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UCSB researcher Samir Mitragotri reports new ultrasound technique for painless blood testing

No Need for Needles

Ultrasound Method That Enables Drug Delivery Is Now Adapted To Make Blood Testing Painless

A team of researchers reports in the March issue of Nature Medicine that ultrasound can be used to test blood sugar levels. This research suggests that in a few years needles will no longer be needed to test substances in the blood.

The new method uses sound waves to open up tiny pores in the skin through which a small amount of skin fluid is extracted using suction. Sugar (glucose) in the extracted fluid is then measured and used to predict glucose in the blood. This method has particular relevance for people with type I diabetes -- about one million Americans who measure their glucose levels three to four times a day by drawing blood.

Key to this new method for diagnostics is the use of low-frequency ultrasound, which is sound waves oscillating at a rate above 20 Kilohertz. Sound waves oscillating at a rate below 20 Kilohertz are what human beings hear. Low-frequency ultrasound refers to sound waves with rates approaching the 20 Kilohertz threshold. This rate is much smaller than that used for fetal diagnostics during pregnancy which approaches a rate of 10 Megahertz.

In the new method of diagnostics, low-frequency ultrasound is applied to the patient's skin for about two minutes. The sound waves cause cavitation -- the blowing and bursting of micro bubbles which, in turn, open up tiny pores in the thin upper skin layer so that it becomes permeable. The skin stays permeable for 15 hours after ultrasound application. That permeability enables interstitial fluid to seep out so that the presence of molecules such as glucose and triglycerides can be determined in terms of their amounts in the blood. The long duration of skin permeability enables the testing of interstitial fluid many times before low frequency ultrasound is again applied. In the clinical trials reported in Nature Medicine, samples were taken every half hour by suctioning. The technique has now been refined to replace suction with passive oozing as the mode of sample collection.

One big question -- answered affirmatively by the research reported in Nature Medicine -- was whether the miniscule bit of interstitial fluid acquired through the ultrasound technique contains glucose in amounts representative of the amount in the patient's blood. This new method was tested on seven subjects. These subjects felt a gentle pressure instead of the painful prick of a needle. The results showed excellent correlation between ultrasonically-measured glucose levels and those measured by the conventional methods. These trials were conducted at Beth Israel Deaconess Medical Center, Boston, and the Clinical Research Center at MIT.

"The current results pertinent to diagnostics represent the second stage of a three-stage research program," said Samir Mitragotri, assistant professor of chemical engineering at the University of California at Santa Barbara

(UCSB), an author of the paper.

The first stage, reported in an August 11, 1995 Science Magazine article by Mitragotri, Robert Langer (Germeshausen Professor of Chemical Engineering at MIT), and Daniel Blankschtein (Professor of Chemical Engineering at MIT) showed that ultrasound could be used to deliver drugs, such as insulin, across the skin. This research was based on the discovery that low-frequency ultrasound is more effective in making skin permeable compared to high-frequency ultrasound. This happens since cavitation disappears as the frequency of the sound wave increases. For that reason attempts in the 1970s and 1980s to deliver drugs via ultrasound at frequencies much higher than 20 Kilohertz produced very limited effects whereby only tiny molecules could be transmitted.

The key discoveries, made by Mitragotri and his collaborators in the mid-1990's, are that low frequency was required for ultrasound drug delivery and that the cavitation induced by low-frequency ultrasound accounted for the increased permeability of the skin.

These discoveries laid the foundation for the second stage of the research that is reported in Nature Medicine. That paper is co-authored by Joseph Kost (first author) of Ben Gurion University, Mitragotri, Robert Gabbay of Penn State Geisinger Health System, Michael Pishko, an assistant professor at Texas A&M University, and Langer. The research was performed at MIT, where Mitragotri worked before joining the University of California at Santa Barbara.

The third stage -- the focus of Mitragotri's research now -- aims to make a device that combines diagnostics with drug delivery. This device, which may be worn as a wrist-watch, will first test blood levels of glucose and, on the basis of the test results, will then deliver insulin. For people with type I diabetes, this device will eliminate painful finger pricks to test glucose levels and the even more painful insulin injections. Type I diabetics perform these procedures several times daily.

"The method reported in Nature Medicine allows a painless and bloodless way of determining blood glucose levels," said Mitragotri. He points out how further refinement of the technique will produce glucose monitors superior to existing methods. "After a few seconds of sonification, the patient will apply a device like a wrist-watch to the now permeable skin. That device will track the levels of glucose. It will, in effect, keep a history of those levels so that the patient can determine whether the level is moving up or down. Let's say a diabetic has 70 milligrams of glucose per deciliter. Whether that's good or bad depends on what the levels were before. If the glucose level is coming down from 100, that may not be good; but if it's going up from 60, that's good. At glucose levels of 50," he added, "patients pass out or go into a diabetic coma, and a lot of people die in that state."

The device that Mitragotri refers to is now being developed by Sontra Medical in Cambridge, Mass. He is one of the company's founders.

In addition to glucose, the Nature Medicine article reports that other substances that could be detected in the ultrasound-derived fluid sample are urea, calcium, and theophylline, a medication used in the treatment of asthma. The researchers have not yet performed the tests that will enable them to determine whether the amount of theophylline in the skin fluid is representative of amounts in blood.

In a related paper to be published in the April issue of Pharmaceutical Research, Mitragotri, Matthew Coleman (an undergraduate student at the University of Colorado), Kost, and Langer report ultrasound-derived detection of four more substances: proteins, triglycerides, lactate, and dextran. Triglycerides are fats, and their levels are a common target of blood testing, especially for people with heart, artery, and blood pressure problems. Eventually Mitragotri envisions that this method can measure several substances that are currently measured in a typical laboratory test of blood chemistry, performed by taking about two-to-three milliliters of blood from the patient.

MIT's publication Technology Review named Mitragotri among 100 top hi-tech young innovators in 1999 for this work. He joined the faculty of the UCSB College of Engineering in January 2000.

Images

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