Monitoring the Setting of Injectable Calcium-Based Bone Cements Using Pulse-Echo Ultrasound

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Abstract— **The existing standards for determining the setting time of injectable bone substitutes suffers from poor reproducibility and subjectivity. We previously presented an ultrasonic pulse-echo technique that can follow the entire setting reaction on-line, without any mechanical manipulation of the sample. For calcium sulfate hemihydrate (CSH), the new method shows good agreement with the standards, but with much better reproducibility.**

One problem with the new technique was its sensitivity to temperature fluctuations. In this paper we present a temperature compensation scheme that automatically corrects the measurements for losses caused by temperature changes.

The modified method is verified with experiments on α-tricalcium phosphate (α-TCP). Because α-TCP has longer setting time than CSH, the initial method, which is sensitive to temperature, did not work.

I. Introduction

When working with injectable bone substitutes [1] for bone defect healing, quantifying the setting process is important. It is essential to know the strength and the setting time of the material, to decide when and how it should be injected into the bone, and when the wound can be closed without the risk of medical complications.

There are currently two standardized methods to study the hardening process, the Gillmore needles method (ASTM C266-89) [2] and the Vicat needle (ASTM C191-92) [3]. The idea of both methods is to expose the cement surface to a certain pressure, and then visually examine the cement surface to decide if the material has reached the setting time, *i.e.* if no mark can be seen on the surface of the cement. The visual examination makes the test methods subjective with large individual variations. Some examples of such variations are: Norian SRS has been said to set at 27 min [4], 22 ± 1 min [5] or 8.5 ± 0.5 min [6], depending on the researcher. Similar variations exist for Cementek (34 min [4], 36 min [5] and 17 ± 1 min [6]) and BoneSource (19 min [4] and 20-25 min [7]).

To overcome this problem we introduce an ultrasonic method that allows us to continuously follow the setting reaction. This method gives more information about the evolution of the setting process than the standardized methods do. Furthermore, this analysis method is objective.

Other advantages with an ultrasonic test method is that more properties than the setting time can be estimated from the measurements, *e.g.* the adiabatic bulk modulus. In [8], we showed that the proposed ultrasonic test method works well for monitoring the setting of pure calcium sulphate hemihydrate (CSH). The measured setting time agree well with the existing standards, but with much better reproducibility. In addition to that, we obtained values of the density and the adiabatic bulk modulus, that agreed well with what can found in the literature.

This paper extends the method proposed in [8] with an automatic temperature compensation algorithm. The new method is verified with experiments on mixtures of CSH and α-tricalcium phosphate (α-TCP). This setting reaction takes much longer time than that of pure CSH, and fluctuations in the ambient temperature became a problem using the old method.

II. Theory

In this section we describe all the theory needed in order to estimate the acoustic impedance, the density, the speed of sound, and the bulk modulus of the cement. In section II.B, we derive the temperature compensation algorithm.

A. Pulse-Echo Principle

The basic principle of the proposed method is to measure the attenuation and speed of sound of an ultrasound pulse. For this we used the setup in Fig. 1. The transducer is used to transmit a short pulse into the PMMA buffer rod. The same transducer is then used to record the reflected echoes, from the PMMA/cement interface and from the cement/reflector interface.

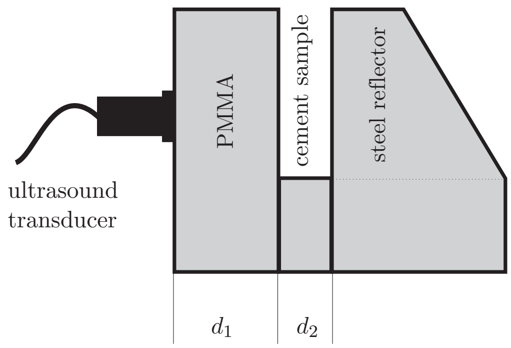

Fig. 1. Device for ultrasonic pulse-echo measurements used in the experiments. The distances d_1 and d_2 are 20 mm and 15 mm, respectively. The center frequency of the ultrasound transducer is 2 MHz.

A calibration measurement with only pure water in the measurement cell was made, before the cell was filled with cement paste. These two measurements are then used to calculate the acoustic impedance, z_c, of the cement, at the PMMA/cement interface. The speed of sound, c, within the cement was determined from the second echo using a standard cross-correlation technique. From these two properties we can calculate the density, $\rho = z_c/c$ and the adiabatic bulk modulus, $\beta = c^2\rho$. To do so, we need to determine the attenuation of sound, at the PMMA/cement interface. This is given by (see for example [9]):

$$A_w(T_1) = A_0 R_{p,w} e^{-\alpha(T_1)\cdot 2d_1}, \tag{1}$$

where A_w is the amplitude of the echo received from the PMMA/water interface, A_0 is the transmitted amplitude, $R_{p,w}$ is the reflection coefficient of the PMMA/water interface, d_1 is the thickness of the PMMA buffer rod, and $\alpha(T)$ is the attenuation coefficient for PMMA, as a function of temperature, T. This gives the outgoing amplitude

$$A_0 = \frac{A_w(T_1)}{R_{p,w} e^{-\alpha(T_1)\cdot 2d_1}} \tag{2}$$

For a PMMA/cement interface, where the temperature is T_2, we then have

$$\begin{aligned} A_c(T_2) &= A_0 R_{p,c} e^{-\alpha(T_2)\cdot 2d_1} = \\ &= A_w(T_1)\frac{R_{p,c}}{R_{p,w}} e^{-2d_1(\alpha(T_2)-\alpha(T_1))}. \end{aligned} \tag{3}$$

This gives the reflection coefficient between the PMMA and the cement paste, as

$$R_{p,c} = \frac{A_c(T_2)}{A_w(T_1)} R_{p,w} \cdot e^{2d_1(\alpha(T_2)-\alpha(T_1))} \tag{4}$$

In the special case when the temperatures T_1 and T_2 are the same, this simplifies to

$$R_{p,c} = \frac{A_c}{A_w} R_{p,w}. \tag{5}$$

The reflection coefficient between PMMA and water is given by

$$R_{p,w} = \frac{z_w - z_p}{z_w + z_p} = \frac{\rho_w c_w - \rho_p c_p}{\rho_w c_w + \rho_p c_p}, \tag{6}$$

where $z_w, z_p, \rho_w, \rho_c, c_w, c_p$ are the acoustic impedance, the density, and the speed of sound of water and PMMA, respectively. All of which are assumed to be known. Similarly, we get

$$R_{p,c} = \frac{z_c - z_p}{z_c + z_p} = \frac{A_c}{A_w} R_{p,w}. \tag{7}$$

Solving this for z_c we obtain

$$z_c = \frac{(1 + R_{p,c})}{(1 - R_{p,c})} z_p \tag{8}$$

In the general case, when we allow a temperature change from T_1 to T_2, this becomes

$$z_c = \frac{1 + \frac{A_c(T_2)}{A_w(T_1)} R_{p,w} \cdot e^{2d_1(\alpha(T_1)-\alpha(T_2))}}{1 - \frac{A_c(T_2)}{A_w(T_1)} R_{p,w} \cdot e^{2d_1(\alpha(T_2)-\alpha(T_1))}} z_p \tag{9}$$

B. Temperature Compensation

Although all experiments were conducted in a climate chamber, the temperature of the measurement cell changes during the initial setting period. Since the attenuation of sound in PMMA is very sensitive to temperature, this has to be compensated for.

We start by first showing how the temperature in the PMMA buffer rod can be estimated from the speed of sound within the PMMA. After that, we derive the temperature dependency of the attenuation coefficient, α. Finally, the temperature dependent energy loss in the PMMA is calculated, in order to obtain a correction factor for the acoustic impedance, z_c, of the cement.

B.1 Estimating PMMA Temperature

When the temperature in the PMMA buffer rod changes, this affects both the transit time in the PMMA buffer rod, and the corresponding attenuation. If this is not compensated for, the estimated acoustic impedance at the PMMA/cement interface will be biased.

From [10] we know that the transit time changes linearly with temperature. In order to estimate this linear dependency, we did the following experiment:

1. The measurement cell was immersed in a water tank and the temperature was set to 30°C. When the temperature stabilized, 200 echoes were measured.
2. The same procedure was repeated for every 2°C up to 44°C. Temperatures above this level are not interesting, since this will never be used in practice.
3. The time-delays Δt between the echoes were estimated using an accurate sub-sample time-delay estimation technique [11].
4. The measured time delays for each temperature were used to obtain a least-squares estimate of the temperature dependence, according to

$$T = T_0 + \gamma \cdot \Delta t, \tag{10}$$

where T_0 is a calibration temperature, Δt is the measured time delay, and γ is the slope (estimated from calibrations). In this way, knowing the transit time delay between a measured echo and a corresponding echo at a known temperature, give us the PMMA temperature.

B.2 Temperature Dependency of α

The amplitude of the reflected echo from a PMMA/water interface at temperature T is

$$\begin{aligned} A(T) &= A_0 R_{p,w}(T)\, e^{-\alpha(T)\cdot 2d_1} = \\ &= A_0 \frac{z_w(T) - z_p(T)}{z_w(T) + z_p(T)} e^{-\alpha(T)\cdot 2d_1}, \end{aligned} \tag{11}$$

where A_0 is the amplitude of the transmitted pulse, ρ_w, ρ_p, c_w, c_p are the known temperature dependent densities and sound velocities for water and PMMA, respectively [10].

Measuring the reflected echo for two different temperatures, T_1 and T_2, gives

$$A(T_1) = A_0 R_{p,w}(T_1)\, e^{-\alpha(T_1)\cdot 2d_1} \tag{12}$$

$$A(T_2) = A_0 R_{p,w}(T_2)\, e^{-\alpha(T_2)\cdot 2d_1}. \tag{13}$$

Assuming $R_{p,w}(T)$ is known, the ratio of the two is

$$\frac{A(T_1)}{A(T_2)} = K e^{-2d_1(\alpha(T_1)-\alpha(T_2))}, \tag{14}$$

where

$$K = \frac{R_{p,w}(T_1)}{R_{p,w}(T_2)} \tag{15}$$

is known.

Taking the natural logarithm of both sides, and solving for the difference in attenuation coefficient, $\Delta\alpha$, we obtain

$$\Delta\alpha = \alpha(T_2) - \alpha(T_1) = \frac{\ln \frac{A(T_1)}{A(T_2)} - \ln K}{2d_1}. \tag{16}$$

Now, assuming α is linear with respect to temperature [10], we get

$$\frac{d\alpha}{dT} = \frac{\Delta\alpha}{T_2 - T_1} = \frac{\ln \frac{A(T_1)}{A(T_2)} - \ln K}{2d_1(T_2 - T_1)}. \tag{17}$$

B.3 Compensating for Losses in PMMA

Getting back to where we started, the amplitude of the received echo from PMMA/cement interface is then

$$A_c = A_0 R_{p,c} e^{-2d_1\alpha}, \tag{18}$$

and we would like to compensate for the change in temperature that might have occurred since the reference measurement. This is the done by first estimating the temperature difference ΔT, given by the transit-time difference Δt. The excess attenuation due to the temperature change is thus

$$e^{-2d_1 \Delta T \frac{d\alpha}{dT}}, \tag{19}$$

and the measured amplitude should therefore be corrected accordingly.

III. Experiments

A. *Experimental Setup*

For each experiment, 30g of powder was prepared, using 80% (by weight; wt%) of α-TCP and 20 wt% of CSH. The powders were mixed with an aqueous solution of 2.5 wt% of Na_2HPO_4 at a liquid-to-powder (L/P) ratio of 0.32 mL g^{-1}, during one minute, to form a paste.

Thereafter, the paste was baked into the measurement cell (see Fig. 1), making sure that it completely covered the ultrasound transducer. Data collection started 3 minutes after the initial mixing, and the cell was immersed in water at 37°C, after a total of 5 minutes. Data was then collected every 2 minutes until the cement was set. The whole experiment continued for 24 hours. For all measurements a 2 MHz ultrasound transducer was used to transmit short-duration pulses (approx. 3.5 μs) into the cement. The time interval between the transmitted pulses was set using the pulse-repetition frequency (PRF) settings of the pulser/receiver (Panametrics, model P5800). Three different experiments were made, using different settings on the pulser/receiver. The ultrasound transducer was excited with either a 25 μJ or a 100 μJ impulse. The first two measurements were made using the 100 μJ setting, with a PRF of 80 Hz and 10 kHz, respectively. The third measurement was with the 25 μJ setting and a PRF of 80 Hz. The purpose of using different settings was to check if the ultrasound had any effect on the setting process.

B. Results

Fig. 2 shows the acoustic impedance of three different measurements on mixtures of 80 wt% of α-TCP and 20 wt% CSH.

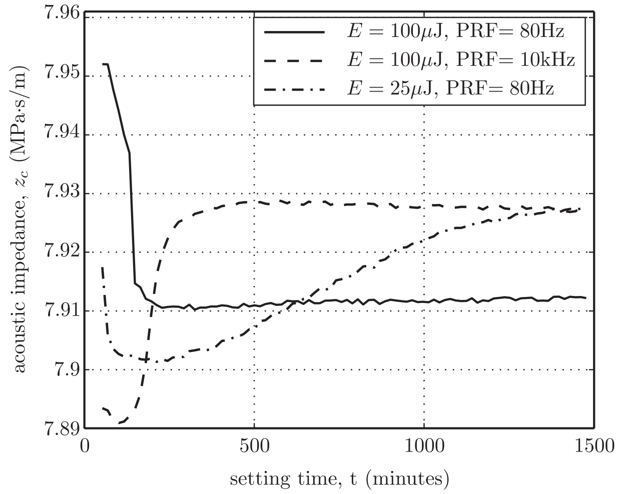

Fig. 2. Acoustic impedance of α-TCP as a function of the setting time, for three different settings of the acoustic parameters.

The solid and the dashed lines in Fig. 2 are the results obtained with a high intensity ultrasound pulse (100 μJ), at a PRF of 80 Hz and 10 kHz, respectively. The dashed-dotted line is the results when using low-intensity ultrasound (25 μJ), at a PRF of 80 Hz.

The results shown in Fig. 2 indicate that the use of an ultrasound pulse with higher intensity, could accelerate the setting of the material.

Because of the high attenuation of sound in the α-TCP/CSH it was not possible to obtain an accurate estimate of the sound velocity in the cement. Without the speed of sound, it was not possible to determine the adiabatic bulk modulus or density in these experiments, but only the acoustic impedance at the interface between the PMMA and the cement.

For pure CSH cement, however, the 2 MHz ultrasound pulse was able to penetrate the paste, and we obtained good measurements of the speed of sound. All experimental results on CSH are presented in [8].

IV. Conclusions and Discussion

We have presented a new ultrasonic technique for monitoring the setting of injectable bone substitutes. The foundations of the technique were established in a previous paper [8], but has been extended with an automatic temperature compensation scheme in order to work during temperature changes.

Experimental results on α-TCP cement show that the new technique can be used to measure the setting time continuously during the entire process, by following the changes in acoustic impedance.

With the present setup, using a 2 MHz ultrasound transducer, it was not possible to measure the speed of sound, and consequently not the adiabatic bulk modulus of the cement.

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