Device-based impedance measurement is a useful and accurate tool for direct assessment of intrathoracic fluid accumulation in heart failure

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Aims

Heart failure patients are often equipped with implanted devices and are frequently hospitalized due to volume overload. Reliable prediction of imminent fluid congestion has the potential to provide early detection of cardiac decompensation and therefore might be capable of enhancing therapy management. We investigated whether implant-based impedance (Z) measurement is closely correlated with directly assessed extravascular lung water and might thus be useful for patient monitoring.

Methods and results

In sheep, pulmonary fluid congestion was induced. Continuous haemodynamic monitoring was performed and extravascular lung water index (EVLWI) assessed. An implanted device with a right ventricular lead measured Z using different electrode configurations. All animals developed gradual pulmonary fluid accumulation leading to inclining lung oedema: EVLWI did increase from 9.5 ± 1 to 21.1 ± 5.1 mL/kg (+127%). A concomitant decrease of Z by up to 23%, depending on the electrode configuration, was observed and regression analysis between Z and EVLWI yielded a significant inverse correlation.

Conclusion

Changes of Z show a strong inverse correlation with changes of directly measured EVLWI. This allows the application of Z as a measure of intrathoracic fluid status and has the potential to optimize patient care, especially in the context of evolving telemedicine concepts.

Keywords

Impedance • Devices • Telemedicine • Heart failure • Patient management

Introduction

Fluid retention is a major component of decompensated heart failure (HF) and responsible for cardiac overload and symptoms of HF. However, fluid retention may remain clinically inapparent and progress undetected to sudden decompensation. Sensitivity of physical examination, chest x-ray,1 and daily weight control is low and an early predictive value of serum brain natriuretic peptide (BNP) has not been settled.2 Thus, the high frequency of hospitalizations for chronic and acute HF is, at least in part, due to the lack of an accurate and reliable monitoring algorithm for patients with a tendency to fluid retention.

Device-based HF monitoring appears attractive since a high percentage of HF patients is equipped with either a pacemaker or an implanted cardioverter–defibrillator (ICD).3,4 Recently, it has been shown that intrathoracic electrical impedance is inversely correlated with left ventricular filling pressure5 and may therefore be used to detect fluid retention and predict cardiac decompensation. The principle of impedance measurement is based on the fact that intrathoracic fluid accumulation improves electrical conductance across the lung. In a recent clinical study, intrathoracic impedance began to fall 15 ± 11 days before symptoms onset.6 An impedance-based algorithm can be incorporated in implantable devices such as pacemakers and ICDs, but its efficacy to predict cardiac decompensation was not yet satisfactory due to low sensitivity and specificity in clinical studies, so far.6,7

The present study aimed to improve impedance based and device incorporable techniques for a reliable prediction of cardiac decompensation. A novel animal model of gradually

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developing fluid overload was used and measurements of multipolar impedance were related to directly assessed intrathoracic blood volume (ITBV) and extravascular lung water (EVLW). The impact of two different electrode configurations was tested on the reliability to measure intrathoracic impedance, since different current pathways might differently be influenced by fluid accumulation.

**Methods**

**Animal model**

The study was performed according to the ‘Principles of Laboratory Animal Care’, the OPRR Public Health Service Policy on the Human Care and Use of Laboratory Animals, and the U.S. Animal Welfare Act, and with the permission of the local commission for animal welfare. In 15 sheep, pulmonary oedema (PE) was induced by intravenous infusion of noradrenaline and a combination of plasmaexpander (e.g. dextran) and crystalloid fluids.

**Surgical procedures**

Each sheep was pre-medicated with intramuscular xylazine. Animals were anaesthetized by intravenous thiopental, intubated, and anaesthesia was maintained with inhalative isoflurane and intravenous fentanyl. Animals were placed in a supine position and received controlled mechanical ventilation; body temperature was kept constant at 37°C by radiant heaters. A standard multilumen central line including an injectate temperature sensor housing cable and a Swan-Ganz catheter were inserted via the right external jugular vein. The Swan-Ganz catheter was advanced into a pulmonary vein to measure pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). The right groin was used to insert an additional iv-line into the femoral vein and a thermistor-tipped arterial PICCO-catheter was placed into the femoral artery for continuous measurement of arterial pressure, cardiac output (CO), and extravascular lung water using the PICCO-Plus system (Pulsion Medical Systems, Munich, Germany). A micro-tip catheter (Millar Instruments Inc., Houston, TX, USA) was advanced into the left ventricle for direct measurement of left ventricular pressure (LVP). Finally, an ICD lead (Kontrex RV-65 S, Biotronik, Berlin, Germany) was advanced via the left external jugular vein into the right ventricular apex and screwed into the myocardium. To confirm an appropriate myocardial contact, pacing threshold and ventricular potential amplitude were assessed. A dummy device was implanted in a subcutaneous pocket in the right parasternal region serving for the electrical can connection. All catheter placements were x-ray guided and controlled.

**Experimental setup**

All signals including ECG, LVP, PAP, arterial haemoglobin oxygen saturation (SO₂ measured by pulse oximeter), and breathing rate (measured by a piezo respiratory belt transducer) were recorded by a multichannel amplifier and AD-converter (Powerlab 8/SP, ADInstruments, Colorado Springs, CO, USA) (Figure 1).

The PICCO system provided continuous monitoring of mean arterial pressure (MAP) and blood temperature (TB) as well as volumetric parameters assessed by the use of the single thermodilution technique, including CO, extravascular lung water index (EVLWI), ITBV, pulmonary thermal volume (PTV), and pulmonary vascular permeability index (PVPI).

An external pacemaker (Inos²⁺, Biotronik, Berlin, Germany) was used to measure intrathoracic impedance (Z) between the right ventricular ICD lead consisting of tip, ring, and coil electrodes and the case of the dummy device. A switchbox enabled switching between two different electrode configurations (Figure 2). For the first configuration (bipolar approach), both current injection and voltage measurement were set between the dummy case and the coil of the ICD lead. For the second configuration (tripolar approach), the current was injected between case and coil, but voltage was sampled between case and tip of the ICD lead.

The measured intrathoracic impedances could be cross-influenced by changes in blood conductivity (σB) and haematocrit (HTC). Thus, blood samples were drawn from the arterial line at any measuring
cycle to analyse blood conductivity by a conductivity meter (SevenEasy, Mettler-Toledo Analytical, Schwerzenbach, Switzerland) and haematocrit after centrifugation (HAEMATOKRIT 210, Andreas Hettich GmbH & Co. KG, Tuttlingen, Germany).

**Experimental protocol and timeline**

Haemodynamics were continuously recorded by the PICCO and the Powerlab system. Sequential blood sampling, wedging (PCWP measurement), thermodilution (EVLW and CO measurement), and short-term Z measurements for the bi- and tripolar approach were performed at least 15–20 times per experiment. Each experimental sequence took ~20 min resulting in a total experimental time of about 5 to 7 h.

When a stable baseline was reached within the first 5 sequences (~100 min), PE was induced by intravenous infusions of dextran and noradrenaline (n = 12 sheep) and maintained for at least 10 sequences to provoke an increase of EVLW by at least 30%. Noradrenaline dosage was stepwise increased to gradually increase severity of PE. Volume management was primarily used to counteract an increase of HTC due to the provocation procedure and a resulting reduction of σB (i.e. an increase in blood impedance). Thus, dextran was administered with the aim to keep σB and HTC as constant as possible. For the control sheep (n = 3), 15 measurement sequences were conducted without administration of dextran and noradrenaline.

**Data evaluation**

Z and pressure signals were averaged over one respiratory cycle before computing the final mean parameters.

**Haemodynamics**

End-diastolic pressure (LVEDP) was derived from the LVP signal at the time instant, where the pressure slope reached 10% of its maximum value. Mean pulmonary artery pressure (PAPm) and PCWP were calculated as the mean of pressure samples gathered over the respiration-averaged heart cycle.

**Intrathoracic volumes**

Transpulmonary thermodilution measurements were performed by central venous injection of a cold (<8°C) NaCl bolus (15 mL). After injection of the indicator, the thermistor in the tip of the arterial catheter measures the downstream arterial temperature changes. Advanced analysis of the thermodilution curve by the PICCO system allows automatic calculation of CO, EVLW, ITBV, PTV (which reflects the sum of EVLW and pulmonary blood volume), and corresponding index values as well as PVPI reflecting the ratio of EVLW to pulmonary blood volume. Thermodilution was repeated three times for confirmation, and values were represented by the mean of the three consecutive measurements.

**Impedance**

For both the tripolar and the bipolar lead configuration, Z was calculated as voltage divided by current. Biphasic pulses (122 μs pulse width, 600 μA constant current amplitude) were used for excitation. The impedance signal was recorded with a resolution of 8 bits. The measurement range was programmable in steps of factor 2 down to the smallest range of 3.3 Ω. Mean intrathoracic impedance was calculated by averaging the impedance samples over all complete respiration cycles of one record stream (lasting for ~30 s).

**Data analysis**

Descriptive and ratio statistics summarizes the data as mean ± standard deviation (SD). Where mentioned, boxplots with pooled animal data were used to describe the mean trends of the variables over the measurement sequences. Boxes show lines at the lower quartile, median quartile, and upper quartile values and means indicated as stars. Whiskers extend from each end of the box to the adjacent values in the data, by default, the most extreme values within 1.5 times the interquartile range from the ends of the box. Outliers are considered as values beyond the ends of the whiskers, and are displayed by circles. Regression analysis was used to evaluate the relationship between impedance, haemodynamic, and volume parameters with the Pearson correlation coefficient (r²). Where mentioned, an exponential regression analysis was also used to describe a nonlinear relationship using the function $y = a e^{-b(x-c)} + d$ for curve fitting. To test statistical significance, paired two-sided Student’s t-tests were used. Significance was assumed for values $P < 0.05$.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Induction of cardiogenic lung oedema**

In the control group (n = 3), all parameters remained stable throughout the measurements. In the lung oedema (LE) group, all 12 sheep developed inclining pulmonary fluid overload leading to severe PE (Table 1). The endpoint (defined by an EVLW increase of more than 30%) was reached in all 12 LE sheep. Figure 3 shows gradual increase of LVEDP and Figure 4 of EVLWI during LE development.

**Infusion of noradrenaline and dextran, and changes of blood parameters**

On average, infusions of $389 ± 136$ mL dextran solution per sequence were required to avoid strong drops in blood conductivity. Pooled over all LE sheep, $\sigma_B$ changed from mean baseline values of $10.30 ± 0.61$ to $9.98 ± 0.64$ mS/cm. The reduction of $\sigma_B$ was paralleled by a mean increase of HTC from $22.8 ± 2.4$% (baseline) to $25.5 ± 2.7$% (LE stage). In all control sheep, $\sigma_B$ and HTC remained stable.

**Changes of haemodynamics**

Haemodynamic changes are summarized in Table 1. Mean arterial pressure increased immediately after infusion of noradrenaline. After the first two sequences of infusion, MAP stabilized at high
levels in spite of further increasing noradrenaline dosages. Ratio statistics yield a relative mean increase per sheep of 190 ± 85%. Changes in MAP were not observed in control sheep.

Left ventricular pressures and pulmonary pressures steadily increased in LE sheep with a significant correlation between LVEDP and PCWP (mean \( r = 0.930 \pm 0.056 \)). During the first cycles of LE induction (measurement sequence 6–15), CO increased from baseline values of 3.2 up to ~9 L/min as a result of noradrenaline and volume triggered continuous increase in heart rate and stroke volume. During the final experimental cycles (measurement sequence 16–20), stroke volume and CO fell despite further administration of noradrenaline and fluid.

### Changes of pulmonary fluid indices

After infusion of noradrenaline and plasmaexpander/crystalloid fluids, all animals developed inclining pulmonary fluid overload. Lung water (EVLWI) increased from 9.5 ± 1.0 mL/kg body weight at baseline to 21.1 ± 5.1 mL/kg body weight at end-stage (Figure 4). Pulmonary vascular permeability index calculated as the ratio of EVLW to pulmonary blood volume showed no increase in the first sequences of LE induction though EVLW already increased during this time. Preceding LE end-stage, PVPI increased, indicating an aggravation of vascular permeability at that stage.

### Reduction of intrathoracic impedance

In all cases, induction of LE was paralleled by a decrease of impedances. There was a broad range of individual absolute impedance data among the sheep, due to individual anatomical and physiological differences. Figure 5 shows a normalized presentation of Z data (tripolar). Comparing the normalized data of baseline measurements and measurements after noradrenalin infusion, the reduction of Z was highly significant for all LE sheep. Z fell by 24.4 ± 7.6% for the tripolar configuration, and by 20.5 ± 7.0% for the bipolar configuration (see also Table 1). Figure 6 shows the reduction of mean Z (tripolar), pooled for the LE group. In the control group Z remained stable.

### Correlation of impedance, haemodynamics, and intrathoracic volumes

Table 2 lists mean correlation coefficients for the relations between filling pressures or volumes, and Z. All measurement sequences have been pooled and are presented in Figure 7.
Each dot represents the mean value pair averaged over one respiratory cycle. The correlations between Z and LVEDP were high, ranging between $r = -0.798$ and $r = -0.959$.

Linear regression analysis between Z and EVLWI also yielded significant inverse correlations for both the bipolar and the tripolar configuration resulting in a mean $r$ of $-0.820$ for the tripolar configuration.
configuration and of −0.790 for the bipolar approach. For high values of EVLWI, no further reduction of Z could be measured (Figure 8). As listed in Table 2, exponential fitting improved correlation coefficients for both the bipolar and the tripolar configuration.

The ratio statistics of Table 1 points out that the mean Z reduction is higher for the tripolar than for the bipolar counterparts, which is true for the phase ‘LE induction’ as well as for the phase ‘LE stage’. A paired Student’s t-test showed that the different decline of impedances (tripolar vs. bipolar) is not significant if applied for the LE induction phase (P = 0.11); however, it is highly significant if applied to the LE stage (P < 0.001). Comparing tripolar and bipolar results in respect to the correlation between impedance and intrathoracic volumes (Table 2), it was significant that the tripolar configuration yielded better coefficients.

Figure 5 Mean intrathoracic impedances (Z, tripolar configuration) for all sheep, normalized to mean baseline values. White circles depict the control (Ctrl) group (n = 3, sheep no. 01 to no. 03), black squares depict the lung oedema (LE) group (n = 12, sheep no. 04 to no. 15). The x-axis gives the time line of developing pulmonary overload; measurement sequence 1–5 baseline, measurement sequence ≥6 lung oedema induction.

Figure 6 Boxplot showing the reduction of mean intrathoracic impedance (Z, tripolar configuration), normalized to mean baseline values, pooled for the lung oedema group (n = 12). The x-axis gives the time line of developing pulmonary overload; measurement sequence 1–5 baseline, measurement sequence ≥6 lung oedema induction.
Discussion

The method described here is an excellent, practical, and novel model for a gradually developing LE, rather than previously reported end-stage models for permeability LE using e.g. instillations of acidic substances.\(^{10–12}\) All sheep in this study developed gradually inclining pulmonary fluid overload paralleled by a significant fall of Z. Both the bipolar and the tripolar configuration indicated an increase in intrathoracic volume with a better prediction by the tripolar approach.

**Table 2** Correlation of intrathoracic impedance with haemodynamics and intrathoracic volumes

<table>
<thead>
<tr>
<th></th>
<th>Z, bipolar</th>
<th></th>
<th>Z, tripolar</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(r^2_{\text{exp}})</td>
<td>(r)</td>
<td>(r^2_{\text{exp}})</td>
</tr>
<tr>
<td>LVEDP(^a)</td>
<td>0.887</td>
<td>0.855</td>
<td>0.887</td>
<td>0.901</td>
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<tr>
<td>PCWP</td>
<td>0.887</td>
<td>0.901</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVLWI</td>
<td>0.790</td>
<td>0.845</td>
<td>0.820</td>
<td>0.873</td>
</tr>
<tr>
<td>ITBV</td>
<td>0.825</td>
<td>0.782</td>
<td>-0.831</td>
<td>0.782</td>
</tr>
<tr>
<td>PTV</td>
<td>0.852</td>
<td>0.917</td>
<td>-0.877</td>
<td>0.936</td>
</tr>
</tbody>
</table>

Correlation coefficient \(r\) (linear regression) and \(r^2_{\text{exp}}\) (nonlinear regression) expressed as mean over all individuals.

EVLWI, extravascular lung water index; ITBV, intrathoracic blood volume; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; PTV, pulmonary thermal volume; Z, intrathoracic impedance.

\(^a\)Correlation on a beat to beat basis.

**Intrathoracic impedance**

Changes in conductance due to changes of pulmonary fluid status alter intrathoracic impedance. Initial studies using external impedance monitors showed in animal models and humans that thoracic impedance fell with intrathoracic fluid accumulation.\(^{13,14}\) Today these external impedance devices are used for haemodynamic monitoring in critically ill patients on intensive care units and their comparability with invasive methods has been demonstrated.\(^{15}\) However, the clinical application of external impedance devices for monitoring of pulmonary fluid status in patients with HF is unfeasible, especially in an ambulatory setting.

A study by Wang et al.\(^5\) showed that intrathoracic impedance, measured between an implantable device and a RV lead, is inversely correlated with left ventricular filling pressure (LVEDP) as an indirect parameter of pulmonary congestion. In the present study, we qualitatively confirmed the prior results by comparing Z with LVEDP during baseline and LE induction and calculated a significant inverse correlation between Z and LVEDP. Even though the LVEDP is regarded as ‘gold standard’ for haemodynamic monitoring, it is a poor reflection of the patients’ volume status.\(^{16}\) In order to accurately monitor the degree of PE, we directly assessed ITBV and EVLW by the PiCCO system via transpulmonary thermodilution. The accuracy of the PiCCO system for measuring ITBV/EVLW has been reported in several recent studies.\(^{17,18}\)

Absolute impedance data varied widely among the individual experiments, presumably due to variation of chest anatomy and slightly different positions of the dummy case and the RV lead. Linear regression analysis between Z (normalized) and EVLWI showed significant inverse correlations for both the bipolar and the tripolar configuration (mean \(r = -0.790\) and \(r = -0.820\),
respectively). Comparing bipolar and tripolar lead configuration for
the determination of Z, a better correlation between Z and
intrathoracic volumes for the tripolar approach was observed. In
respect to the differences of the used configurations, one might
discuss that with using the bipolar configuration, all electrode inter-
face effects and near-field effects (e.g. lead movements) are
additionally contained in the impedance signal, and are even in
the same order of magnitude as the contribution of the lung. In
contrast, by use of the tripolar configuration, these negative side
effects are suppressed. The influence of the electrode surrounding
tissue is minimized, and thus this approach reflects more precisely
the real transthoracic impedance. So, the tripolar configuration
described here potentially leads to better specificity and sensitivity
for detection of developing HF. The correlation was not linear
over the whole range tested; for high values of lung water
(EVLW doubled from baseline) no further reduction of Z was
noticed. But, these massive intrathoracic fluid accumulations
reflect more than end-stage PE and therefore have to be con-
sidered as unphysiological conditions, far off of daily clinical obser-
vations. Thus, these extreme LE-stages should not be considered
when working on HF-detection algorithms based on intrathoracic
impedance measurements, especially not for algorithms intended
to detect the development and early stages of pulmonary
volume overload in HF patients.

Study limitations
The progression of PE in this animal model occurred during about
5 to 7 h. In a patient with chronic HF, the development of cardiac
decompensation usually takes several days to weeks, so the clinical
progression is different from this model for acute HF. Furthermore,
the thorax anatomy of sheep, especially the position of the heart,
differs from human anatomy. These factors may affect impedance
measurement and have to be considered when applying the
results to patients. Two previous animal studies showed circadian
diurnal variation in intrathoracic Z, a fact that remained uncon-
sidered in this study because of presumably low impact in our
setting.

Although the lung is the largest organ in volume inside the thor-
acic cavity, and changes in its conductive properties should be
reflected by the measured intrathoracic impedance, several other
factors may also contribute to changes in Z. In HF, fluid accumu-
lates in the interstitium and alveoli of the lung as well as in soft
tissue and skeletal musculature, in blood vessels in terms of
venous congestion and in the third spaces (e.g. pleural effusion).
Furthermore dilatation of the cardiac cavities in worsening HF
may contribute to impedance changes. Other factors which may
also contribute to changes in intrathoracic impedance have been
recently reviewed by Wang.

Clinical applicability
There is an increasing rate of device (CRT and ICD) implantations
in patients suffering from chronic HF. Intrathoracic imped-
cance measurement as a tool for HF monitoring can be
implemented with currently available device-technology and does
not require additional sensors or leads. Recent studies about the
feasibility of device-based intrathoracic impedance monitoring in
humans were promising. Several clinical studies showed a statisti-
cally significant inverse relationship between changes in intrathor-
acic impedance and NT-pro-BNP, an established marker for the
diagnosis of decompensated HF. However, the contribution
of Z for clinical assessment of impending pulmonary congestion
was limited due to low sensitivity and specificity.
Impedance to monitor intrathoracic fluids

Other promising device-based tools for early cognition of changes in volume load and LV function such as the intracardiac impedance measurement\(^2\) or the invasive RV pressure measurement\(^2\) have been reported recently. Furthermore, modern ICD and CRT devices collect detailed information about heart rate, arrhythmia burden, and heart rate variability which also may be useful in assessing patients’ conditions and in predicting hospitalizations for acute decompensated HF.\(^2\)\(^9\)\(^3\)

It is unclear which of these monitoring parameters is best suitable for detecting early stages of HF. Since volume overload is a dominant factor in causing HF symptoms, it is anticipated that changes in intrathoracic impedance might have a substantial potential reflecting the clinical status of HF patients. But, likely, a combination of different surrogate parameters will have to be incorporated into a reliable device-based HF detection algorithm to increase sensitivity and specificity.

**Conclusion**

The tripolar configuration for intrathoracic impedance measurement described here potentially leads to better sensitivity and specificity for predicting impending HF exacerbation, thus it may be a future clinically useful tool in HF management. Early intervention may prevent hospitalization, reduce health care costs, and improve quality of life. Since there are several other monitoring parameters that can be also assessed by modern implantable devices, an improved accuracy of HF detection by a combination of different methods is extremely likely. Furthermore, a combination of these device-based features with existing telemedicine concepts has a tremendous potential to improve outpatient HF management. The clinical usefulness of these promising methods has to be further evaluated in prospective, randomized clinical trials.

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