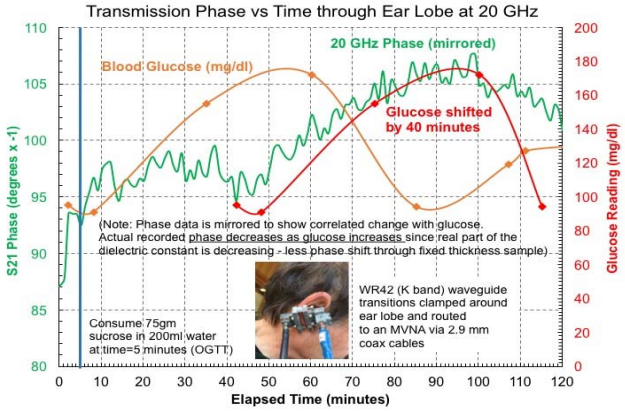

Fig.2. OGTT blood glucose (red; right scale) and MMT phase (green; left scale) at one representative frequency. Phase data is inverted.

Finally, for overlap with our previous experiments on anesthetized rats [2],[3], the frequency was stepped up to 26-36 GHz using a pair of clamped WR28 waveguide-to-coax transitions. Losses through the ear are significantly higher, but a similar trend is observed in the MMT phase recording – that is, the phase delay decreases as the glucose increases, and then rolls back to pre-OGTT levels after 3 hours (data not shown).

III. Discussion

Although the magnitude data in Fig. 1 is quite noisy due to the very low transmitted power levels, the RF signal change over time follows the same trend that we have observed in transmitting through the ears of anesthetized rats when glucose is administered via subcutaneous injection [2] or via intravenous catheter infusion directly into the blood stream [3]. That is, the insertion loss decreases as glucose is metabolized in the tissue, with a typical delay of 30 to 45 minutes compared to the concentration peak in the blood. Blood glucose concentration changes during the OGTT spanned from 90 to 200 mg/dl and the tracking capability of the noninvasive MMT was sufficiently sensitive within this physiologically normal range.

The phase plot in Fig. 2 provides additional insights, in that the change from baseline-to-peak of approximately 7 degrees, corresponds to a decrease in the real part of the permittivity of 3.5-3.7%, assuming fixed tissue thickness, and a nominal ε_r' at 20 GHz between 32 (blood) and 24 (skin). This is a larger change than the variation in ε_r observed in vitro in blood [7], where the glucose concentration was varied by 135 mg/dl. It may make the practical realization of a noninvasive glucometer based on MMT phase monitoring more sensitive than initially expected. Although not shown, the observed change in phase at different frequencies was as large as 14 degrees.

IV. Conclusions

Our results show good correlation between noninvasive MMT through in vivo human tissue and glucose concentrations recorded by an invasive blood glucometer. Both magnitude changes (correlated mostly with variations in absorption loss), and phase variations (correlated more with changes in the real part of the tissue refractive index), show time dependent behavior during OGTT that tracks blood glucose concentration at physiological relevant levels. The direction of the observed changes in MMT magnitude and phase is also consistent with in vitro measurements in blood [7] and prior animal measurements [2], [3] – increasing glucose levels decrease RF absorption and decrease the real part of the tissue dielectric constant. The MMT peak representing glucose level changes in the tissue, has a substantial delay relative to peak blood glucose level. This is in agreement with our earlier animal MMT measurements [3], and with glucose oxidase electrochemical measurements [4], and iontophoresis measurements [5] in the subcutaneous tissue. The observed MMT sensitivity was similar at all measured frequencies (15-36 GHz), and the choice (at least in this range) will depend much on the practical realization of the circuitry and the desired transceiver footprint. We also attempted to use a novel 19-21 GHz CMOS-based heterodyne transceiver developed for this application [8], but were unable to couple sufficient power between the two PC-board mounted antennas to make consistent measurements through the ear or skin folds. We plan to improve the coupling in the coming year, and to validate the waveguide experiments with a miniaturized CMOS device.

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