Evaluation of a new fiber-optic pressure recording system for cardiovascular measurements in mice

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Woldbaek, Per Reidar, Tæve Andreas Stromme, Jørn Bodvar Sande, Geir Christensen, Theis Tønnessen, and Arnfinn Ilebekk. Evaluation of a new fiber-optic pressure recording system for cardiovascular measurements in mice. Am J Physiol Heart Circ Physiol 285: H2233–H2239, 2003. First published June 26, 2003; 10.1152/ajpheart.01123.2002.—We have tested a new fiber-optic pressure recording system, Samba, with a thin fiber [outer diameter (OD) = 0.25 mm] and a pressure sensor (length and OD = 0.42 mm) attached to the end. The accuracy of the system tested in vitro was good, with a coefficient of variation of 2.54% at 100 mmHg. The drift was <0.45 mmHg/h, and the temperature sensitivity was −0.07 mmHg/°C between 22 and 37°C. The frequency response characteristics were similar to a 1.4-Fr Millar catheter (0–200 Hz). Introduction of the Samba sensor from the right carotid artery into the left ventricle in six mice caused no drop in mean aortic pressure, whereas introduction of a 1.4-Fr Millar catheter (OD = 0.47 mm; n = 6) caused a pressure drop from 91.6 ± 9.2 to 65.1 ± 6.2 mmHg; P < 0.05. Thus the Samba sensor system may represent a new alternative to assess hemodynamic variables in the murine cardiovascular system.

catheter size; fiber optics; aortic pressure

GENETICALLY MODIFIED MICE have become important for studies of cardiovascular pathophysiology (1). Accurate invasive hemodynamic measurements in these species are technically challenging because of the small size of the cardiovascular system and the rapid heart rate. Pressure measurements through very thin fluid-filled catheters are possible but not ideal because of dampening of the pressure signals and a low frequency response. Accordingly, micromanometer high-fidelity catheters have been introduced for hemodynamic pressure recordings in small animals (2, 5, 6). Currently, the 1.4-Fr Millar catheter is commonly used for hemodynamic measurements under normal (5) and pathological (8, 12) conditions in the mouse. However, this catheter has some limitations, such as temperature sensitivity and some degree of instability during prolonged in vivo experimental procedures. The catheter may also cause increased resistance to blood flow in the aorta during measurements of left ventricular pressure. In addition, the location of the pressure recording membrane at the side of the tip prevents pressure recordings in small-sized vessels.

Recently, Sondergaard et al. (10) tested a new fiber-optic pressure recording system, Samba (Samba Sensor, Gothenburg, Sweden). They used the system to measure intratracheal pressure during pediatric respiratory monitoring and found it suitable for such monitoring. The system has not previously been tested for pressure recordings in the cardiovascular system. However, the thin fiber [outer diameter (OD) = 0.25 mm] and the small end sensor (OD = 0.42 mm, length = 0.42 mm) make it conceivable that this system is suitable for recording cardiovascular function in small animals. In the present study, we tested the frequency response, accuracy, temperature sensitivity, stability (drift), and fiber-bending properties of the system in vitro. Moreover, we examined whether retrograde introduction of the Samba sensor into the left ventricle via the right carotid artery caused fewer hemodynamic alterations than introduction of a Millar catheter.

METHODS

Samba Pressure Recording System

The details of the Samba fiber-optic pressure recording system were presented previously (10). In short, a silicon sensor chip with an OD of 0.42 mm and a length of 0.42 mm is attached to the tip of an optical fiber with an OD of 0.25 mm. When the membrane on the sensor chip is exposed to a pressure rise, the light returning to the control unit is altered in accordance with the pressure deformations of the membrane and the altered interference conditions inside the cavity of the sensor, according to the interferometric principle (13). The control unit has a resolution of 12 bits with an acquisition frequency of a maximum of 3,000 Hz. The analog signals are transferred to both digital (RS232, max 500 Hz) and analog (in the range of 0–10 V) values in the control unit and recorded with PC-based real-time data-acquisition hardware (DaqBoards model 200A, Iotech, Cleveland, OH). The pressure recording system tolerates concomitant magnetic resonance imaging examinations, and the fiber can be delivered with a length up to 10 m.

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Experimental setup. To determine the accuracy, drift, and temperature sensitivity of the system in physiological pressure and temperature ranges, six catheters were examined. The experimental setup is shown in Figs. 1 and 2. The fiber was inserted through a rubber membrane into a waterproof chamber. The chamber was filled with water and attached to a water pillar. The pressure in this water pillar could be precisely adjusted to 0, 50, and 100 mmHg. The temperature of the water in the chamber could be set to 10, 22, and 37°C. A thermocouple (TEGAM) measured temperature in the recording chamber (Fig. 1).

Experimental protocol. The experimental protocol is outlined in Fig. 3. Examinations were performed at 10, 22, 37, 22, and 10°C, in that order. At the three temperature levels pressures were recorded at 0, 50, and 100 mmHg, and this procedure was repeated three times with 10-min intervals. Our equipment allowed the temperature to be raised from 10 to 22°C in ~30 min and, furthermore, up to 37°C also in 30 min. However, reducing the temperature required a longer time, ~45 min for each of the two steps. Accordingly, the first part of the in vitro experiment with temperature increments lasted for ~2 h, whereas the last part lasted for ~3 h.

Frequency response analysis. To examine the frequency response of the Samba sensor system a 1.4-Fr Millar micro-manometer-tipped catheter (model SPR-671, Millar Instruments, Houston, TX) was used as reference. These two pressure recording systems were coupled to a spectrum analyzer (model 5820A, cross channel spectrum analyzer, Warettek Rockland), and a randomly generated voltage excitation signal (“pink noise”) from this unit was transferred to the pressure recording systems. Both the Samba sensors (n = 6) and the Millar catheter were placed in a pressure chamber (model 601A, Bio-tek Instruments, Winooski, UT) and exposed to a static pressure at 40 mmHg. The frequency response characteristics, amplitude ratio, and phase response of the Samba sensors were compared with those of the Millar catheter in the range of 0–200 Hz.

Samba fiber-bending tests. In the pressure chamber the Samba sensors (n = 6) were exposed and calibrated to 0 and 100 mmHg, and the fibers were bent ~20 cm from the pressure chamber in preformed curves with arcs of 90° and 180° as parts of circles with diameters of 10, 8, 6, 4, 3, and 2 cm. The pressure data presented are expressed as changes from baseline.

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Animals. Eighteen male BALB/c mice (6–8 wk old, weight 18–23 g; Møllegaard and Bomholtgard Breeding and Research Center A/S, Ry, Denmark), were examined in this study. Anesthesia was induced by an injection of 0.2 ml of propofol (10 mg/ml) into a tail vein. After an anterior cervical midline incision, a tracheotomy was performed by inserting a 20-gauge intravenous cannula into the trachea. The mice were connected to a rodent ventilator (model 874 092, B. Braun, Melsungen, Germany) and ventilated with a mixture of 2% isoflurane and 98% oxygen with a ventilation frequency of 90 min⁻¹. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health [Publication No. (NIH) 85–23, revised 1996] and is in accordance with the Norwegian Animal Welfare Act and approved by the Norwegian Animal Research Authority.

Animal preparation. Through the cervical midline incision both the right and the left carotid arteries were isolated. With a surgical microscope (Leitz Wild M650, Wild Surgical Microscopes, Heerbrugg, Switzerland) a Samba sensor was inserted into the left carotid artery and left in this artery during the experiments for continuous measurements of transmitted aortic pressure and heart rate. Through the right carotid artery either another Samba sensor or a 1.4-Fr (OD = 0.47 mm) Millar catheter was inserted and advanced into the ascending aorta (“in”), subsequently into the left ventricle, and finally retracted back again into the ascending aorta (“out”). At each step during insertion and advancement into the aorta and the left ventricle as well as during retraction, transmitted aortic pressure to the left carotid artery was recorded with DASYLab version 5.1 software (Datalog, National Instruments, Mönchengladbach, Germany), and hemodynamic data from 10 consecutive beats were analyzed with a specially constructed program designed with a mathematics software package (MATLAB, The MathWorks,

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Inset: close-up image, which demonstrates the size of the Samba sensor.
Natick, MA). Finally, the mice were killed and the aortic valves were examined to see whether any damage to the aortic valve cusps had occurred.

**Statistical analysis.** The data are expressed as means ± SE. Statistical analyses were performed with scientific statistical software (SigmaStat version 2.0, Jandel Scientific, Erkrath, Germany). For comparison between the experimental groups, either the Student’s t-test or one-way ANOVA was used. Multiple comparisons were corrected for by using the Student-Newman-Keuls test. A probability of $P < 0.05$ was regarded as statistically significant.

**RESULTS**

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**Pressure accuracy.** Table 1 shows the pressures recorded when the Samba sensor was exposed to 0, 50, and 100 mmHg at 10, 22, and 37°C, respectively. Exposed to a pressure of 100 mmHg, the precision of the measurements recorded, expressed as the standard deviation of the mean values, was 0.30, 1.02, and 2.57 mmHg at 10, 22, and 37°C, respectively. At the start of the in vitro experiment, the Samba sensor system was calibrated at 10°C, and this might explain why at 37°C a pressure of $101.36 ± 1.05$ mmHg was recorded when the system was exposed to 100 mmHg. However, the coefficient of variation at 100 mmHg was only 2.54%.

**Pressure stability (drift).** Each Samba sensor was exposed to 0, 50, and 100 mmHg twice, both at 22 and 10°C, in accordance with the experimental protocol (Fig. 3). When sensors were exposed to 100 mmHg at 10°C the second time, 4.5 h after the first measurements, a nonsignificant decline in pressure (drift) of $0.42 ± 0.31$ mmHg was recorded. Also, at 22°C a nonsignificant pressure difference of $-0.64 ± 0.11$ mmHg between the start and end of the 2.25-h testing period was demonstrated at 100 mmHg. The average pressure declines at these temperatures were 0.42 and 0.44 mmHg/h, respectively. However, this tendency for a pressure decline did not reach the level of statistical significance for 100 mmHg and 50 mmHg, but only for the recordings of 0 mmHg at 10°C (Table 1).

**Temperature sensitivity.** The bias, or systematic error, of the pressures recorded by the Samba sensor calibrated at 10°C, and this might explain why at 37°C a pressure of $101.36 ± 1.05$ mmHg was recorded when the system was exposed to 100 mmHg. However, the coefficient of variation at 100 mmHg was only 2.54%.

**Fig. 2.** In vitro experimental setup and the various components of the Samba sensor pressure recording system. See METHODS for further explanations.

**Fig. 3.** Details of the in vitro experimental protocol with time points for pressure recordings at 0, 50, and 100 mmHg at 3 different temperatures (10, 22, and 37°C) obtained with 6 different Samba sensors over a time span of 5 h. The different pressures were measured by increasing temperature from 10 to 22 and 37°C during the first 2 h and then by decreasing temperature to 22 and 10°C during the next 3 h.

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system was nominally smallest when sensors were exposed to 100 mmHg at 22°C [0.42 ± 0.44 mmHg (start) and −0.23 ± 0.55 mmHg (end)] and largest when they were exposed to 100 mmHg at 37°C (Table 1). Between 22 and 37°C the systematic error recorded rose from ~0.33 to 1.36 mmHg, or by ~0.07 mmHg/°C. Comparable results were also obtained when exposing the sensor to pressures of 0 or 50 mmHg at these temperatures.

**Table 1. Pressure recordings at 10, 22, and 37°C**

<table>
<thead>
<tr>
<th>Pressure</th>
<th>10°C (start)</th>
<th>22°C (start)</th>
<th>37°C</th>
<th>22°C (end)</th>
<th>10°C (end)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mmHg</td>
<td>−0.12 ± 0.11</td>
<td>0.25 ± 0.56</td>
<td>1.07 ± 1.11</td>
<td>−0.86 ± 0.69</td>
<td>−1.84 ± 0.28*</td>
</tr>
<tr>
<td>50 mmHg</td>
<td>50.60 ± 0.20</td>
<td>51.38 ± 0.36</td>
<td>52.30 ± 0.94</td>
<td>50.49 ± 0.54</td>
<td>50.24 ± 0.38</td>
</tr>
<tr>
<td>100 mmHg</td>
<td>99.53 ± 0.10</td>
<td>100.42 ± 0.44</td>
<td>101.36 ± 1.05</td>
<td>99.77 ± 0.55</td>
<td>99.11 ± 0.41</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 6 in all groups. *P < 0.05 vs. 10°C (start).

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Figure 5 shows the mean aortic pressures (MAP) transmitted to the sensor in the left carotid artery when either a Samba sensor (n = 6) or a Millar catheter (n = 9) was positioned in the right carotid artery, the ascending aorta (in), the left ventricle, and the ascending aorta (out). Introduction of the Millar catheter from the right carotid artery into the aorta caused a decline in MAP from 91.6 ± 9.2 to 80.4 ± 7.4 mmHg (P < 0.05). By further advancement of the catheter into the left ventricle, MAP dropped by an additional 15.3 ± 1.2 mmHg. Retraction of the catheter from the left ventricle into the ascending aorta caused an increase...
These changes in MAP indicate that the Millar catheter causes a marked resistance to flow in the ascending aorta and in the left ventricular outflow tract. When the same experimental protocol was followed with a Samba sensor, no significant changes in MAP occurred from advancing the sensor from the right carotid artery (78.5 ± 11.2 mmHg) to the ascending aorta (in; 77.9 ± 9.7 mmHg) or out again to the ascending aorta (out; 76.4 ± 9.5 mmHg). These results imply that the Samba sensor causes fewer hemodynamic alterations than the Millar catheter during measurements of left ventricular pressure. No significant differences in heart rate or occurrence of arrhythmias were demonstrated when the Samba sensor and the Millar catheter were introduced into or retracted from the left ventricle.

**Postmortem examinations.** In the present study 18 mice were originally examined, but data from 3 mice were excluded because of tears in the aortic valve cusps observed postmortem. This kind of damage to the aortic valve was demonstrated in two mice after introduction of the Millar catheter and in one mouse after use of the Samba sensor.

**Samba sensors.** The six Samba sensors that were tested in vitro were subsequently used in the 18 animal experiments reported here and in 26 other experiments on mice in which the Samba sensor was introduced into the left ventricle. The same surgeon (P. R. Woldbaek) introduced the Samba sensor each time. Five other sensors were excluded during these studies because of damage to the sensor membrane or breakage of the fiber (verified by Samba Sensor, Gothenburg, Sweden).

**DISCUSSION**

One main advantage of this new fiber-optic pressure sensor system developed by Samba Sensor (Gothenburg, Sweden) is the small size allowing hemodynamic measurements in small animals such as the mouse without affecting central hemodynamics. Furthermore, the system is stable with a high accuracy. Temperature sensitivity is minimal, and the frequency response characteristics are similar to those of a 1.4-Fr Millar catheter in the range of 0–200 Hz. Bending the fiber in an arc of 180° with a diameter of 2 cm causes a slight pressure decline. The major limitations of the Samba sensor system are the fragility of the fiber and the possibility of injury to the membrane by repeated measurements.

Currently, echocardiography is established for cardiac assessments in the mouse (3, 4, 11). However, echocardiographic equipment is expensive and accurate evaluation of cardiac pathology is greatly influenced by the skill of the investigator. Therefore, we think that complete characterization of cardiac performance requires left ventricular pressure measurements. Because fluid-filled catheters have major limitations such as low frequency response, invasive pressure measurements with high-fidelity micromanometer catheters like the Millar catheter are commonly used to determine both normal ventricular function (5, 6) and function after induction of ischemic heart failure (7, 8). However, this catheter does have important limitations in vivo studies such as temperature sensitivity, electric instability, and calibration problems. It is also conceivable that the size of the tip of a 1.4-Fr Millar catheter (0.47 mm) might increase resistance to aortic flow because the transverse aortic diameter in a 22-g mouse is 1.2 mm (9). Thus retrograde introduction of this catheter into the left ventricle through the right carotid artery may influence general hemodynamics as demonstrated in the present study.

Previously, Sondergaard et al. (10) demonstrated the feasibility of the Samba microfiber-optic pressure sensor system for determining intratracheal pressures in humans. Its feasibility for estimating cardiovascular function has, however, not previously been examined. The present study shows that the accuracy of the...
system is well within acceptable limits for most physiological examinations with a frequency response flat up to at least 200 Hz. The stability for recording low pressures within the cardiovascular system has up to now been difficult with available techniques. With this new system, however, we recorded zero pressure at $10^\circ$C with a pressure deviation of only $-0.12 \pm 0.11$ mmHg. Because of the good stability for low-pressure measurements, the Samba sensor may be feasible for pressure recordings in the venous bed. The system was only once calibrated at $10^\circ$C, which may explain why the accuracy was somewhat lower at $37^\circ$C. The pressure stability (drift) and temperature dependence of the system, expressed as the difference and deviation of the average pressures recorded at the first and second times, were all within the limits of acceptance for in vivo hemodynamic measurements. Although we have not examined the accuracy of the Samba sensor system for prolonged periods in vivo, our in vitro tests were long lasting (4–5 h), which makes it conceivable that the system also may work appropriately during long-term pressure recordings in vivo. Because the Samba sensor system also can be exposed to MRI and the length of fiber (up to 10 m) facilitates MRI examinations, this system may represent a new alternative to assess cardiovascular function in models of cardiovascular diseases in the mouse.

Even though the heart rate in mice is high, the Samba sensor system allows stable recordings of left ventricular pressure (Fig. 6). Because introduction of the Samba sensor into the aorta and the left ventricle caused no significant changes in left carotid arterial blood pressure, it is likely that this sensor only modestly affects aortic flow. In comparison, introduction of the 1.4-Fr Millar catheter to the same positions caused a significant drop in mean aortic blood pressure, indicating that this catheter affects central hemodynamics. This must be taken into account when evaluating cardiac function with the Millar catheter.

The present study also revealed some limitations of the Samba sensor system. We observed that the Samba fiber may break during introduction into the carotid artery and advancement from the aorta into the left ventricle. However, during our in vitro examinations, bending the fibers in arcs of both $90^\circ$ and $180^\circ$ with the smallest curve diameter of 2 cm caused no breakage. Thus, by experience and with improved microsurgical technique, this problem may to a great extent be overcome. Damage of the sensor membrane was also demonstrated during the in vivo experiment. This was probably due to the larger diameter of the sensor than the fiber. Further technical improvements, such as smoothing of the transition zone between the fiber and the sensor and better protection of the recording membrane, may be helpful in preventing breakage and membrane damage, especially when the Samba sensor is introduced or retracted through the aortic valve or through a narrow vessel opening.

In conclusion, the Samba sensor is feasible for determination of blood pressure and left ventricular pressure without affecting central hemodynamics in the mouse. The location of the membrane on the sensor tip makes blood pressure measurements in small vessels possible. This pressure recording system appears to be accurate with little drift and temperature sensitivity and thus well suited for cardiovascular measurements in small animals like the mouse.

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DISCLOSURES

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