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Development of a Flexible Implantable Sensor for Postoperative Monitoring of Blood Flow

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Abstract

We have developed a blood flow measurement system using Doppler ultrasound flow sensors fabricated of thin and flexible piezoelectric-polymer films. These flow sensors can be wrapped around a blood vessel and accurately measure flow. The innovation that makes this flow sensor possible is the diffraction-grating transducer. A conventional transducer produces a sound beam perpendicular to its face; therefore, when placed on the wall of a blood vessel, the Doppler shift in the backscattered ultrasound from blood theoretically would be 0. The diffraction-grating transducer produces a beam at a known angle to its face; therefore, backscattered ultrasound from the vessel will contain a Doppler signal. Flow sensors were fabricated by spin coating a poly(vinylidene fluoride–trifluoroethylene) copolymer film onto a flexible substrate with patterned gold electrodes. Custom-designed battery-operated continuous wave Doppler electronics along with a laptop computer completed the system. A prototype flow sensor was evaluated experimentally by measuring blood flow in a flow phantom and the infrarenal aorta of an adult New Zealand White rabbit. The flow phantom experiment demonstrated that the error in average velocity and volume blood flow was less than 6% for 30 measurements taken over a 2.5-hour period. The peak blood velocity through the rabbit infrarenal aorta measured by the flow sensor was 118 cm/s, within 1.7% of the measurement obtained using a duplex ultrasound system. The flow sensor and electronics operated continuously during the course of the 5-hour experiment after the incision on the animal was closed.

Keywords

diffraction-grating transducer; Doppler ultrasound; poly(vinylidene fluoride–trifluoroethylene); vascular surgery

Blood supply is crucial for tissue survival. Although blood flow can be measured by magnetic resonance imaging, x-ray angiography, and particularly by duplex Doppler ultrasound systems, these methods are not applicable for continuous or long-term measurement. For intraoperative or laboratory use, blood flow may be measured by transit

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time flow meters,¹ electromagnetic blood flow meters,² or Doppler flow probes³; however, the power needed by these devices requires external leads to pass through the skin for implantable use, making them unsuitable for long-term implantation. The Cook-Swartz Doppler probe,³ although requiring an external connection, is cleared to be implanted in humans for up to 29 days.

Here we report a new Doppler ultrasound flow sensor; it uses diffraction-grating transducers⁴ now fabricated on a thin flexible film made of biocompatible material. It requires very little power; therefore, we believe that it may be suitable for long-term implantation. The method of operation, fabrication, and preliminary evaluation of this device in monitoring blood flow in a phantom and an animal model are described.

Theory of Operation and Fabrication of the Diffraction-Grating Flow Sensor

The new flow sensor uses a simplified version of a phased array ultrasound transducer, where successive elements are driven with opposite phases of a sinusoidal signal with frequency f . The beam angle, θ , produced is governed by the following equation:

$$f = c / (\sin \theta \cdot d), \quad (1)$$

where c is the speed of sound, and d is double the distance between array elements. Two beams are produced, at $+\theta$ and $-\theta$, perpendicular to the surface of the array. The physics of operation for this configuration of narrow, closely spaced ultrasonic apertures is the same as that for optical diffraction gratings, and Equation 1 is known as the “grating equation,”⁵ which is why this transducer has been named a diffraction-grating transducer.⁴ Using this configuration, a beam is produced by a single-frequency signal applied to all elements of the array, in contradistinction to the usual operation of a phased array, which requires each element to be driven by a unique signal.

A further simplification is achieved by fabricating the elements of the array to have alternating polarization directions, eg, making every other element expand on a downward-oriented E-field (ie, voltage) and the other elements contract. This process allows for all elements to be driven by one signal cable and a sheet electrode while still having alternate elements move in opposite directions to produce the two beams at the angles determined by Equation 1.

Developing Light and Inexpensive Diffraction-Grating Transducers

Diffraction-grating transducers made of piezo-ceramics have been previously used to measure blood flow.⁶ Piezo-ceramic materials contain lead and other dense materials that make them heavy, and they are not flexible, so transducers made of them would be a considerable mechanical load if used as implantable Doppler blood flow sensors. Piezo-polymers⁷ have attributes that make them better suited for on-vessel implantable flow sensors, including light weight and biocompatibility. One such piezo-polymer, poly(vinylidene fluoride–trifluoroethylene) [P(VDF-TrFE)]⁸ copolymer, in dissolved form can be spin coated⁹ onto a substrate and, when dry, becomes a piezoelectric. Unlike piezo-ceramics, transducer array elements made of this material do not have to be isolated from each other by cutting grooves between them because very little energy travels laterally during excitation.¹⁰ This aspect allows diffraction-grating transducers to be fabricated by forming electrodes photolithographically on a substrate, spin coating the copolymer onto the electrode pattern, and covering the copolymer with a sheet electrode. After polarizing the copolymer with opposite voltages on alternate electrodes, a single cable can be used to excite the diffraction-grating transducer. A copolymer, although having these useful characteristics, is not an “efficient” piezoelectric material: its conversion of electrical to

ultrasonic energy, k_t ,¹¹ is only approximately 60%¹² that of piezo-ceramic.¹³ The design of the copolymer diffraction-grating transducer flow sensor was developed to overcome this weakness by (1) taking advantage of the ease of fabrication of high-frequency copolymer transducers,¹⁴ (2) using the biocompatibility of the copolymer to minimize the acoustic path to the flowing blood, and (3) using the flexibility of this structure on a plastic film to wrap it around the vessel and create a focal gain. In particular, because blood scatters ultrasound proportionately to the fourth power of the frequency,¹⁵ an increase to 40 MHz from the usual duplex Doppler frequency of 5 MHz increases the Doppler signal from the blood by a factor of $(40/5)^4 = 4096$. By placing the biocompatible transducer directly on the vessel, the high tissue attenuation at 40 MHz, 40 dB/cm, produces less than 3 dB of ultrasound signal lost as it passes into and out of the vessel. Partially wrapping the transducer around the vessel, as shown in Figure 1, causes the receiver to intercept a steradian (or more) of scattered ultrasound, rather than the small fraction of a steradian intercepted when an external duplex Doppler examination is made. A steradian is a measured solid angle and is equal to $A/(4\pi r^2)$, where A is area, and r is radius; for a duplex Doppler measurement, A is the area of the Doppler receiver, and r is the distance from the sample gate. The increased signal intercepted further improves the signal level of the implantable flow sensor compared to external duplex Doppler. In addition, there is a focusing gain for the blood in the center of the vessel where the peak velocity generally occurs.

Flexible Film Flow Sensors

Printed circuit technology has developed means of photolithographically creating fine metal traces on thin and flexible films. In particular, Kapton film (DuPont, Wilmington, DE), which is a polyimide, is often used to make flexible circuits for many industrial applications. In addition to being a good substrate for printed circuits, Kapton is biocompatible.¹⁶ We found that it was possible to spin coat a copolymer onto a 0.001-in (25- μ m) flexible Kapton film for the fabrication of copolymer diffraction-grating transducers and conventional “slab” receive transducers. The resultant transducers were light at less than 0.1 g, which is less than a 10th of the weight of a lead-zirconatetitanate diffraction-grating transducer assembly based on the difference in density and sound velocities of these materials. The transducers were also flexible enough to be repeatedly wrapped around a 2-mm rod without failure after at least 100 cycles. These characteristics of lightness and flexibility minimize the mechanical load of the transducer on the blood vessel.

Figure 1 shows a schematic representation of a flexible flow sensor partially wrapped around a blood vessel. The diffraction-grating transducer produces two beams, one of which passes under a simple slab transducer. The region where the continuous wave transmit beam from the diffraction-grating transducer crosses the receiving beam of the slab transducer is called the sensitive volume, from which moving blood cells scatter ultrasound from the diffraction-grating transducer and produce a Doppler-shifted signal on the slab transducer. With this configuration, there is no need for positioning a sample gate, as used in pulsed Doppler ultrasound, because the geometry defines the blood flow being measured. Eliminating the need for a sample gate reduces the complexity of flow sensor circuitry and removes the need for a skilled operator. As seen in the side view of Figure 1, although much of the lumen is in the sensitive volume (shown as dark), the region near the vessel walls is underinterrogated. In addition, there is higher insonation near the center of the vessel, as seen in the end view, which will affect the shape of the Doppler power spectrum. The peak velocity, however, can still be accurately measured.¹⁷ The sensitivity of the configuration of Figure 1 is greater than that of a conventional duplex Doppler configuration because a large percentage of blood in the lumen contributes to the Doppler signal, whereas the sensitive volume of a duplex Doppler configuration consists of only the “gate” portion of the thin sheet of ultrasound crossing the lumen. As low power consumption is a major requirement

for long-term monitoring of blood flow, this increased sensitivity is an important benefit of the wrapped transducer configuration made possible by flexible transducers.

The Doppler equation¹⁸ is

$$f_d = (V/\lambda) \cos\phi, \quad (2)$$

where f_d is the Doppler frequency; V is the velocity of the scatterer; λ is the wavelength of the ultrasound used; and ϕ is the angle between the insonating beam and the velocity vector. For the configuration shown in Figure 1, ϕ is the complementary angle to θ defined in Equation 1. Because $\cos\phi$ equals $\sin\theta$, the beam generated by the diffraction-grating transducer is at an angle $\sin\theta$ equal to $c/f \cdot d$ or λ/d because f/c equals λ . Therefore, the Doppler equation becomes

$$f_d = (V/\lambda) (\lambda/d) = V/d. \quad (3)$$

The Doppler frequency produced by this transducer configuration is the velocity divided by the periodic spacing of the elements, d . For example, for a diffraction-grating transducer with 25 μm between the elements ($d = 50 \mu\text{m}$), the Doppler frequency by blood at a peak velocity of 100 cm/s would be 100/0.005, or 20 KHz.

Materials and Methods

Fabrication of Prototype Flow Sensors

A photograph of the flexible circuit (Metrigraphics LLC, Wilmington, MA) used in the fabrication of the prototype flow sensors is shown in Figure 2. The electrode pattern was formed by depositing 500-nm-thick gold on 25- μm -thick Kapton. The circuit, which measured 12×14 mm, contained two diffraction-grating transducer and one slab transducer electrode patterns, although only one diffraction-grating transducer and slab transducer electrode pattern was used to make flow sensors for this study. The diffraction-grating transducer electrode pattern consisted of 12 μm -wide element traces separated by 12 μm alternately connected to the larger positive and negative signal traces as labeled in Figure 2. The flow sensors were designed to operate at 40 MHz; therefore, the angle of the beams generated with respect to blood flow was 39° based on $d = 48 \mu\text{m}$ and $\lambda = 37.5 \mu\text{m}$. A mixture of P(VDF₇₄-TrFE₂₆) copolymer powder (PiezoTech, Hérouville, France) and acetone was spin coated on top of the flexible circuit covering the diffraction-grating transducer and slab transducer electrode patterns. The resultant copolymer film was approximately 12 μm thick after drying and annealing at 130°C . A thin silver-platinum ground electrode was then sputtered on top of the copolymer layer covering the diffraction-grating transducer and slab transducer electrode patterns. The diffraction-grating transducer and slab transducer were then polarized at room temperature using a direct current voltage of approximately ± 450 V. The copolymer over successive diffraction-grating transducer traces was alternately polarized to create the characteristic double beam. The positive and negative diffraction-grating transducer signal traces were then connected to the center conductor of a coaxial cable using a silver epoxy (E-Solder 3022; Von Roll Isola Inc, New Haven, CT). Silver epoxy was also used to connect the diffraction-grating transducer ground plane to the coaxial cable shield. An additional coaxial cable was connected to the slab transducer signal trace and ground plane using the same technique. An epoxy stiffening board with suture holes was then bonded to the flow sensor before dip coating it with an approximately 125- μm -thick layer of biocompatible silicone (MED 12-6650; NuSil Technology LLC, Carpinteria, CA). A photograph of one of 20 prototype flow sensors constructed is shown in Figure 3. Each prototype flow sensor's thickness excluding the

coaxial cables and stiffening board was approximately 300 μm . Both the transmit diffraction-grating transducer and receive slab transducer had bandwidths of greater than 40%.

Flow Sensor Electronics

The flow sensor system used continuous wave Doppler ultrasound to minimize the circuitry and power requirements. A single printed circuit board, previously used as a complete crystal-controlled analog Doppler system with a 20-MHz piezo-ceramic diffraction-grating transducer to measure blood flow in a vascular graft,¹⁹ was modified for 40-MHz use. This circuit drove the transmitter, amplified the return signal, demodulated that signal into the in-phase and quadrature channels, and filtered and amplified those signals to be sent to an analog-to-digital converter for Fourier analysis of the Doppler signal. The circuit powered the flow sensor with approximately 1 V_{rms} (root mean squared) of drive that produced a greater than 30-dB signal-to-noise ratio. This value was measured as the ratio of the power per fast Fourier transform bin in the Doppler signal portion of the detected power spectrum to the power level in the fast Fourier transform bins in the part of the power spectrum above the Doppler frequency. For comparison purposes, the Cook-Swartz Doppler probe requires more than 16 times this power for its excitation, and the EMG flow probe requires more power than the Cook-Swartz Doppler probe. The specifications section in the Cook Medical DPM-250 Doppler probe and monitoring system instructions for use state system drives its flow probe at 12 $V_{\text{p-p}}$ (peak to peak) into 50 Ω at 20 MHz.³ The power required for flow sensor operation was half that used in the previously developed implanted graft flow monitor⁶; that graft monitor required approximately 40 mW for driving its piezo-ceramic transducer and transcutaneously transmitting the data; using a conventional pacemaker battery, the present circuitry could make more than 12,000 measurements and wirelessly transmit the data, eg, 4 measurements per day for 9 years.¹⁷

The analog signals produced by the flow sensor electronics of up to 80 KHz were cable connected to a laptop computer with an analog-to-digital converter sampling at 175 KHz. The system generated one hundred twenty 1000-point spectra per second from which the velocity, up to 3.8 m/s, and related parameters were calculated. In addition, custom-developed flow sensor software installed on the laptop provided a graphical user interface that was used to control and monitor the experiments. The graphical user interface displayed velocity waveforms as well as calculated the average blood flow rate, peak and average velocities, and heart rate for each measurement. The maximum velocity in the insonated lumen was determined in each of the 80 Doppler power spectra obtained each second, calculated using the algorithm of Evans and McDicken,¹⁸ and were plotted as the velocity waveform; the peak velocities in a 3-second measurement interval were displayed as the "peak velocity." The heart rate was detected from the peaks in the velocity waveform, and the blood flow rate was calculated for an integer number of complete pulses, as determined from the velocity measurements, to avoid variations caused by different numbers of heartbeats during the 3-second measurement interval.

Flow Phantom Experiment

The prototype flow sensors were tested using a custom-designed and fabricated flow phantom. This phantom contained a blood-mimicking fluid²⁰ that was pumped through a 3-mm-diameter plastic tube. A gear pump hydraulically alternately compressed one of a pair of bellows containing the blood-mimicking fluid, producing velocities and flow profiles in the physiologic range, and then compressed the other bellow to restore the fluid to the original bellow. The distance from the pump outlet to the measuring area where the sensor was placed was sufficient to ensure laminar flow with parabolic velocity distribution with continuous flow.¹⁹ After passing by the flow sensor, the blood-mimicking fluid flowed into

a graduated cylinder to measure the true blood flow rate, and as the area of the tube was known and the flow laminar, the true maximum velocity ($V_{\max}$) in the flow was $V_{\max} = 2 \times$ flow rate/area, as the maximum velocity is twice the average velocity for laminar parabolic flow. Under these conditions, the flow sensor calculated the Doppler signal-derived maximum velocity, and the flow rate differed by less than 2% from the physically measured flow rates (by a graduated cylinder and stopwatch). Thirty equally spaced, 3-second measurements with the flow sensor and electronics were taken over the course of 2.5 hours to determine the stability and reproducibility of the flow sensor measurements.

Animal Experiment

To establish clinical feasibility, a prototype flow sensor was used to measure blood flow in the infra-renal aorta of a 4.7-kg New Zealand White rabbit. The experimental procedure followed a protocol approved by the Animal Care and Use Committee at the Keck School of Medicine of the University of Southern California. The abdomen of the rabbit was opened along its midline, and the infrarenal aorta was dissected from the surrounding tissue. Shortly after dissection, the vessel diameter and blood velocity were measured and recorded with an HD11XE duplex ultrasound imaging system (Philips Healthcare, Bothell, WA), which was calibrated according to hospital standards. The vessel lumen diameter measured was 2.6 mm, and the duplex Doppler peak systolic velocity measured was 120 ± 0.5 cm/s. Sterile gel was placed on the flow sensor, and it was loosely wrapped around the vessel and sutured into place (Figure 4). The velocity was measured again and was unaffected by the placement of the flow sensor. The midline incision was then closed for the remaining 5 hours of the experiment. During that time, blood flow was automatically calculated (assuming laminar flow) by the flow sensor for 3 seconds every 5 minutes. At the completion of the 5-hour closed-animal experiment, the rabbit was euthanized, and the midline incision was reopened to check the position of the sensor and to remove it so it could be examined for any effects caused by body fluids. The removed sensor, when tested on the flow phantom, showed no change in its performance.

Results

Figure 5 is a screen shot from the flow sensor display during the flow phantom experiment. A plot of the maximum velocity for thirty 3-second measurements, one taken every 5 minutes, is shown at the bottom. The maximum Doppler-derived velocity over that time was 122 cm/s, and the minimum was 110 cm/s. The coefficient of variation, which is the ratio of the standard deviation of the velocity values divided by the mean velocity, was 2.9%. This result was very good considering that the reproducibility error of the flow rates, caused by the slight variations in the stability of the pump, was 2%. The maximum deviation in the blood velocity measurement over the 2.5-hour period was 4.7%. Finally, the flow sensor was evaluated over a range of measured laminar flow rates from 60 to 500 mL/min, and the maximum difference between the Doppler-derived flows and the measured flows over that range was 5.9%, independent of the flow rate. (As described by Vilkomerson et al,¹⁹ the accuracy achievable with such systems can be within 1% error.)

The peak velocity calculated by the flow sensor after implantation around the rabbit's infrarenal aorta was 118 ± 0.5 cm/s. This value was 1.7% lower than the peak velocity calculated by the duplex ultrasound system. The calculated blood flow rates through the infrarenal aorta for the sixty 3-second measurements taken during the 5-hour period after the midline incision was closed are shown in Figure 6. The flow rate values displayed in this plot were calculated using the Doppler-derived average velocity over each 3-second period and assuming laminar flow in a vessel lumen diameter of 2.6 mm. The mean flow rate over the 5-hour period was 91.4 mL/min. It should be noted that there was one important event during the experiment caused by a reduction in anesthesia by the veterinary staff at

approximately the 95th-minute mark. As a result, the flow sensor system observed a 20% decrease in blood flow compared to the mean along with a substantial increase in the heart rate and decrease in blood pressure. The level of anesthesia was restored for the duration of the experiment just after the 100th-minute mark.

Discussion

We have developed and demonstrated the use of a flexible implantable Doppler ultrasound blood flow sensor. This flow sensor can be wrapped around a blood vessel and can accurately measure flow. The innovation that makes the flow sensor possible was a diffraction-grating transducer fabricated using a piezo-polymer film. The power required by this device is considerably lower than that of other types of flow sensors, so long-term monitoring of blood flow with an implantable driver and transcutaneous radiofrequency transmission of the flow data appears feasible. Using this technology, approximately 12,000 measurements and transmissions could be made using a commercial pacemaker battery; many measurements and transmissions could be made per day for a shorter time, or fewer during a longer period. As the implantable transceiver can receive information as well as transmit it, the measurement rate can be adjusted depending on the medical requirement. Rechargeable implant electronics could add further flexibility to the modes of operation.

It should be noted that the calculated flow data used here assume, as do most ultrasound flow calculations, a parabolic velocity distribution, which is at best an approximation; however, this factor may not be a serious drawback, as the probable medical use of the device is to detect changes in blood flow, which depends more on repeatability rather than absolute accuracy. In addition, whereas the flow sensor is light and flexible and made of biocompatible materials coated with silicone rubber, long-term studies of both the body's effects on the sensor and the sensor's effects on the body have not been conducted.

The flow sensor being developed is potentially useful for measuring blood flow following cardiac and vascular procedures or any procedure that implants, relocates, or bypasses blood vessels. Some examples include coronary artery bypasses, vascular reconstructions and bypasses, free tissue flap transfers, and organ transplants and organ reconstructions. Real-time beat-to-beat monitoring of blood flow can detect alterations that potentially could lead to vessel/graft occlusion, allowing for early correction and maintenance of vessel/graft patency; for example, continuous monitoring of blood flow in coronary artery bypass grafts (CABGs) may be a potential use of the flow sensor. Coronary artery bypass graft operations use the saphenous vein, radial artery, or internal mammary artery to bypass diseased, stenotic, or occluded segments of the coronary vasculature. A recent large trial showed that more than 10% of patients undergoing CABG procedures had recurrent coronary problems within 12 months of the operation.²¹ Development of stenoses and occlusions within the bypass conduits resulted in recurrent angina, myocardial infarction, reoperations, and sometimes death. In another recent article, reporting on differences of vein graft life depending on how the saphenous vein is harvested, showed that in 4 years, more than 40% of patients who underwent CABG procedures had occlusion of 1 or more grafts, leading to a greater than 20% rate of death, myocardial infarction, or another revascularization procedure.²² A flow sensor as described in this report could be implanted at the time of the CABG and used to longitudinally monitor the blood flow within the bypass conduit in real time. Currently no such capability exists. Alterations in flow could then be detected early and corrected in most instances by endovascular techniques before occlusion of the bypass. The use of CABG flow sensor monitoring could potentially improve overall graft patency, thereby substantially reducing long-term morbidity and mortality rates in patients with major coronary artery disease.

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Abbreviations

CABG	coronary artery bypass graft
P(VDF-TrFE)	poly(vinylidene fluoride–trifluoroethylene)

Figure 1.

Cross section of the flow sensor partially wrapped around a blood vessel. The flow sensor's diffraction-grating transducer (DGT) produces two transmit ultrasonic beams, as indicated by the dashed lines, one of which crosses under a slab transducer (ST), with the receive beam also indicated by dashed lines. Any blood traveling through the region where the diffraction-grating transducer's beam overlaps the slab transducer's beam, shown as dark, will scatter ultrasound from the diffraction-grating transducer's beam to the slab transducer. As shown in the end view on right, the wrapped transducer will intercept much of the scattered ultrasound, increasing the system's sensitivity.

Figure 2.

Flexible circuit designed for the prototype flow sensors used in this study. Two diffraction-grating transducers (DGT) are on either side of the central slab transducer (ST). The 500-nm-thick gold traces for the diffraction-grating transducer and slab transducer are labeled. The positive and negative diffraction-grating transducer electrodes were electrically shorted together after the P(VDF-TrFE) film was polarized. The dimensions of the flow sensor from centers of the suture holes were 12×10 mm.

Figure 3.
Prototype flow sensor. The black thread through the stiffening board and flexible circuit is a 5-0 suture used to secure the flow sensor in place around a blood vessel.

Figure 4.
Flow sensor wrapped around the 2.6-mm-diameter rabbit infrarenal aorta.

Figure 5.

Three-second measurement of flow in a phantom using blood-mimicking fluid through a 3-mm lumen tube at a pulse rate similar to that of a rabbit. At the bottom is a plot of the average calculated peak velocity (assuming laminar flow; see “Materials and Methods”) versus time for 30 measurements. (The maximum calculated velocity over this time was 122 cm/s; the minimum was 110 cm/s; and the coefficient of variation was 2.9%.) The center graph shows the calculated peak velocity, in centimeters per second, over a 3-second measurement interval, and the numbers above refer, respectively, to the timeaveraged velocity, average peak velocity (in cm/s), number of complete beats, standard deviation of the calculated peak velocity during the measurement interval, volume flow rate (in mL/min) assuming laminar flow in a diameter input previously, Doppler power in an arbitrary scale (in dB), beats per minute, and power level (in dB), compared to a maximum input level. The measured flow rate during this measurement was 260 mL/min, ie, within 2% of the Doppler-derived flow. At the right of the screen is the indication for the automatic data collection period, and in the top row are the analog-to-digital sampling rate and the total number of data points collected.

Figure 6. Five-hour Doppler-derived blood flow rate, assuming laminar flow, in the rabbit infrarenal aorta. Dashed lines show $\pm 20\%$ around the mean value of 91.4 mL/min, indicated by the solid line.