Non-invasive monitoring of central blood pressure by Electrical Impedance Tomography (EIT): first experimental evidence

Josep Solà [1], Andy Adler[2], Arnoldo Santos[3], Gerardo Tusman[4], Fernando Suárez Sipmann[3] and Stephan H. Bohm[1]

[1]*CSEM – Centre Suisse d'Electronique et de Microtechnique, Neuchâtel, Switzerland*

[2]*Systems and Computer Engineering, Carleton University, Ottawa, Canada*

[3]*Department of Critical Care, Fundación Jiménez Díaz-UTE, IIS-FJD,CIBERES, Madrid, Spain*

[4]*Department of Anesthesioloy, Hospital privado de Comunidad, Mar del Plata, Argentina*

Corresponding Author:

Josep Solà,

e-mail: jsa@csem.ch

tel: +41327205112

Abstract

There is a strong clinical demand for devices allowing continuous non-invasive monitoring of central Blood Pressure (BP). In the state of the art a new family of techniques providing BP surrogates based on the measurement of the so-called Pulse Wave Velocity (PWV) has been proposed, eliminating the need for inflation cuffs. PWV is defined as the velocity at which pressure pulses propagate along the arterial wall. However, no technique to assess PWV within central arteries in a fully unsupervised manner has been proposed so far. In this pilot study we provide first experimental evidence that Electrical Impedance Tomography (EIT) is capable of measuring pressure pulses directly within the descending aorta. To obtain a wide range of BP values we administrated noradrenalin and nitroglycerine to an anesthetized pig under mechanical ventilation. An arterial line was inserted into the ascending aorta for measuring reference BP. EIT images were generated from 32 impedance electrodes placed around the chest at the level of the axilla. Regions of Interest (ROI) such as the descending aorta and the lungs were automatically identified by a novel time-based processing algorithm as the respective EIT pixels representing these structures. The correct positions of these ROIs were confirmed by bolus injections of highly conductive concentrated saline into the right heart and into the ascending aorta. Aortic Pulse Transit Time (PTT) values were determined as the delay between the opening of the aortic valve (obtained from arterial line) and the arrival of pressure pulses at the aortic ROI within the EIT plane. For 11 experimental conditions, with mean BP ranging from 73 to 141 mmHg, strongly significant correlation ($r = -0.97$, $p < 0.00001$) between central BP and aortic PTT was observed, suggesting that EIT-derived aortic PTT is a potential non-invasive surrogate of central BP.

Introduction

There is an increasing demand for devices monitoring human cardiovascular function continuously non-invasively and non-obtrusively under clinical and ambulatory conditions: the goal is to reduce the need for long hospitalizations and costs, while improving patient comfort and safety. In recent years, electrocardiograms, intermittent Blood Pressure (BP) monitors and pulse oximeters have been successfully released into the market paving the way towards the monitoring of cardiac and vascular parameters in hospitals and out-patients [8]. Unfortunately, these parameters still provide an incomplete picture of a patient´s health status and do not fully meet clinical demand. In particular, discontinuous intermittent measurements of BP as provided by inflation of brachial cuffs are unsuitable for monitoring short-term BP regulation mechanisms, for which ideally beat-by-beat BP measurements should be performed. In addition, they may not yield representative BP during sleep as these repeated inflations induce arousal reactions, which may interfere with the measurement and lead to non-representative overestimated values [1]. Thus, the development of new techniques to monitor BP continuously with less frequent or even no inflations of pneumatic cuffs is justified.

Pulse Wave Velocity (PWV) is the velocity at which pressure pulses propagate along the arterial tree. In addition to being considered the gold standard methodology for assessing arterial wall stiffness [5], PWV has been shown to strongly depend on arterial BP. In particular, in central segments of the arterial tree where arterial walls are mainly elastic, PWV values depend exclusively on the subject-dependent arterial wall stiffness and the mean BP [6]. Therefore, and since changes in arterial stiffness occur only over long-term periods of time, PWV has been proposed as an adequate surrogate measure of short-term BP variability. Combined with intermittent cuff-based BP calibration procedures, several PWV-derived methods to provide continuous absolute BP measurements have been recently proposed: see [10] for a review. To date continuous PWV monitors have been limited to the monitoring of distal superficial large or cutaneous small arteries. Due to their autoregulation, wave reflections and differences in stiffness

these peripheral arteries do not match the requirement of an ideal central point of measurement.

Electrical Impedance Tomography (EIT) is a non-invasive monitoring technology based on the analysis of bioimpedance signals [3]. From an electrical perspective, the thoracic cavity is composed of distributed impedance volumes. While the lungs (filled with air) form high impedance volumes, the heart and blood vessels (filled with blood) form low impedance volumes. EIT creates tomographic reconstructions of the distribution of these impedance volumes within the thorax at high sampling rates. As input signals, EIT requires a set of impedance measurements performed around the chest (see Figure 1). Basic a-priori knowledge about chest anatomy allows then reconstruction algorithms to estimate the most likely distribution of regional impedances. During each cardiac cycle vascularized structures within the thorax receive bursts of electrically conductive blood, which decrease local impedance. Hence, when looking at a sequence of EIT images local pulsations of the impedance signal (impedance pulse) are observed which are associated with the underlying pulsation of the blood (pressure pulse). One example of an EIT-based visualization of a pressure pulse propagating from the heart to the lungs of an anesthetized pig is illustrated in figure 1.

The aim of this pilot study was to experimentally test whether EIT could be used to measure central blood pressure continuously and non-invasively by providing unsupervised estimations of aortic pulse transit time.

Methods

Animal preparation

This pilot study was approved by the Animal Ethics Committee of the Instituto de Investigación Sanitaria, Fundación Jiménez Díaz, Madrid, Spain. Electrical Impedance Tomography (EIT) and respective reference data were gathered in an anesthetized domestic piglet, weighing approximately 25 kg. After fasting over night with free access to water, anesthesia was induced with intramuscular Ketamine (10 mg kg-1), Xylacine (10 mg kg-1) and Atropine (1 mg). Anesthesia

was maintained with Remifentanyl (0.05 to 0.10 μg kg-1 min-1) and Propofol (0.05 to 0.15 mg kg-1 min-1) once tracheal access by a cuffed 7 mm ID orotracheal tube (Mallinckrodt, Athlone, Ireland) was secured. No muscle relaxation was administered. The healthy lungs were normoventilated in the supine position at 5 cmH_2O PEEP in a volume controlled mode using a Servo i ventilator (Maquet Critical Care, Solna, Sweden). The animal was monitored by standard ECG and pulse oximeter via an MP50 device (Philips Medical, Böblingen, Germany). Ringer's lactate was administered to maintain fluid balance.

Data acquisition

Cardiac output and other hemodynamic parameters were measured in one femoral artery using the $PiCCO_2$ system (Pulsion Medical Systems, Munich, Germany). A catheter for continuous monitoring of aortic pressures and for determining the aortic valve opening was inserted into the ascending aorta via the other femoral artery under radiographic guidance and contrast agent injections. A central venous catheter was advanced through the introducer until it reached the right ventricle and the correct location was confirmed by X-ray.

The skin was shaved, electrode gel applied and the 32 electrodes of the EIT device Enlight® (Timpel SA, Sao Paulo, Brazil) placed equidistantly around the circumference of the thorax just below the level of the axilla. This system produces 50 real time images per second. Small electrical currents (<10 mA; 125 kHz; meeting the electrical safety requirements of standard IEC 60601) were administered in a rotating sequence through pairs of electrodes, with three non-injecting electrode interposed between them. The resulting potentials were measured by the non-injecting electrodes, amplified, measured and fed into an image reconstruction algorithm. Note that although electrical currents propagate three-dimensionally within the thorax, the EIT reconstruction algorithm creates projections of impedance changes in thoracic volumes in the form of a 2-D tomographic image located within the electrode plane.

Detection of aortic region of interest by saline bolus injections

An initial estimate of Regions of Interest (ROI) comprising EIT pixels with information on heart, lungs and aorta was obtained by injecting boluses of 20% hypertonic saline at two anatomical locations: the right ventricle and the ascending aorta. Similar to the approach described in [2] the hypertonic saline solution was used as contrast agent: by locally increasing the electrical conductivity of blood by approximately four-fold, the passage of the bolus was identified by a circumscribed local transient decrease in impedance. After injecting the contrast agent into the ascending aorta its downstream propagation was tracked, and the descending aorta ROI was identified by the arrival of the contrast at the dorsal EIT electrode plane.

Unsupervised detection of aortic region of interest

The exact location of the descending aorta ROI within a series of EIT images was finally determined by a novel unsupervised method based on the estimation of pixel-specific Pulse Arrival Times (PAT), as illustrated in figure 2.

After leaving the ventricles, pressure pulses propagate along the systemic and pulmonary arterial trees and induce increases of the local volume of conductive blood, thereby decreasing the local electrical impedance (Figure 1). This phenomenon generates impedance pulses. Although the amplitude information contained within these impedance pulses (in Ohms) cannot necessarily be associated with the actual amplitude of the pressure pulses (in mmHg), its coded timing information, however, is identical. In particular, the onset of a pressure pulse at a given anatomical location instantaneously induces the onset of its associated impedance pulse. The PAT value depicts thus the time at which this arrival event occurs. From a sequence of EIT images containing at least one cardiac cycle, one is then able to calculate a PAT-based image where the numerical value of each pixel corresponds to the arrival time of the pressure pulse at its underlying anatomical region.

For this pilot study, the generation of PAT-based EIT images was performed as follows: ensemble averaging [4] of impedance pulses at each EIT pixel (N=1024) was performed during ventilation pauses using the onset of the pressure pulse in

the aortic catheter as a trigger (cardiogenic trigger). The arrival time of each averaged impedance pulse was then calculated via a robust parametric detection algorithm [9]. A numerical model $m_\Omega(t)$ of pressure pulse was fitted to each of the 1024 impedance pulses, depicting information of its arrival time (μ) and morphology, *i.e.* amplitude (A), slope (σ) and offset (C):

$$m_\Omega(t) = A \tanh\left(\frac{t-\mu}{\sigma}\right) + C \qquad (1)$$

The fitting of the model $m_\Omega(t)$ to each impedance pulse p(t) was performed by finding the set of parameters Ω={A, μ , σ ,C} that minimized the quadratic error between $m_\Omega(t)$ and p(t), via a multi-parametric steepest descent search [9]. A PAT-based image was finally generated by assigning to each EIT pixel its associated μ value. Those pixels for which the fitted parametric model was either unreliable or the fitting algorithm did not converge, were excluded (parameter-based clustering).

The novel unsupervised aorta detection method relied thus on the analysis of the above mentioned PAT-based EIT images. In particular the method was able to identify the descending aorta ROI based on the fact that after the opening of the aortic valve the first segment of the arterial tree within the EIT plane to receive the arriving pressure pulse is the descending aorta. Hence, for this pilot study the aortic ROI was identified as those pixels located centrally behind the lungs for which the PAT values were lowest.

EIT aortic pulse transit time as a surrogate for aortic blood pressure

Impedance pulses of pixels belonging to the aortic ROI were hypothesized to represent the underlying aortic pressure pulse phenomenon. Their arrival times, estimated as the μ parameter of the numerical model, were assumed to be non-invasive surrogates of the aortic Pulse Transit Time (PTT). Accordingly, EIT-derived aortic PTT values were compared to aortic BP values for several hemodynamic conditions. The goal of this analysis was to test if EIT-derived aortic PTT values could be used as surrogate measurements of BP, by testing if both measurements were negatively correlated, *i.e.*, increased aortic pressure should result in shorter pulse transit time from the aortic valve to the descending aorta, and *vice versa*. Different hemodynamic conditions were generated aiming at

mean arterial pressures values within the wide range between 60 and 150 mmHg. Pressure values were actively adjusted and stabilized at each level for several minutes using infusions of either nitroglycerine or noradrenaline. Data from all devices were recorded simultaneously during ventilation pauses of 30 seconds on each pressure level immediately after stabilization, and PAT-based EIT images calculated for each condition.

Results

Detection of aortic region of interest by saline bolus injections

The upper panel of figure 3 illustrates the identification of the ROIs corresponding to both lungs when a 10 ml bolus of hypertonic saline solution was injected into the right ventricle: after an initial accumulation of saline within the ventricle for about 2 seconds (t=2.4s), the bolus propagated towards the pulmonary artery (t=4.8s) before reaching the left and right lungs (t=6.4s, blue ROIs).

The lower panel of figure 3 illustrates the identification of the aortic ROI when a similar bolus was injected in the ascending aorta, right downstream of the aortic valve. During the injection of EIT contrast agent (t=0.0s, upper region of red ROI) the bolus rapidly spread into the aortic arch (t=0.8s). At the end of injection (t=2.8s) only little saline remained within the aortic arch and the upper thoracic aorta, but finally appeared in the descending aorta (t=3.6s, lower region of red ROI). The descending aorta was thus localized at the medial-dorsal outline of the left lung.

Note that although the ascending aorta, the aortic arch and the descending aorta belong to different transverse planes along the cranio-caudal axis, they were all projected into one single EIT plane (red ROI).

Unsupervised detection of aortic region of interest

Figure 4 shows the PAT-based image, averaged for all hemodynamic conditions. A PAT value was assigned to each pixel, corresponding to the μ parameter estimated from the impedance pulses at that pixel. A set of 7 pixels was identified

as having aorta-like behavior (*i.e.* lowest PAT values being located centrally behind the lungs) and clustered into a single aortic ROI. Note that the location of the aortic pixels identified by the proposed unsupervised algorithm matched with the aortic ROI as identified by the hypertonic saline bolus.

EIT aortic pulse transit time as a surrogate for aortic blood pressure

Table 1 shows jointly for all hemodynamic condition the correlation scores between aortic PTT values as calculated for the aortic EIT pixels and the invasively-measured mean BP. Very strong negative correlations were encountered, suggesting that EIT-derived aortic PTT is a potential surrogate of aortic BP. Pixels {21,22} and {22,22} provided the best correlation scores: $r=-0.967$, $p<0.00001$. For illustrative purposes these two pixels have been highlighted in figure 4 (yellow circle). Figure 5 provides a correlation plot comparing EIT-PTT to aortic BP for pixel {21,22}. Note that EIT-PTT values are expressed as [%], depicting the μ value of the fitted parametric model [9] divided by the maximum μ search range.

Discussion

We provided first experimental evidence for the feasibility of using EIT to measure pulsatility within the descending aorta in a non-invasive way. Given a sequence of EIT images of several cardiac cycles, we presented a novel method to identify an aortic Region of Interest (ROI) in an unsupervised manner. The correct location of the aortic ROI was confirmed by hypertonic saline bolus injections directly into the aorta. Since the aortic EIT-PTT obtained by the unsupervised EIT method correlated inversely and strongly with the corresponding invasive aortic BP, we suggest that EIT-PTT is a candidate-technology for the continuous non-invasive and non-occlusive monitoring of central BP. If robust, the EIT-PTT technique offers significant advantages over other unsupervised PTT based schemes; specifically, EIT-PTT analyzes blood-pressure-related impedance pulses in the aorta, while state-of-the-art ambulatory PTT schemes require measurement of pulses in peripheral arteries. Since pulsatility of peripheral arteries is affected by autoregulation, wave reflections and local wall stiffness EIT-PTT has the advantage of providing unique central hemodynamic measurements: EIT-PTT

may be understood as placing a “virtual catheter” into the central vessel, being thus free of peripheral interferences.

For this study, the invasively-obtained arterial pressure curve was used as both, a cardiogenic trigger for performing ensemble averaging, and as a timing reference for the opening of the aortic valve. The ECG, or signals from other EIT-regions such as the heart ROI, should be explored in the future as alternative non-invasive proximal timing references. Both alternatives were discarded from the presented study since the goal was to show EIT to be a valid technology to detect the arrival time of impedance pulses at the descending aorta. For this purpose, a ground-truth proximal timing reference was required directly at the aortic valve.

Although a wide range of mean BP values (from 60 to 150 mmHg) were obtained in this single pig, the low amount of intra-individual experimental data (N=11) is a main limitation of this study, impeding any reproducibility analysis. Even more, the one-animal nature of this pilot study limits the extrapolation of the obtained conclusions to other pigs, other species or even humans. However, these initial encouraging results warrant the prospective systematic evaluation of the proposed method in a sufficiently large number of animals.

Future studies should compare EIT-PTT not only with BP but also directly with PTT measured by two catheters within the aorta, one located at the aortic valve, the other one exactly within the EIT plane.

Further development work needs to be done to be able to measure aortic EIT-PTT values at even higher and lower blood pressures and also during mechanical ventilation and spontaneous breathing. Future studies including additional cardiovascular maneuvers such as NO administration and cold stress need to be performed in order to assess the sensitivity of the proposed EIT-PTT parameter to vasomotion phenomena [7].

The use of dedicated EIT reconstruction algorithms and the reduction of the number of EIT electrodes are to be studied as well. Even more, although for this study a standard EIT electrode configuration with electrodes equally-spaced

around the thorax was used, better resolution in particular regions of interest such as the aorta may be achieved in the future by designing dedicated electrode placements. Finally the feasibility of performing EIT-PTT measurements at lower imaging rates (<50 frames per second) is to be evaluated.

In conclusion, the presented data provide first experimental evidence that EIT is a candidate technology for the assessment of arterial pulsatility at the descending aorta, suggesting a way towards a new family of non-invasive continuous monitors of central blood pressure.

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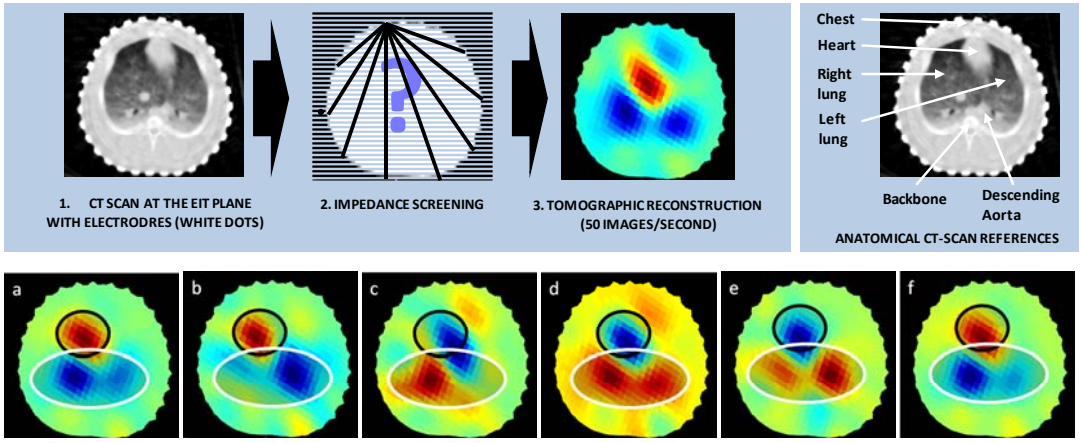

Figure 1. Tracking the propagation of arterial pressure pulses by EIT: After placing several electrodes around the chest (1), impedance measurements are performed for each electrode pair (2) and used to construct a tomographic impedance image (3). A CT-scan of pig chest is provided as anatomical reference. Lower panel shows an example of pulse propagation during an entire cardiac cycle: in a) and b) the filling of the heart is observed (red pixels). In c) the heart empties while the right lung (here on the left hand side) is starting to be perfused with conductive blood. In d) and e) both lungs are perfused. Finally, in f) the pulmonary blood returns to the left heart (blue lung pixels) and the cardiac cycle starts again.

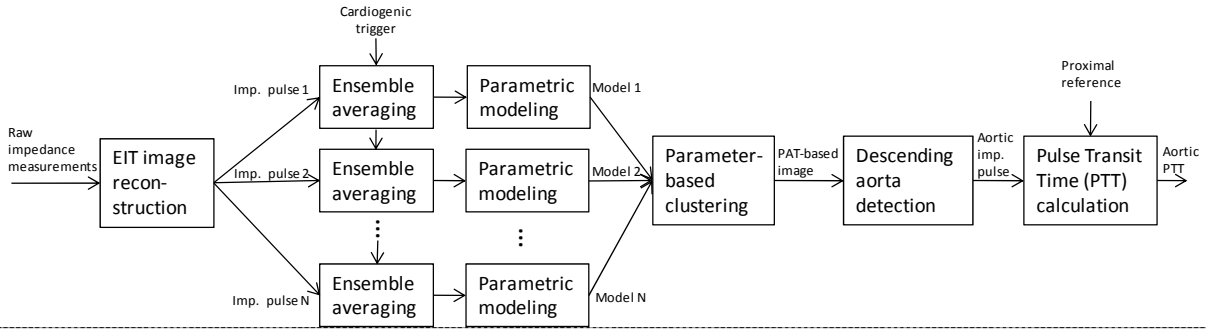

Figure 2. Estimation of an aortic Pulse Transit Time (PTT) value from a sequence of EIT images. Initially, an ensemble-averaged impedance pulse [4] for each of the N pixels in the sequence of EIT images is calculated. A parametric model [9] is then fitted to each impedance pulse. A PAT-based image is generated by assigning a parameter of the fitted model to each pixel. Those pixels containing information on the descending aorta are identified by an unsupervised clustering technique. From the identified pixels, a single impedance pulse representing the pulsatility information of the descending aorta is obtained. A non-invasive aortic PTT value is finally calculated by incorporating a proximal timing reference for the opening of the aortic valve.

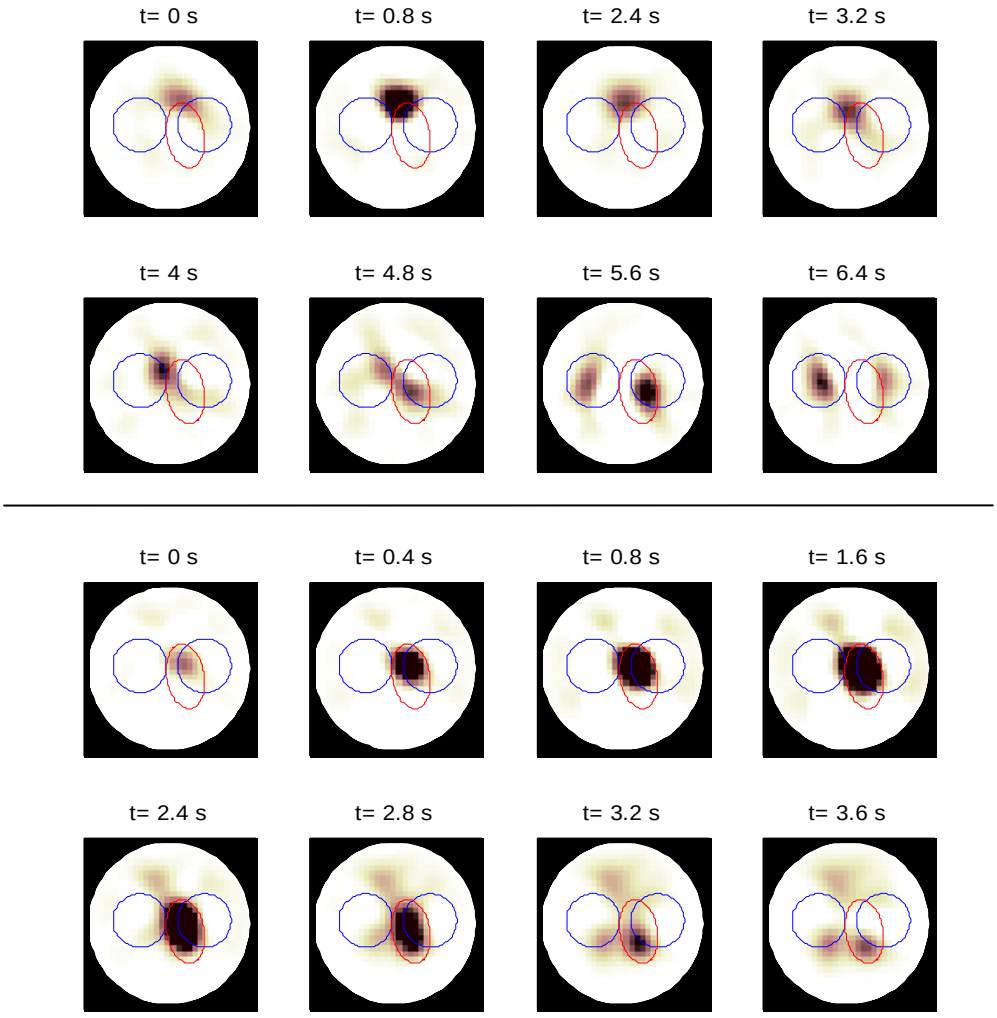

Figure 3. Upper Panel: Downstream propagation of a hypertonic saline bolus injected into the right ventricle. **Lower Panel:** Downstream propagation of a hypertonic saline bolus injected into the ascending aorta. Blue circles identify lung ROIs and red ellipse the aortic ROI.

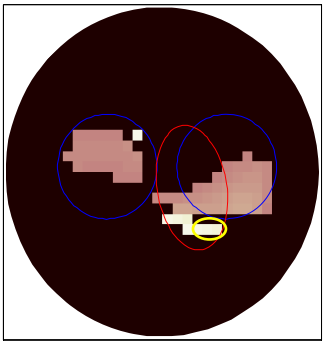

Figure 4. Averaged PAT-based EIT image for the 11 hemodynamic conditions. Bright pixels depict an early arrival of pressure pulses (aortic pixels), and dark pixels depict a late arrival (lung pixels). Black pixels correspond to pixels for which the parametric modelling did not provide reliable estimations. Blue circles and red ellipse correspond to lungs and aorta, as identified by hypertonic saline bolus injections (see figure 3). Yellow ellipse marks the pixels for which best negative correlations were found between EIT-PTT and mean aortic BP.

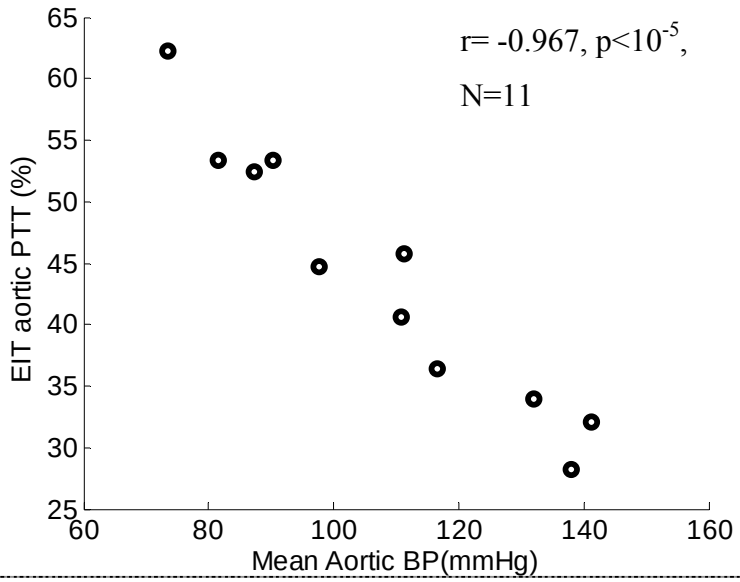

Figure 5. Correlation plot comparing EIT-derived aortic PTT values with mean aortic BP values for pixel {21,22} (marked in yellow in figure 4). Hypotensive and hypertensive conditions were generated by noradrenalin and nitroglycerine administration. PTT: Pulse Transit Time, BP: Blood Pressure

Table 1. Correlation coefficients when comparing EIT aortic PTT values with mean aortic blood pressure values for each of the 7 pixels within the aortic ROI.

Pixel	Correlation
{17,21}	-0.867 ($p<10^{-3}$)
{18,21}	-0.864 ($p<10^{-3}$)
{19,21}	-0.829 ($p<10^{-2}$)
{19,22}	-0.885 ($p<10^{-3}$)
{20,22}	-0.931 ($p<10^{-4}$)
{21,22}	-0.967 ($p<10^{-5}$)
{22,22}	-0.967 ($p<10^{-5}$)