Long-term recording of cardiac output via an implantable haemodynamic monitoring device

Å. Ohlsson, T. Bennett, F. Ottenhoff, C. Bitkover, B. Kjellström, R. Nordlander, H. Åström and L. Rydén

Departments of Cardiology and Thoracic Surgery, Karolinska Hospital, Stockholm, Sweden; Heart Failure Management, Medtronic Inc, Minneapolis, MN, U.S.A.

Long-term monitoring of central haemodynamics with implanted monitoring systems might be valuable in managing heart failure patients. Such systems offer an opportunity for repeated ‘semi-invasive’ cardiac output determinations according to the Fick principle.

Five patients, four with chronic heart failure and one with chronic pulmonary disease, underwent supine exercise testing during cardiac catheterization at 0, 2, 6 and 11 months after implantation of a right ventricular mixed venous oxygen saturation sensor connected to an implantable haemodynamic monitor. The monitor provided a continuous measure of oxygen saturation via a radio-telemetry link to a metabolic cart capable of measurement of breath-by-breath oxygen consumption. Cardiac output was computed using oxygen consumption, mixed venous oxygen saturation, arterial oxygen saturation by pulse oximetry and haemoglobin oxygen capacity.

Biosensor-derived oxygen saturation compared to blood samples from the pulmonary artery showed an excellent correlation over time, $r^2=0.94$ (implant), $r^2=0.91$ (6–11 months). There was a strong correlation between semi-invasive-determined cardiac output using the biosensor and the invasive technique, which persisted over the entire follow-up period.

Repeated semi-invasive cardiac output measurements using an implanted haemodynamic monitoring system in chronic heart failure patients is feasible and the data may be of value for optimizing therapy.

(Eur Heart J 1996; 17: 1902–1910)

Key Words: Cardiac output, long-term monitoring, Fick principle, implantable.

Introduction

Cardiac output is an essential parameter for prognostic and therapeutic evaluation during acute as well as chronic heart disease. Originally, cardiac output was determined according to the Fick principle\textsuperscript{[1]}, which is based on total oxygen uptake and arteriovenous oxygen difference. Cardiac output determination via the Fick principle necessitates catheterization of both the pulmonary and a systemic artery to determine oxygen saturation, together with a simultaneous recording of oxygen uptake. In the absence of arteriovenous shunts, cardiac output according to the Fick principle represents the true value. Other techniques for cardiac output determination have been calibrated against the Fick technique. Among them, dye-dilution and thermodilution are the most commonly used. Although these techniques eliminate the demand for oxygen uptake and arteriovenous oxygen difference, they still require right heart catheterization\textsuperscript{[2,3]}. This limits the possibility of using cardiac output determinations during long-term haemodynamic monitoring.

Oxygen saturation in blood can be measured by biosensor technology, a technique that has been applied for rate triggering of cardiac pacemakers\textsuperscript{[4–6]}. During pacing it is variations in oxygen saturation rather than the absolute levels that are required. With the aim of developing a long-term haemodynamic monitoring system, we studied the possibility of measuring mixed venous oxygen saturation via a modified biosensor lead in the right ventricle. Oxygen saturation from this position correctly expressed the mixed venous saturation in the pulmonary artery, with excellent stability over a period of 24 h\textsuperscript{[7]}.

With the hypothesis that it would be possible to follow haemodynamic parameters over periods of months, a haemodynamic monitoring system was developed. This paper describes how this equipment offers an opportunity for repeated, semi-invasive cardiac output...
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Pat no</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Aetiology</th>
<th>NYHA (class)</th>
<th>EF (%)</th>
<th>Heart volume (ml. m⁻²)</th>
<th>Cardioactive drugs (daily dosage in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>70</td>
<td>IHD</td>
<td>III</td>
<td>30</td>
<td>550</td>
<td>aspirin 160, digoxin 0.13, furosemide 80, ismn 60</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>60</td>
<td>DCMP</td>
<td>III</td>
<td>20</td>
<td>690</td>
<td>aspirin 75, digoxin 0.25, captopril 75, amiloride 5, furosemide 120</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>57</td>
<td>IHD</td>
<td>III</td>
<td>24</td>
<td>850</td>
<td>aspirin 160, captopril 75, furosemide 120, metoprolol 50, bendroflumethiazide 5</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>43</td>
<td>IHD</td>
<td>III</td>
<td>17</td>
<td>700</td>
<td>aspirin 160, furosemide 60, ismn 20, enalapril 20, metoprolol 50, theophyllamin 270, budesonid 0.8, amiloride 5</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>71</td>
<td>COL</td>
<td>NA</td>
<td>56</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>60 ± 11</td>
<td>29 ± 16</td>
<td>638 ± 170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EF=ejection fraction; IHD= ischaemic heart disease, DCMP=dilated cardiomyopathy; COL=chronic obstructive lung disease; ismn = isosorbide mononitrate; NA = not applicable.

determinations according to the Fick principle. Long-term stability and reliability were tested by means of repeated conventional catheterizations.

Materials and methods

Patients

Five patients with implanted haemodynamic monitoring systems were studied. Four of them had chronic heart failure and were in NYHA functional class III. The fifth patient had severe chronic pulmonary disease requiring intermittent oxygen supplementation. Pertinent clinical characteristics of the patients are presented in Table 1. All patients had given their written informed consent and the study protocol was approved by the ethical committee of the Karolinska Hospital.

The implantable haemodynamic monitor

The implantable haemodynamic monitor (Medtronic Inc., Minneapolis, MN, U.S.A.) is designed as a conventional single-lead pacemaker system. A lead with two incorporated sensors for continuous measurement of oxygen saturation and pressure was positioned in the right ventricular apical region. The oxygen sensor contains two light emitting diodes. The lights are of wavelengths 660 nm (red) and 880 nm (infra-red). Reflected light is detected by a photosensitive diode. The magnitude of the reflected light is converted to time intervals that are inversely proportional to the magnitude of the oxyhaemoglobin[15,6,8]. The lead is connected to a monitor and memory device contained within an ordinary pacemaker can, which is implanted beneath the left clavicle.

Data from the biosensors are continuously averaged to be stored in the memory. Stored data and real time signals can be transferred to a computer-based programmer by telemetry. In this study continuous real time measurements of oxygen saturation from the biosensor was linked by telemetry to the gas exchange analyser computer (see below).

Reference system

A 7F Swan–Ganz fiberoptic catheter (Opticath, Abbot Laboratories, Chicago, IL, U.S.A.) was inserted via a femoral or an arm vein to be positioned with the tip in the pulmonary artery. Oximetry (Oximetrix III System, Abbot Laboratories, Chicago, IL, U.S.A.) was used continuously to measure oxygen saturation. Blood samples from the pulmonary artery were obtained from this catheter. Arterial blood samples were obtained from a short polythene cannula inserted into the femoral or brachial artery. These blood samples were analysed with a spectrophotometer (IL 482 CO-Oximeter System, Instrumentation Laboratory, Lexington, MA, U.S.A.).

Oxygen consumption was calculated with an automated breath-to-breath system (Medical Graphics Corp, St Paul, MN, U.S.A.). The patient breathes through a mouthpiece attached to a non-rebreathing valve. Air is removed from the valve and delivered to a flow meter and carbon-dioxide and oxygen analysers. A pneumo-tachymeter is used for air flow, a dual beam infra-red absorption chamber for carbon dioxide and a zircon-based electrochemical cell for oxygen. A waveform analyser and a computer provides graphic presentation of all derived data. Arterial oxygen saturation was measured with pulse oximetry (BIOX 3700 Ohmeda, Louisville, CO, U.S.A.) from a finger tip and was stored in the gas exchange analyser computer.

Study protocol

Data achieved from the haemodynamic monitoring system were compared to data derived from the reference system at the time of implantation and after 2, 6 and 11 months. The patients were studied at rest and during provocative procedures applied in order to induce
Invasive Method:
• $\text{SaO}_2$: Arterial Catheter
• $\text{SvO}_2$: Swan Ganz Catheter in the Pulmonary Artery
• Intermittent Measurement

Non-Invasive Method:
• $\text{SaO}_2$: Pulse Oximetry
• $\text{SvO}_2$: Biosensor in the Right Ventricle
• Continuous Measurement

$Q = \text{VO}_2/\text{AV O}_2$ Difference
$\text{AV O}_2$ Difference = $(\text{SaO}_2 - \text{SvO}_2) \times \text{O}_2$ Capacity

Figure 1  Schematic presentation of the experimental set up illustrating the Fick principle and the semi-invasive and invasive data used for calculations. $Q$ = cardiac output; $\text{VO}_2$ = oxygen uptake; $\text{AV O}_2$ difference = arteriovenous oxygen saturation difference; $\text{SaO}_2$ = arterial oxygen saturation; $\text{SvO}_2$ = mixed venous oxygen saturation.

haemodynamic changes. Provocation included 5 min of supine exercise at a work load of 30–40 watts and 15 min on 5.0 mg buccal nitroglycerine (Suscard®, Astra-Hässlé, Mölnadal, Sweden). Resting periods of 20 min were inserted before, between and after the provocative procedures.

Oxygen saturation recorded from the implanted biosensor, the Oximetrix System, and the pulse oximeter were continuously monitored and stored on digital tape using a high fidelity instrumentation recorder (TEAC RD 100T, Montebello, CA, U.S.A.). Data from the biosensor and the pulse oximeter were linked and stored in the gas exchange analyser computer. Metabolic assessment was performed during the last 5 min of all the resting periods, throughout the entire supine exercise period and during the last 5 min on nitroglycerine. Blood samples were obtained from the Swan–Ganz catheter and from the arterial line during the last 30 s of the resting periods and haemodynamic provocations.

Cardiac output was simultaneously determined according to the Fick principle with the arteriovenous oxygen difference calculated from the blood samples and from the biosensor and pulse oximetry data (Fig. 1). For these calculations, oxygen uptake was averaged during the last 30 s of the resting periods and during the last 60 s of the haemodynamic interventions. The semi-invasively derived cardiac output based on arteriovenous oxygen difference calculated from data produced by the biosensor and by pulse oximetry, was presented on line on the gas exchange analyser computer together with all registered parameters (Fig. 2).

Statistics

Results are given as mean ± standard deviation. Statistical significance of differences between values was tested by Student’s t-test for paired values. The correlation between values obtained with the different methods was calculated according to a linear regression model. A $P$ value <0.05 was considered statistically significant.

Results

All patients were followed for at least 7 months. At that time one patient (3) developed symptomatic ventricular tachycardia, but this was not related to the monitoring device since it persisted following explantation. The patient received an implantable cardioverter-defibrillator. By the time of data collection all remaining patients had completed the full study protocol. No complications were noted during and after the implantation of the monitoring device or during follow-up.
Cardiac output via an implantable haemodynamic monitor

Figure 2 On line data as presented by the gas exchange analyser during a supine exercise test in a typical patient (3). For abbreviations see Fig. 1. ● = arterial oxygen saturation from blood samples, ▲ = oxygen saturation from blood samples, ■ = cardiac output calculated from blood samples.

Figure 3 Difference (%) between oxygen saturation (SvO₂) derived from the biosensor in the right ventricle and from blood samples in the pulmonary artery at the time of implantation and after 2, 6 and 11 months. Mean ± standard deviation (n₁ = number of patients, n₂ = number of observations).

**Biosensor stability and accuracy**

To evaluate the biosensor stability over time, biosensor-derived oxygen saturation was compared to blood samples from the pulmonary artery. A plot of biosensor-derived data and oxygen saturation measured from the blood samples at the time of implant and after 2, 6 and 11 months of follow-up is shown in Fig. 3. At implant, the mean of the difference between the two methods was 0.4 ± 3.8% after 2 months 2.2 ± 5.4%, after 6 months 1.3 ± 3.5% and after 11 months (n=4) −1.0 ± 3.9%, respectively. These differences were not statistically significant. Individual data at different times of follow-up are given in Fig. 4, panels (a)–(d). As can be seen, the correlation was excellent at the time of implantation (a) and remained so during the time of follow-up (b)–(c). The accuracy of the biosensor was apparent over a wide range of values from an oxygen saturation of 15 to 75% (d).

**Cardiac output**

Cardiac output from the post-implant comparisons between the semi-invasive biosensor data and those determined via the Fick invasive technique are shown in
Figure 4 Correlation between oxygen saturation derived from the right ventricular biosensor and from blood samples obtained in the pulmonary artery at the time of implantation (a), and after 2 (b), 6 and 11 months (c). All data for the complete period of follow-up is shown in (d). The identity line is marked in all panels. In panel (b) and (d) patients 1 and 2 at the 2 months exercise test are marked as X (see text).

Fig. 5 (a). Findings after 2, 6 and 11 months of follow-up are given in panels (b) and (c). There was a strong correlation between the two methods which persisted over the complete follow-up period. Figure 6 shows pooled values for cardiac output determined according to the invasive Fick method and calculated via the biosensor from all patients at the different haemodynamic interventions at all follow-up catheterizations. There were no significant difference between the two methods. This illustrates the magnitude of the response to exercise and the ability of the semi-invasive system to accurately register this change compared to the invasive method.

Comments

Two patients (1, 2) had high (compared to blood samples), biosensor-derived oxygen saturation values at the 2 months supine exercise test (Fig. 4(b)). Consequently, cardiac output calculated from these values were also high (Fig. 5(b)). Subsequent biosensor oxygen saturation data at 6 and 11 months agreed more closely to the reference values in both patients. Possibly, there was transient decrease of the biosensor response at 2 months, which subsequently recovered. These measurements were carried out during peak exercise, when maintenance of the radiofrequency telemetry link is
Figure 5  The difference between semi-invasive cardiac output obtained from biosensor-derived data and cardiac output calculated from invasive data shown as Bland Altman plots, at the time of implantation (a), after 2 (b), 6 and 11 months (c) and all data compiled (d). Mean ± 2 standard deviations (SD). In (b) and (d), cardiac outputs from patients 1 and 2 at the 2 months exercise test are marked as X (see text).
Figure 6  Pooled values for cardiac output determined by the invasive Fick method (●) and non-invasively (■) by biosensor-derived data during different haemodynamic provocations at the follow-up catheterizations. Mean ± standard deviation for the group (CO = cardiac output, n = number of observations).

typically most difficult. Thus, it is possible that transient corruption of the telemetered signals caused these spurious observations.

Two patients (4, 5) had significant changes in their biosensor-derived oxygen saturation between the initial post-implant study and the 2 months study. Since the sensors were still responding appropriately to changes in oxygen saturation, we determined new coefficients for the conversion of red and infra-red reflection signals into actual oxygen saturations. These corrections were carried out using the 2 months' values and were subsequently kept constant for all remaining studies in these patients.

Discussion

This study introduces a new concept for continuous or repeated, semi-invasive measurements of cardiac output according to the Fick principle. It opens an opportunity for long-term haemodynamic monitoring via a biosensor connected to a completely implantable monitoring system.

The biosensor

The idea of incorporating oxygen sensors in implantable devices is not new. The possibility of using variations in oxygen saturation for rate modulation of cardiac pacemakers was originally suggested by Wirzfield et al. and has subsequently been modified and utilized by others. These reports were based on sensor technology, very similar to the present. Pacemaker rate response is based on changes in oxygen saturation and not on absolute values. For haemodynamic monitoring, two important requirements need to be fulfilled. Mixed venous oxygen saturation must be expressed as an absolute value and stability over time must be documented. Steinhaus et al. measured oxygen saturation for up to 12 months in 10 patients with severe heart failure. They took telemetered values using a system similar to ours. Long-term stability was documented by blood samples of mixed venous oxygen saturation obtained during the period of follow-up. In their study, however, no attempts were made to measure cardiac output.

The present study supports our previous observation that it is possible to obtain absolute values of mixed venous oxygen saturation from a sensor located in the right ventricle. In our original study the period of observation was limited to 24 h. The present report confirms our findings and documents sensor stability over a long period, up to one year of follow-up.

Reference methods and recording accuracy

The reference methods are both well established. The spectrophotometric and fibreoptic derived oxygen saturations were well in accordance, thus representing valid measures against which the biosensor was checked.

Biologically significant deviations of the biosensor-derived oxygen saturation were noted in two patients between the initial post-implant recordings and data retrieved at the 2 month follow-up. This change, already suspected when reading data from the implanted monitor, was confirmed during catheterization. Since the change in oxygen saturation recorded from the biosensors during the provocative protocol was completely in accordance with changes measured by the Oximetrix equipment and blood sampling, both biosensors were recalibrated. The subsequent function accorded well with expectations throughout the remaining period of follow-up. The mechanism behind the drift in these two devices is still unknown. One explanation could be fibrin coating or clotting around the biosensor. Although we experienced no further problems of this kind, studies still needs to verify whether it will cause clinical problems. It is possible that coating the lead with heparin could be used as a preventative measure. The high biosensor-derived oxygen saturation values observed during exercise in two patients were occasional events only. Values obtained at rest during the same procedure did not differ from values obtained from the blood samples. The most likely explanation for this problem was a transient loss of the telemetry connection during exercise.

Cardiac output

With on-line availability of telemetrically transmitted mixed venous oxygen saturation from the biosensor it was easy to apply the Fick principle for repeated evaluation of cardiac output. Arterial oxygen saturation was determined transcutaneously using standard equipment. Although this parameter does not change much over time in most individuals such an assumption could introduce a bias when recording cardiac output in patients with low and variable arterial oxygen.
Cardiac output via an implantable haemodynamic monitor

Activity

Heart rate

Had a few beers at a party

Sweden won Olympic gold medals in ice hockey

SvO₂

Figure 7  Example of trend data derived from the implantable haemodynamic monitor during a 2-week period. Activity, heart rate and mixed venous oxygen saturation (SvO₂), are presented as averaged values over 17 min. (Hz=Hz, beats.min⁻¹=beats per minute). □=a.m.; ■=p.m.

saturation. Oxygen consumption can be determined by commercially available breath-to-breath oxygen analysers with good accuracy. To simplify calculations, storage and presentation of data all parameters were entered into a personal computer. An example of the form of presentation used during on line recording during exercise testing is given in Fig. 2. Since mixed venous oxygen saturation was accurately expressed by the biosensor it was not surprising that there was excellent similarity between semi-invasively determined cardiac output and cardiac output based either on pulmonary arterial blood sampling or oximetry-derived data. The provocations used demonstrated that this relationship was valid over a wide range of values. The repeated catheterizations documented stability over time. As can be seen from Fig. 2, the biosensor-based technique for determining cardiac output offers a possibility of following this parameter continuously. It is more flexible than dye- and thermo-dilution techniques, which are dependent on repeated injection of tracers and the time needed for recording the dilution curves.

Besides giving the opportunity to measure cardiac output directly, mixed venous oxygen saturation values are stored over time in the monitor. Accordingly, it is possible to gain an impression of the haemodynamic state over time due to the known relationship between mixed venous oxygen saturation, arteriovenous oxygen difference and cardiac output. In the monitor in current use, oxygen saturation data may be stored for 2-week periods as averaged values every 17 min. Shorter sampling periods permits averaging over shorter periods of time and with continuous telemetry, beat-by-beat data are available. By relating mixed venous oxygen saturation with diaries of patient activity it is possible to evaluate the haemodynamic state since their last follow-up. Data derived over time may be presented in various forms. An example is given in Fig. 7 (in which also heart rate and activity levels as recorded via the monitor are presented).

Study limitations

This is, to our knowledge, the first report of a long-term semi-invasive recording of cardiac output following the Fick principle. In this pilot study, five patients were included, one of whom had chronic pulmonary disease with normal left ventricular function. Despite the low number of patients and a long period of observation, repeated catheterizations over several months and the provocative haemodynamic protocol provided a large number of observations over a wide range of mixed

Eur Heart J, Vol. 17, December 1996
venous oxygen saturation levels. However, in future studies a larger number of patients will have to be included to verify the clinical implications of these preliminary results.

The catheterizations and haemodynamic provocations were carried out in the supine position. It may be argued that venous oxygen saturation in the right ventricle could vary with body position. However, this seems unlikely. Data, some obtained during the invasive parts of the study protocol, and some derived during various types of upright exercise did not disclose any changes in oxygen saturation that made it reasonable to suspect a change in biosensor accuracy related to body position. As already emphasized, further information is needed regarding the possible interference from sensor coating. The present data, together with previous reports on long-term experiences with rate-modulated pacemakers[5,6] are encouraging. However, haemodynamic monitoring using this technology should be performed while keeping in mind the possibility of drifting data. If suspected, it is easy to recalibrate the sensor simply by obtaining blood samples from the pulmonary artery, as described in two of our patients.

Clinical implications

The ability to monitor cardiac output according to the Fick principle may have both long- and short-term applications. The present technology offers an opportunity for long-term monitoring of patients in severe heart failure. When therapeutic adjustments necessitate haemodynamic measurements, these patients have to be hospitalized for catheterizations. Such procedures are, besides being uncomfortable, limited to time periods of only a few days. Long-term monitoring with an implantable device may allow therapeutic adjustments to be made during daily activity with the patient ambulatory. The technology may also improve the understanding of the pathophysiology of severe congestive heart failure. Although considerable improvements in therapy have been gained over the last decade, such patients still have poor prognosis[10]. Further information on haemodynamic changes induced by daily life, including physical as well as emotional stress may contribute to improved care. Another category of patients that may benefit from a continuous access to haemodynamic data are those with serious pulmonary disorders including primary pulmonary hypertension. Haemodynamic monitoring based on biosensor technology may also be of value for short-term purpose. In such circumstances, there is no need to implant the monitor and memory components. Data may easily be combined with commonly used systems for bedside monitoring in intensive care units.

This study was supported by research grants from the Swedish Heart and Lung Foundation, the Foundation of Clas Groschinsky, Sweden, the Karolinska Institute, Sweden and Medtronic Inc, Minneapolis, MN, U.S.A.

Parts of the data in this manuscript were presented at the 44th Annual Scientific Session of the American College of Cardiology in New Orleans, Louisiana, U.S.A. in March, 1995.

References