EXHIBIT 2001

Earbud-Based Sensor for the Assessment of Energy Expenditure, HR, and $\dot{V}O_{2max}$

STEVEN FRANCIS LEBOEUF[1], MICHAEL E. AUMER[1], WILLIAM E. KRAUS[2], JOHANNA L. JOHNSON[2], and BRIAN DUSCHA[2]

[1]Valencell, Inc., Raleigh, NC; and [2]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC

ABSTRACT

LEBOEUF, S. F., M. E. AUMER, W. E. KRAUS, J. L. JOHNSON, and B. DUSCHA. Earbud-Based Sensor for the Assessment of Energy Expenditure, HR, and $\dot{V}O_{2max}$. *Med. Sci. Sports Exerc.*, Vol. 46, No. 5, pp. 1046 1052, 2014. **Introduction/Purpose**: The goal of this program was to determine the feasibility of a novel noninvasive, highly miniaturized optomechanical earbud sensor for accurately estimating total energy expenditure (TEE) and maximum oxygen consumption ($\dot{V}O_{2max}$). The optomechanical sensor module, small enough to fit inside commercial audio earbuds, was previously developed to provide a seamless way to measure blood flow information during daily life activities. The sensor module was configured to continuously measure physiological information via photoplethysmography and physical activity information via accelerometry. This information was digitized and sent to a microprocessor where digital signal-processing algorithms extract physiological metrics in real time. These metrics were streamed wirelessly from the earbud to a computer. **Methods**: In this study, 23 subjects of multiple physical habitus were divided into a training group of 14 subjects and a validation group of 9 subjects. Each subject underwent the same exercise measurement protocol consisting of treadmill-based cardiopulmonary exercise testing to reach $\dot{V}O_{2max}$. Benchmark sensors included a 12-lead ECG sensor for measuring HR, a calibrated treadmill for measuring distance and speed, and a gas-exchange analysis instrument for measuring TEE and $\dot{V}O_{2max}$. The earbud sensor was the device under test. Benchmark and device under test data collected from the 14-person training data set study were integrated into a preconceived statistical model for correlating benchmark data with earbud sensor data. Coefficients were optimized, and the optimized model was validated in the 9-person validation data set. **Results**: It was observed that the earbud sensor estimated TEE and $\dot{V}O_{2max}$ with mean ± SD percent estimation errors of 0.7 ± 7.4% and 3.2 ± 7.3%, respectively. **Conclusion**: The earbud sensor can accurately estimate TEE and $\dot{V}O_{2max}$ during cardiopulmonary exercise testing. **Key Words:** EAR, ACCELEROMETER, PHOTOPLETHYSMOGRAPHY, PULSE

Modifiable health risk factors, such as high stress, poor diet, and sedentary lifestyle, account for 25% of all medical expenses and millions of deaths per year worldwide (2). The U.S. population is becoming increasingly overweight and unhealthy, with an estimated 66% of adults categorized as obese or overweight by the CDC (26). Nonetheless, more than half of American adults exercise on a regular basis (11), spending more than \$55 billion in weight loss programs and more than \$17 billion on fitness products (31). The disconnect between dollars spent on weight loss and obesity levels may be explained by recent findings that traditional diets do not work (24) alone to prevent weight gain and to promote weight loss. Dietary measure must be combined with energy expenditure to accomplish long-term weight loss and maintenance.

Weight loss programs aimed at promoting fitness through direct measurement of physical activity (PA) via pedometer feedback have shown promise. In particular, incorporating a pedometer in daily life activities has been shown to result in a significant reduction in body mass index (BMI) and blood pressure (7). Furthermore, combining engaging feedback with an online user experience correlates with improved maintenance of weight loss in long-term diet/weight management studies (10). These observations indicate that even better outcomes may result from a more direct feedback about energy expenditure and aerobic fitness level, such as $\dot{V}O_2$, calories burned, and $\dot{V}O_{2max}$.

Indeed, there is a clear opportunity to encourage a broader population to embrace active lifestyles by integrating mobile fitness monitoring devices with compelling user experiences. However, compelling user experiences must be meaningful, and to be meaningful, the fitness monitoring gadgets must provide information that is sufficiently accurate to be actionable. This goal is challenged by the fact that commercial pedometers are inaccurate by greater than ± 20% in reporting calories burned (8,29).

Address for correspondence: Steven Francis LeBoeuf, Ph.D., Valencell, Inc., 2800-154 Sumner Blvd., Raleigh, NC 27616; E-mail: LeBoeuf@valencell.com.

Submitted for publication March 2013.
Accepted for publication October 2013.

0195-9131/14/4605-1046/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000000183

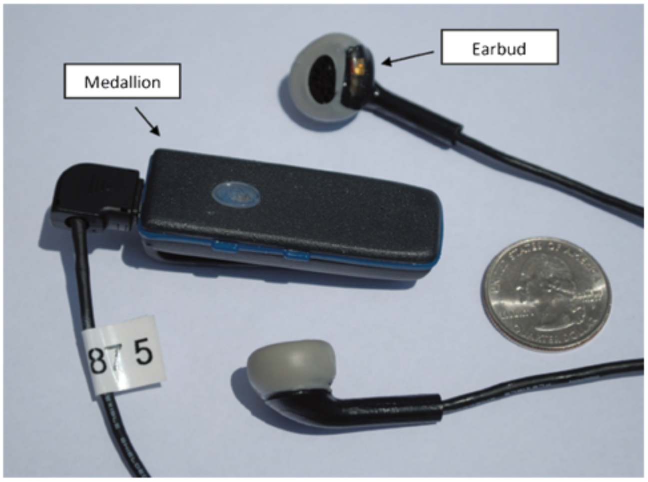

FIGURE 1 The components and size of the device under test (DUT). Shown are the earbud and the medallion containing the majority of the computational components. Shown for scale is a U.S. quarter. Note the position of the sensor module at the bottom of the antitragus. The sensor module is configured to fit between the concha and the antitragus of the ear.

Recent energy expenditure studies, using a wearable ActiHealth chest strap monitor for measuring both PA and HR, have demonstrated greater accuracy (5,6). These researchers achieved such predictive accuracy through branched equation modeling, using HR information and accelerometry information as independent variables. Although these findings are quite encouraging, researchers using the ActiHealth monitor point out several shortcomings. First, despite the relatively high precision achievable through branched equation modeling, poorer accuracy is observed if individual calibrations are not used (5,6). This means that the wearable monitors must be calibrated for each user, in a process that is both time consuming and burdensome. Furthermore, as audio earbuds are packaged with smartphones and digital media players that are sold in volumes of hundreds of millions of units a year (16), the audio earbud form factor provides the opportunity to reach a larger consumer audience than that of an HR chest strap, which is sold in volumes of less than 10 million per year.

The goal of this study was to determine the feasibility of a highly miniaturized, noninvasive optomechanical earbud sensor technology for accurately monitoring physiological metrics such as HR, total energy expenditure (TEE), and maximum oxygen consumption ($\dot{V}O_{2max}$), and this study is reported herein.

METHODS

To overcome these reported limitations, an earbud sensor module—as opposed to an ActiGraph wrist-, arm-, or leg-worn sensor—was selected in this study (Fig. 1). Details of the mechanism of operation are described elsewhere (17–21), but in summary, the earbud comprised a highly integrated sensor module capable of measuring subtle blood flow changes via reflective photoplethysmography (PPG) and changes in body motion through a three-axis accelerometer. This sensor module was designed 1) to capture and digitize the optical PPG signal and 2) to send the digitized information to a digital signal processor (DSP) for removing motion artifacts and environmental noise from the PPG signal and to continuously generate estimates of HR and $\dot{V}O_2$ metrics in real time based on a statistical model comprising PPG and accelerometry information. The DSP was in electrical communication with a Bluetooth chipset so that the real-time metrics could be called upon by a client device (such as a laptop or smartphone). A preliminary feasibility study of this PerformTek® earbud sensor module had previously demonstrated accurate HR measurements during exercise, thus potentially eliminating the need for an electrocardiographic chest strap in many use cases. This was a critical finding for the issue of user compliance, as 58% of U.S. headphone owners listen to headphones while exercising and 34% wear headphones during everyday life activities (such as doing work around the house) (13), 10 times greater than the number of Americans who exercise with chest straps.

Subjects. In this study, 23 subjects of good physical health were divided into a training group of 14 subjects and a validation group of 9 subjects. This sample size is justified by the high "effect size" observed for calibrated correlations of $\dot{V}O_2$ and HR (22) and is further supported by the very high R^2 coefficient observed (23) when comparing the earbud-determined HR to 12-lead ECG-measured HR during exercise. The training group (Table 1a) comprised 12 men and 2 women: age = 39 ± 11.8 yr, weight = 73.5 ± 12.2 kg, height = 69 ± 2.9 cm, BMI = 23.6 ± 2.1 kg·m^{-2}. The validation group (Table 1b) comprised five men and four women: age = 36 ± 6.9 yr, weight = 67.6 ± 15.7 kg, height = 173 ± 7.4 cm, BMI = 22.3 ± 4.0 kg·m^{-2}. Each

TABLE 1. Descriptive characteristics (mean ± SD) of (a) training group and (b) validation group.

(a) Training Group		(b) Validation Group	
Parameter	**Value (Mean ± SD)**	**Parameter**	**Value (Mean ± SD)**
Sex	2 females, 12 males	Sex	4 females, 5 males
Age	30 ± 11.8 yr	Age	36 ± 6.9 yr
Weight	73.5 ± 12.2 kg	Weight	67.6 ± 15.7 kg
Height	175 ± 7.4 cm	Height	173 ± 7.4 cm
Distance	2.95 ± 0.5 km	Distance	2.80 ± 0.3 km
Energy expenditure	213 ± 47.8 kcal	Energy expenditure	178 ± 51.5 kcal
Maximum VO_2	55.9 ± 6.5 mL·kg ^{1}·min ^{1}	Maximum VO_2	55.1 ± 5.5 mL·kg ^{1}·min ^{1}
BMI	23.6 ± 2.1 kg·m ^{2}	BMI	22.3 ± 4.0 kg·m ^{2}

subject underwent the same exercise measurement protocol, including a treadmill-based cardiopulmonary exercise (CPX) test, at 0° incline, to reach $\dot{V}O_{2max}$. The achievement of $\dot{V}O_{2max}$ was determined by reaching at least two of the three following criteria: plateau in $\dot{V}O_2$ over the last minute of exercise, achievement of at least 1.10 RER, and achievement of at least 17 in perceived exertion on the Borg scale. The mean ± SD $\dot{V}O_{2max}$ values of the training group and the validation group were 55.9 ± 6.5 and 55.1 ± 5.5 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively. Benchmark sensors included a 12-lead ECG for measuring HR, a calibrated treadmill for measuring distance traveled, and a gas-exchange analysis instrument for measuring TEE and $\dot{V}O_{2max}$. The earbud sensor served as the device under test. All subjects provided informed consent as approved by the investigational review board of the Duke University School of Medicine.

CPX testing. Subjects began the study by first being prepped for wearing the benchmark sensors. A Quinton12-lead ECG system was used as a benchmark for HR, and a TrueMax 2400 ParvoMedics (ParvoMedics, Sandy, UT) gas-exchange analysis mouthpiece was used as a benchmark for energy expenditure and continuous measures of $\dot{V}O_2$. The benchmark sensors were calibrated according to the standard maintenance guidelines of the manufacturers. The subjects were then fitted with an earbud sensor (Fig. 1) powered by the aforementioned PerformTek physiological monitoring technology. Participants were then asked to sit at rest in a supine position in a reclining chair for a few minutes while wearing the benchmark equipment and earbud sensor. After the resting period, subjects were instructed to move from the chair to the calibrated treadmill and execute the CPX testing with graded intensity ranging from 0 to 9.1 mph speeds. The protocol used consisted of 2-min stages, increasing the workload by approximately one metabolic equivalent per stage. Measurements from the benchmark sensors and earbud sensor were collected continuously throughout the treadmill run. Participants were asked to continue running during each increasing speed until they were completely exhausted. The last 40 s of benchmark gas-exchange analysis data were averaged to determine measured peak $\dot{V}O_2$.

Earbud sensor. The novel noninvasive earbud sensor (Fig. 1) used in this study was designed by Valencell, Inc. (Raleigh, NC). The earbud sensor comprised a sensor module, a microprocessor, and a wireless Bluetooth® chipset. The optomechanical sensor module, comprising the sensor elements, was embedded within the right audio earbud, as shown in Figure 1, such that the sensor module would rest between the concha and the antitragus of each subject upon earbud placement. The right and the left earbuds were designed to be pluggable to a wireless Bluetooth "medallion" via a detachable connector (as shown in Fig. 1). The medallion housed the microprocessor and the Bluetooth chipset.

At the heart of this noninvasive earbud sensor is a highly miniaturized optomechanical module (17–21,23) that measures optical and mechanical information from the area of a user's ear between the antitragus and the concha. This novel sensor module comprises an infrared light-emitting diode, a photodetector element, a three-axis accelerometer, and an optomechanical housing. Designed to fit flush with the body of a standard audio earbud, the earbud essentially maintains the form factor of a typical audio earbud and does not require an ear clip or an in-ear-canal sensor to function.

The optical and mechanical information collected from the ear are sampled via methods akin to reflective PPG and three-axis accelerometry, and this sampled information is then processed by novel algorithms (17,18) coded on firmware within the microprocessor for extracting weak blood flow signals from excessive motion noise. It is well known that motion artifacts are the greatest limiting factor to accurate vital signs monitoring via PPG (3,14,27). However, Valencell's PerformTek biometric algorithms actively process noisy body signals and extract accurate biometrics even during aggressive running and PA (23). These biometric signals are then combined with contextual accelerometry information within a statistical model to generate assessments of HR zone, calories burned, aerobic capacity ($\dot{V}O_{2max}$), and other parameters (17–21). A phone, computer, or other mobile device can communicate directly with the microprocessor via a Bluetooth link. In this particular study, the earbud sensor data were streamed directly to a laptop via Bluetooth.

Statistical methodology. A multiple linear regression model had been developed previously by Valencell to provide a linear relation between estimated TEE, as predicted by the earbud sensor measurements, and the measured TEE, as recorded by the benchmark gas-exchange analysis device. This linear model comprised fixed and time-varying terms. The fixed terms included weight (W), age (A), and sex (G) having a binary value of 0/1 for women/men, respectively. The time-varying terms included the earbud-estimated TEE (EB TEE) and the linear operations of real-time PPG and accelerometry (ACC). Although the details of the linear model are outside the scope of this article, the formalism of the resulting linear equation may be described by EB TEE = $f(g(\text{PPG}), h(\text{ACC}), W, A, G)$, where g and h are functions of PPG and ACC, respectively. It is important to note that this linear model was directed toward estimating TEE, and not the individual elements of resting energy expenditure (REE) or activity-related energy expenditure (AEE), as TEE is what is measured by the gas-exchange analysis.

A separate model had been previously developed by Valencell to estimate $\dot{V}O_{2max}$ based on the HR and accelerometry data collected during several prior rounds of CPX testing. The methodology behind this $\dot{V}O_{2max}$ estimation is described elsewhere (18), and the equation follows the formalism of EB $\dot{V}O_{2max}$ = $f(\text{Max HR}, \text{Min HR}, k(\text{ACC}))$, where EB $\dot{V}O_{2max}$ is the earbud-derived $\dot{V}O_{2max}$, Max HR is the maximum reliable HR measured by the earbud sensor, Min HR is the minimum reliable HR measured by the earbud sensor, and k is a function of the accelerometer readings measured throughout the CPX testing.

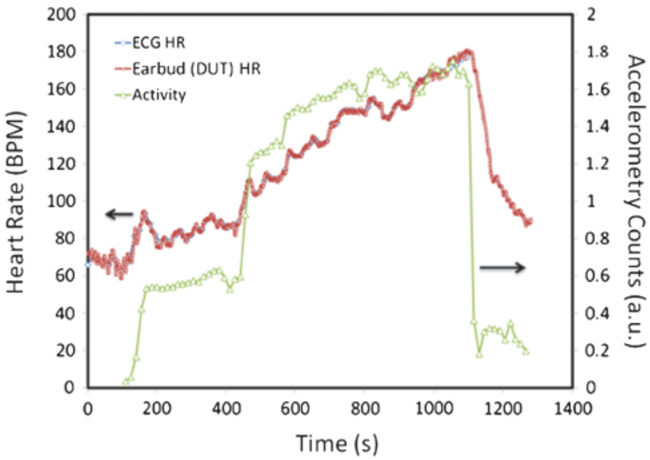

FIGURE 2 CPX testing output from a characteristic test. In this characteristic CPX test, the time of the progressive exercise test conducted on a standard treadmill is shown on the abscissa; the PA intensity using accelerometer counts in arbitrary units (a.u.; green line) is shown on the rightward ordinate; the HR in beats per minute from either the PerformTek earbud device (red) or from the simultaneously measured ECG (blue) is shown on the leftward ordinate. The earbud-determined HR and the ECG-measured HR show complete alignment in this exemplary characteristic test.

After the 14-person training data study, the best-fitting coefficients for the TEE and $\dot{V}O_{2max}$ models were determined, and the resulting optimized equations were used in the nine-person validation data study to estimate TEE and $\dot{V}O_{2max}$ in real time. The resulting earbud-estimated values (EB TEE and EB $\dot{V}O_{2max}$) were then compared with benchmark-measured values in accordance with the Bland–Altman plot (1,4).

RESULTS

HR. As previously described, the earbud measurements of HR and PA are part of the foundational formulas for EB TEE and EB $\dot{V}O_{2max}$. Therefore, it is important that these measurements are accurate. An exemplary characteristic plot of real-time ECG, PerformTek HR, and *h*(ACC) for a subject undergoing a CPX test is shown in Figure 2. Note that for this test, the benchmark ECG and the earbud HR are nearly identical throughout the run, such that they completely overlap each other. Although complete overlap was not always observed, complete overlap was typically observed. Only rarely did the earbud or the ECG diverge to a substantial degree, as exemplified by the tight correlation shown in Figure 3. Also, on the rare occasions when divergence was observed, it was often attributable to either the earbud moving out of the ear or the ECG leads decoupling from the subject's skin. For the sake of objectivity in this study, all HR data points measured by the earbud and ECG sensors are shown in Figure 3, even for the case where earbud or ECG failures are subjectively believed to have occurred.

A Bland–Altman plot comparing earbud-estimated HR (EB HR) versus the benchmark 12-lead ECG measured from the 14-person training group is presented in Figure 3. This figure illustrates the excellent agreement between EB HR and ECG throughout a full range of activity from rest to >200 bpm; the mean difference (bias) was −0.2%, the SD was ±4.4%, and the coefficient of determination (R^2) was 0.98. In contrast with other reported optical HR measurement devices reported in literature (3,14,27), the EB HR measurement is quite robust throughout a full range of activity because the PerformTek biometric signal extraction algorithms are capable of characterizing motion noise during numerous activities and attenuating motion artifacts from the optical signal in real time.

In contrast with hip and pocket-worn pedometer-based approaches for calculating distance (8,15,29), the PA level measured by the earbud prototype provides a good reference for body displacement during walking, jogging, and running without requiring knowledge of the user's sex, height, age, weight, or fitness. Furthermore, neither a calibration regimen nor a GPS is required to tune parameters to the wearers' gait. The earbud prototype distance measurement was highly accurate, with a bias of 0.3%, an SD of 4.2%, and an R^2 of 0.93. This distance measurement was obtained through a novel transformation of three-axis accelerometer data, and its accuracy is aided by the sensor location at the ear.

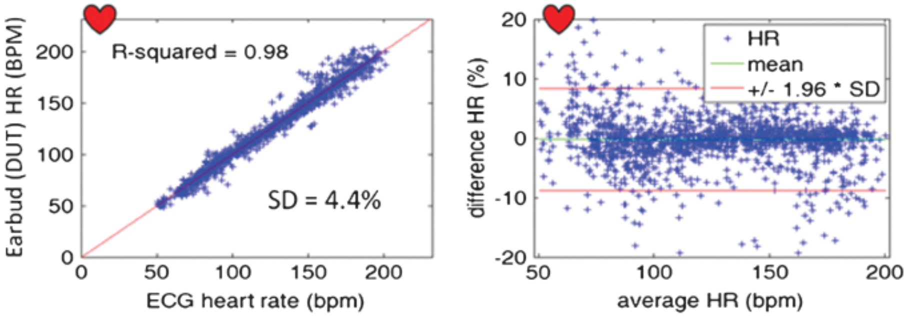

FIGURE 3 HR using the earbud (device under test [DUT]) and the simultaneously measured ECG benchmark. A. Regression relation comparing estimated (earbud) versus measured (ECG) HR for all data points collected for each participant. B. The Bland Altman plot of same. All the data points were taken from the training data collected during the Duke CPX test. The mean difference (bias) was 0.2% and the SD was 4.4%. The mean is shown by the green line, and the 1.96 SD (95% limits of agreement) boundaries are shown by the red lines.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | **sales@docketalarm.com** | **1-866-77-FASTCASE**

fastcase®
Smarter legal research.