

SUPPLEMENTAL DIGITAL CONTENT

Assessment of Right Heart Function during Extracorporeal Therapy by Modified Thermodilution in a Porcine Model

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1 DETAILED METHODS

ANIMALS AND ANIMAL CARE

Sixteen healthy Edelschwein pigs (10 females and 6 males, weight 45.5 [42 to 47] kg) were included in the research trial. In conformity with the ethical approval by the local authorities, pigs were transported from the farm of origin to the Faculty of Veterinary Medicine, Vetsuisse, University of Berne, 72 hours prior anaesthesia, where they were housed in single boxes (1.45 m²) on straw bedding, but could maintain visual, olfactory and auditory contact with a co-mate. A light/dark cycle of 12 hours was warranted. Pigs were fed twice per day with a commercial diet for grower pigs and had ad libitum access to water. Food but not water was withdrawn 12 hours before general anaesthesia. Physical pre-anaesthetic exam was carried out the day before general anaesthesia by a board certified specialist in Veterinary Anaesthesia and Analgesia.

ANESTHESIA AND SURGERY

A protocol of balanced anesthesia has been selected to promote cardiovascular stability and optimize analgesia. This combined anesthetic approach has been the standard in our experimental facility as it provides very stable hemodynamic conditions and deep, multimodal analgesia and anesthesia. Injectable anesthesia was preferred over inhalational anesthesia due to the use of extracorporeal gas exchange which denies the possibility of effectively providing inhalational anesthesia through the endotracheal tube. The insertion of a spinal catheter allowed re-administering analgesia if required. Nociception and unawareness were evaluated over the procedure through continuous hemodynamic, EEG monitor and with intermittent evaluation of nociceptive withdrawal reflexes. Doses of intravenous anesthesia and further administration of spinal anesthesia were titrated accordingly.

Sixteen ASA 1 Edelschwein pigs underwent, after sedation with ketamine (15mg kg⁻¹), midazolam (0.5mg kg⁻¹) and methadone (0.2 mg kg⁻¹) i.m., induction of general anesthesia through propofol to effect (1-4 mg kg⁻¹ IV). Anesthesia was maintained with continuous rate infusion of propofol (2- 8 mg kg⁻¹ h⁻¹) and fentanyl (5 - 10 µg kg⁻¹ h⁻¹). Volume controlled mechanical ventilation (PEEP 5cmH₂O, FiO₂ 0.60, tidal volume of 10 mL kgBW⁻¹) was started after tracheal intubation (C6 Ventilator, Hamilton Medical, Bonaduz, Switzerland). Additional neuraxial analgesia was provided with ropivacaine 0.75%, and morphine 0.1 mg kg⁻¹ up to a total volume of 0.1 ml kg⁻¹ injected into a spinal catheter introduced through median access at the lumbosacral space and advanced to the thoraco-lumbar junction. During anesthesia, continuous monitoring of SpO₂, invasive blood pressure, central venous pressure, electroencephalogram, electrocardiogram (II lead), esophageal temperature and inhaled and

exhaled gas (CO₂ and O₂) was provided (GE, Carescape B850). In particular, the depth of anesthesia was continuously monitored through a 4 frontal electrodes EEG and EEG-derived index (BIS®) and nociception was assessed through the autonomic variables heart rate, respiratory rate and blood pressure. At regular interval, nociceptive withdrawal reflexes (Pain tracker, Dolosys, GmbH, Germany) and flexion response were tested. Systemic analgesia was adapted, if necessary, to correct any hemodynamic modification overcoming the 20% increase of two out of three parameters (RR, HR, blood pressure). Ropivacaine was injected in case the analgesia was deemed insufficient, based on the tracking of the threshold of the nociceptive reflexes. Before heart surgery, 150 mg of amiodarone was administered. Antiarrhythmic therapy was repeated if necessary during surgery. Vasopressors (noradrenaline) and inotropes (adrenaline) were administered to effect to maintain mean arterial blood pressure above 60 mmHg.

After a midline cervical incision, an 4 Fr introducer sheath was placed into the left carotid artery for pressure measurements and a four-lumen central venous catheter in the right internal jugular vein for administration of medication and vasoactive drugs.

The thoracic cavity was accessed via midline sternotomy and the pericardium opened. After administration of 80 IE kgBW⁻¹ sodium heparin the right atrium and ascending aorta were cannulated (29 Fr 3-stage venous cannula MC2X and 18 Fr elongated-one-piece arterial cannula, Medtronic, Minnesota, USA) and connected to an ECMO circuit (Stockert SCPC Centrifugal Pump, Stockert, Freiburg, Germany with Capiiox FX15 Oxygenator, Terumo, New Jersey, USA). Transit time ultrasonic flow probes (Transonic PAU series, Ithaca, USA, size 20/18 mm and 8 mm) were placed around the pulmonary artery main trunk and the left pulmonary artery and the arterial ECMO outlet (Transonic; ME9PXL1507, Ithaca, NY, USA). A Foley balloon catheter was placed in the left pulmonary artery for partial occlusion. It was not used during this experiment. A one-lumen central venous line was placed in the left atrium for pressure measurement. Furthermore, another one-lumen catheter line was surgically inserted in the right ventricle for the application of cold saline boli.

Two rapid response thermistors (both from pulmonary artery catheters, CCCCombo 7778 F, Edwards Lifesciences, Irvine, California) were placed into the pulmonary artery by surgical puncture and the ECMO circuit using a Y-introductory sheath (Y-Adapter 9,5 F, B.Braun Medical AG, Melsungen, Germany), respectively. The thermistor in the ECMO circuit was placed 60 centimeters deep into the venous cannula.

Placement of catheters in the superior vena cava was verified by open palpation and fluoroscopy. The pressure measurements were level with the right atrium, also verified with the fluoroscope and zeroed against atmospheric pressure. Calibration of pressures was done with a water column in a u-shaped tube. Flow probes were calibrated ex vivo according to the manufacturer's instructions. Finally, the pericardium, sternum and wound layers were closed with thorax drains installed.

MANAGEMENT OF THE EXTRACORPOREAL CIRCUIT

The animals were heparinized with a titrated infusion of heparin targeting an activated clotting time (ACT) of 180 to 220 sec. Extracorporeal blood flow was regulated via the centrifugal pump. Sweep gas was blended from air and oxygen with two mass flow controllers (Vögtlin RED-Y, Basel-Land, Switzerland) to achieve a F_{dO_2} of 0.6. Sweep gas flow was set to match extracorporeal blood flow, i. e. a V/Q ratio of 1.

HEMODYNAMIC SUPPORT

During the stepwise reductions in the extracorporeal blood flow (see experimental protocol) stable hemodynamics and adequate right ventricular function were supported by infusion of bolus of Ringer's lactate or Hetastarch 130/0.4 (Voluven, Fresenius Kabi, Switzerland) and perfusions of norepinephrine or epinephrine at the discretion of the responsible veterinary anesthesiologist with the aim of a mean arterial pressure of 60 mmHg.

DATA ACQUISITION

Measurements included: Sweep flow at the ECMO, ECMO blood flow, blood flow through the lungs, airway pressure, tidal volumes, airway flow, end-tidal oxygen and carbon dioxide (etO_2 , $etCO_2$), pressures from the carotid artery, right atrium, left atrium and pulmonary artery, body temperature, exhaust oxygen and carbon dioxide tensions from the ECMO and mixed venous saturation, which was calibrated every three hours.

Pulmonary vascular resistance was calculated as pulmonary blood flow divided by the difference of mean pulmonary artery pressure and left atrial pressure.

All data output from thermistors, pressure transducers and ultrasonic blood flow probes were recorded at 100 Hz in Labview™ (National Instruments Corp., Austin, TX, USA and Soleasy, Alea Solutions, Zürich, Switzerland). Ventilator parameters were recorded at 50Hz using a dedicated recorder (Memory Box, HAMILTON Medical, Bonaduz, Switzerland).

THERMODILUTION MEASUREMENTS AND EXPERIMENTAL PROTOCOL

Thermodilution signals were recorded using two rapid response thermistors (Baxter Vigilance Monitor, REF VGS2V, Deerfield, Illinois, USA). Injections were performed with 3, 5 or 10 ml of ice-cold sodium chloride 0.9% ($T < 4.0^\circ$, measured and controlled) directly into the ECMO, into the right atrium or into the right ventricle via a surgically placed one-lumen central venous catheter. Figure 1 shows the installations and injections ports. The experimental protocol (figure 1) consisted of three steps:

Step 1) injections of 5x3, 5x5 and 5x10ml into the ECMO at 4 L min^{-1} ECMO flow settings were performed in order to find the catheter constants.

Step 2) we initiated a weaning protocol by reducing ECMO flow from an initial value of 4 L min^{-1} in steps of 1 L min^{-1} . At each stage (i.e. 4, 3, 2, 1 L min^{-1} ECMO Flow) we performed 5 injections of 10ml into the right atrium.

Step 3) injections of 5x3, 5x5 and 5x10ml into the right ventricle were performed to assess possible retrograde indicator loss into the ECMO circuit (figure 1).

CALCULATION OF CONSTANTS AND PULMONARY BLOOD FLOW

Constants were calculated by injecting directly into the venous canula of the extracorporeal membrane oxygenator (ECMO constant). At the end of the experimental protocol we performed injections directly into the lung circuit via the right ventricle in order to assess heat loss into the ECMO during these injections.

The constants were calculated by applying a linear regression to the data and solving formula 1 for c_{iv} (BT = Body Temperature, ΔBT = Thermodilution Signal, IV = Injection Volume, IT = Injectate Temperature, BF = measured Blood Flow).

$$BF = c_{iv} * IV * \frac{(BT - IT)}{\int \Delta BT * dt} (1)$$

The catheter constant is dependent upon the injection volume E^1 . This relationship was investigated in the published set of constants for all Edwards catheters E^2 . A highly linear relationship was found and we therefore considered c_{iv} to be a function of IV, where c_x is the slope and c_a is the intercept (formula 2).

$$c = IV * c_x + c_a (2)$$

A constant valid for all experimental data was determined, depending on injection volume. c_x and c_a derived from ECMO Injections were used in all calculations.

Step 2 then consisted of injections into the mixing chamber, i.e. the right atrium. The thermodilution signal in both ECMO and lung were recorded simultaneously. Now that c_{iv} is known, formula 1 can be solved for injection volume (IV_{ECMO}) using measured blood flow at the ECMO and the ECMO thermodilution curve. As the total injection volume is 10ml, $(10 - IV_{ECMO})$ must represent the injection volume passing the lung circuit (Formula 3).

$$IV_{Total} = IV_{ECMO} + IV_{Lung} = 10 [ml] \quad (3)$$

Finally, we implemented the calculated injection volume in formula 4 to calculate pulmonary blood flow.

$$BF_{Lung} = c_{iv} * (10 - IV_{ECMO}) * \frac{(BT - IT)}{\int \Delta BT * dt} \quad (4)$$

C_{iv} was calculated as a function of injection volume, thus introducing the variable “IV” twice into formulas 1 & 4 (Formula 5).

$$BF = (IV * c_x + c_a) * IV * \frac{(BT - IT)}{\int \Delta BT * dt} \quad (5)$$

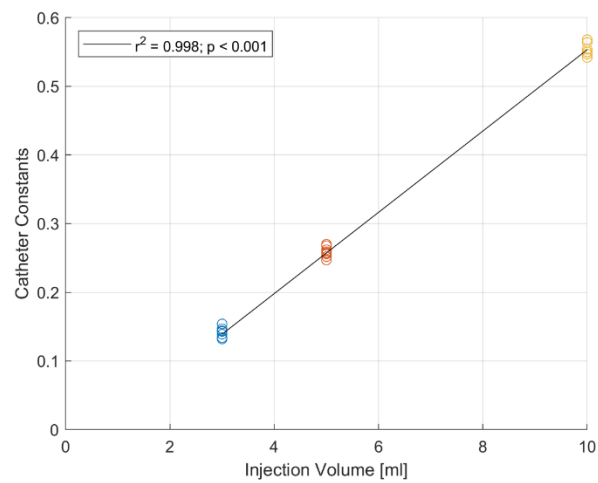
Calculations were performed for all individual measurements.

Ejection fraction (EF) was calculated using an exponential fit modeling the exponential decay of the thermodilution signal, as previously published and validated E³, E⁴, E⁵. The ratio of the decay between each heart cycle (T2/T1, T3/T2, etc.) must represent 1 – EF. Stroke volume (SV) was calculated by either dividing the blood flow from thermodilution (calculated stroke volume) or from the flow probe (measured SV) by heart rate. End-diastolic volume was then either calculated from measured SV (EDV (measured)) or calculated SV (EDV (calculated)). End-systolic volume was defined as end-diastolic minus stroke volume. To further assess right ventricular performance we extracted the median central venous pressure (CVP) and the mean pulmonary artery pressure (PAP) during each measurement period. Additionally we calculated pulmonary vascular resistance as 80 times mean PAP – mean left atrial pressure divided by pulmonary blood flow.

All calculations can be followed for one injection and animal with the attached Matlab script in chapter 3.

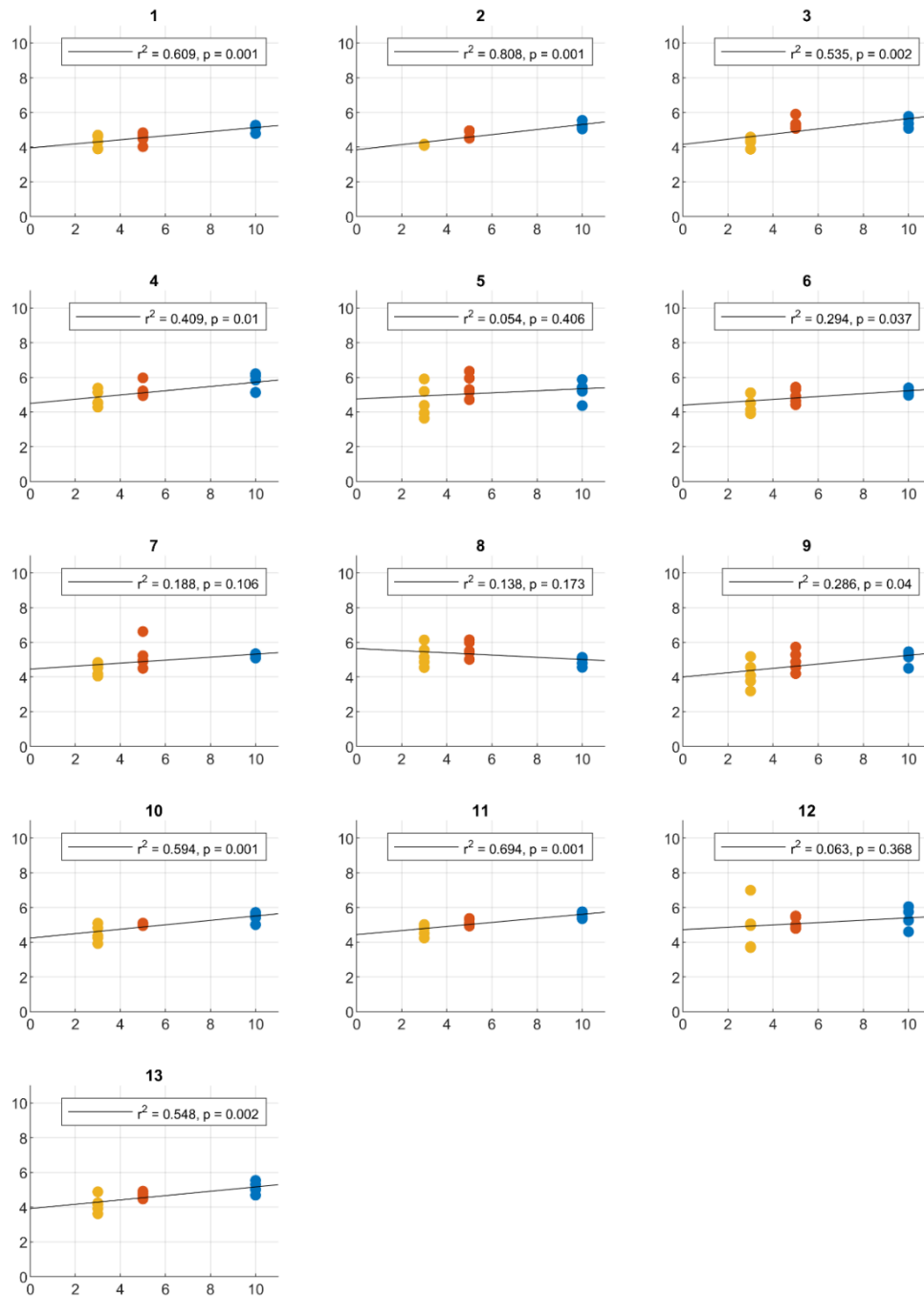
DETERMINING THE RELATIONSHIP BETWEEN INJECTION VOLUME AND CATHETER CONSTANT VALUE

We used a data set of published catheter constants ² to find the mathematical relationship between catheter injection volumes and values of the constants. The relationship was highly linear, where the linear regression provides $c = 0.06 * x - 0.03$ (Supplementary Figure E1).

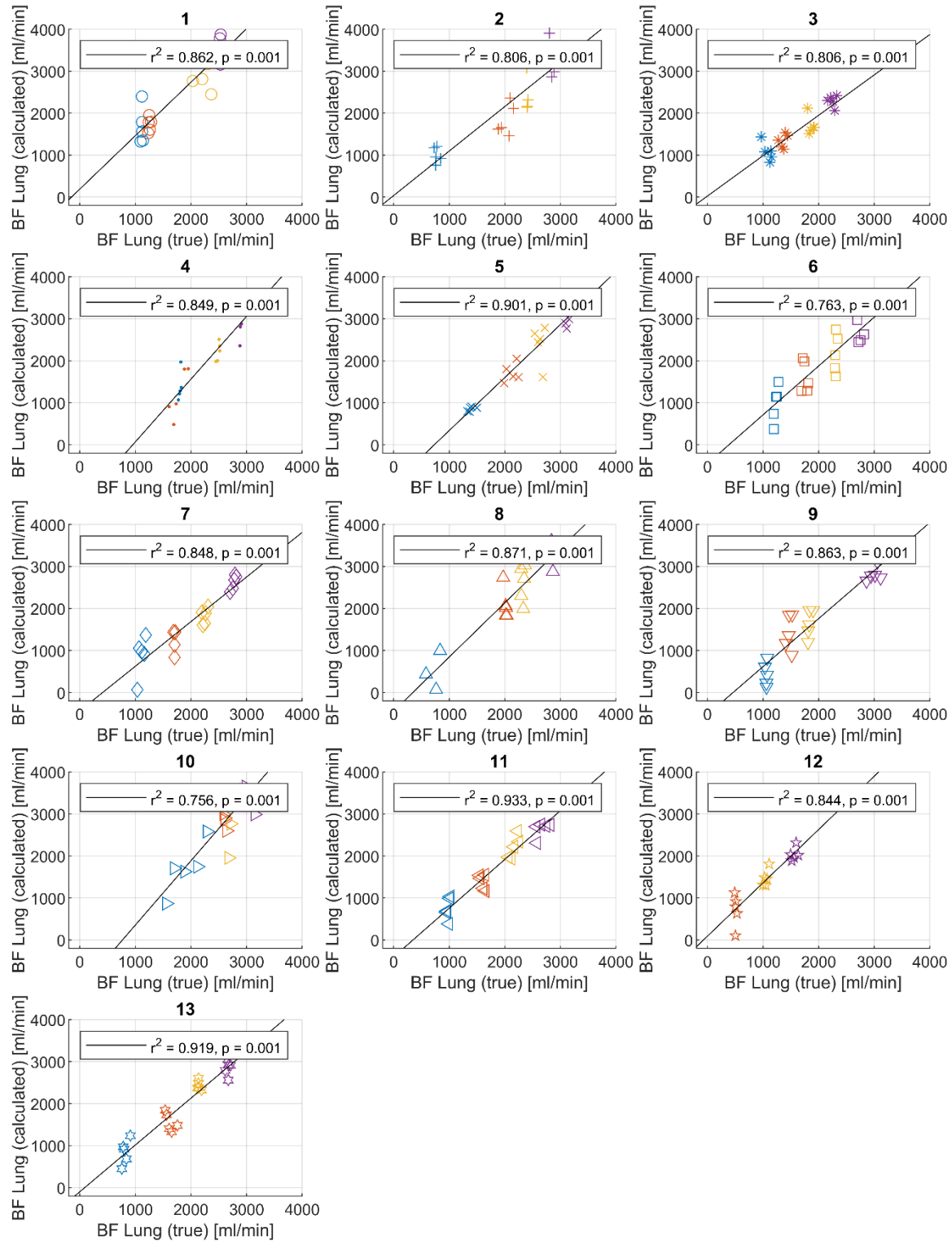


2 SUPPLEMENTARY FIGURES - INDIVIDUAL DATA AND REGRESSIONS FOR ALL ANIMALS

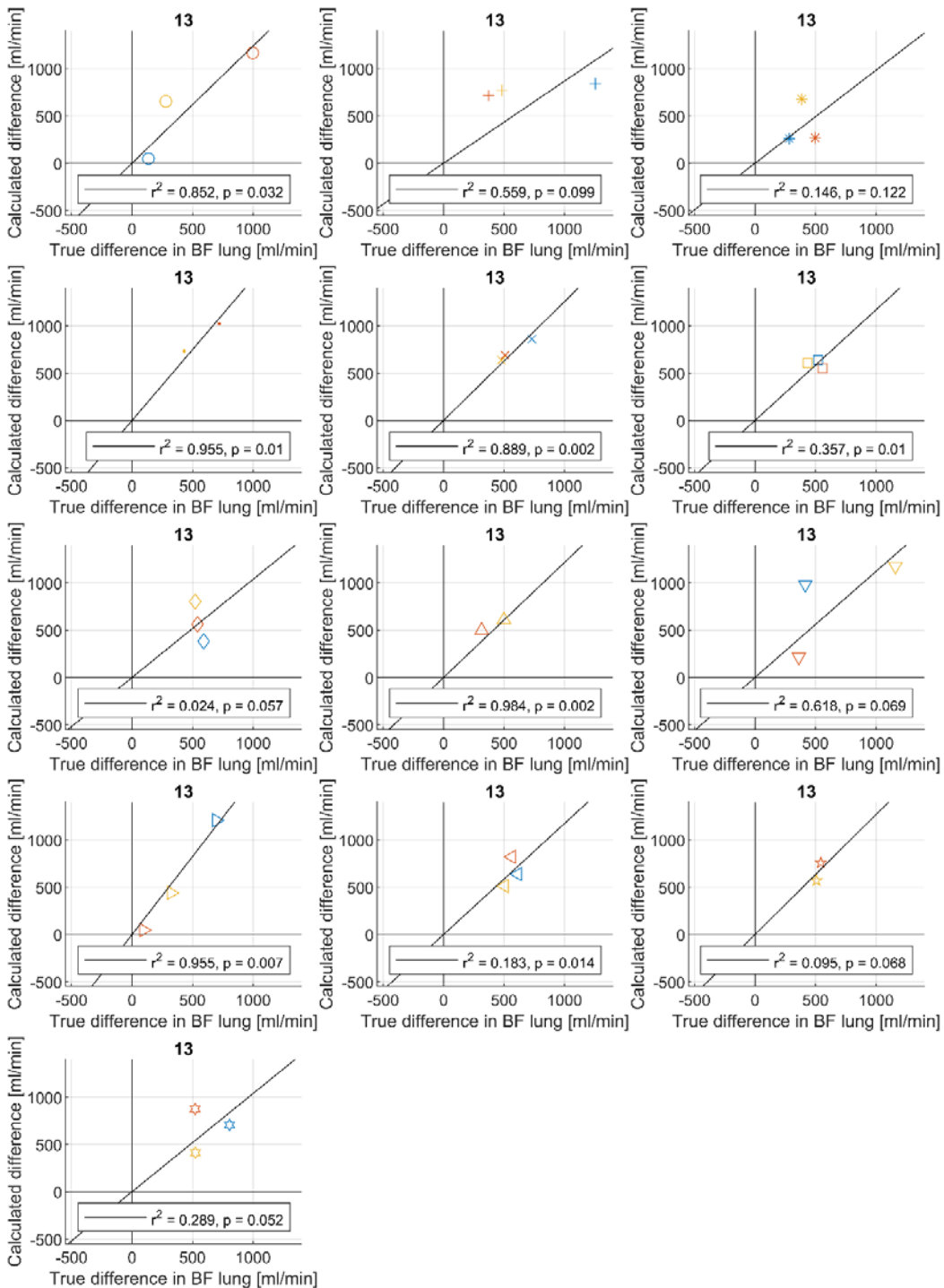
SUPPLEMENTARY FIGURE E2 - ECMO CONSTANTS



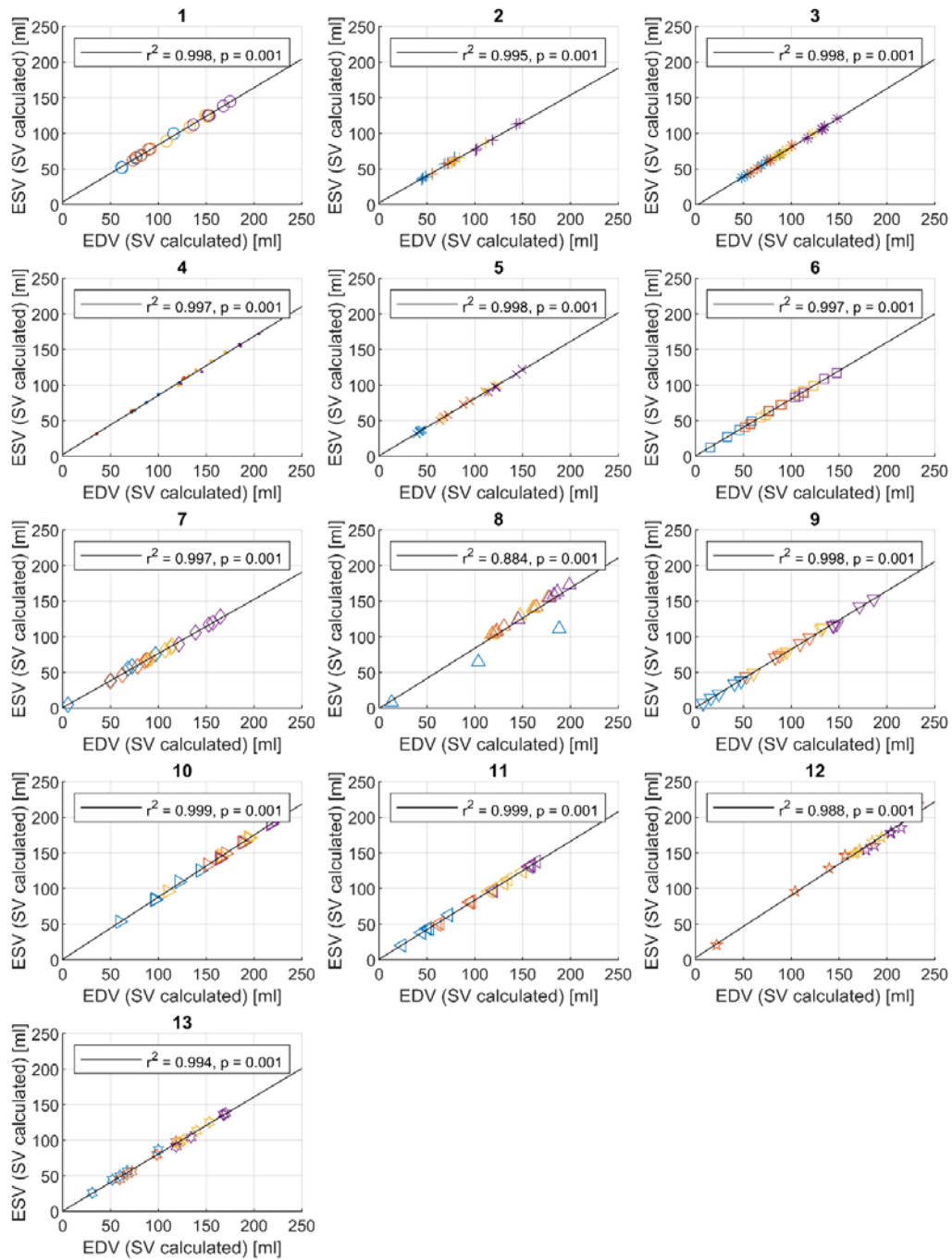
SUPPLEMENTARY FIGURE E3 - BLOOD FLOW CALCULATIONS



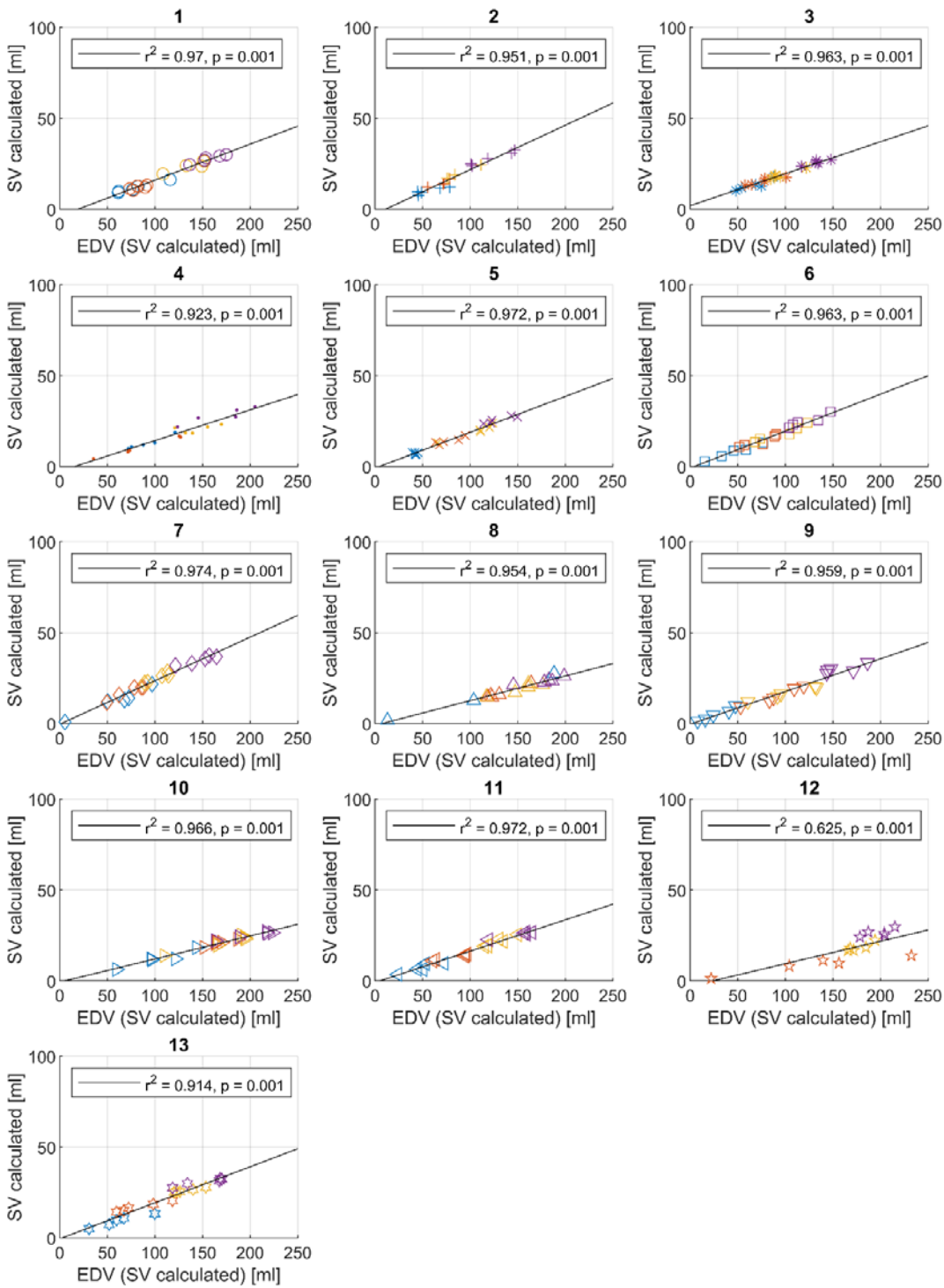
SUPPLEMENTARY FIGURE E4 – BLOOD FLOW CALCULATIONS – INDIVIDUAL 4 QUADRANT PLOTS



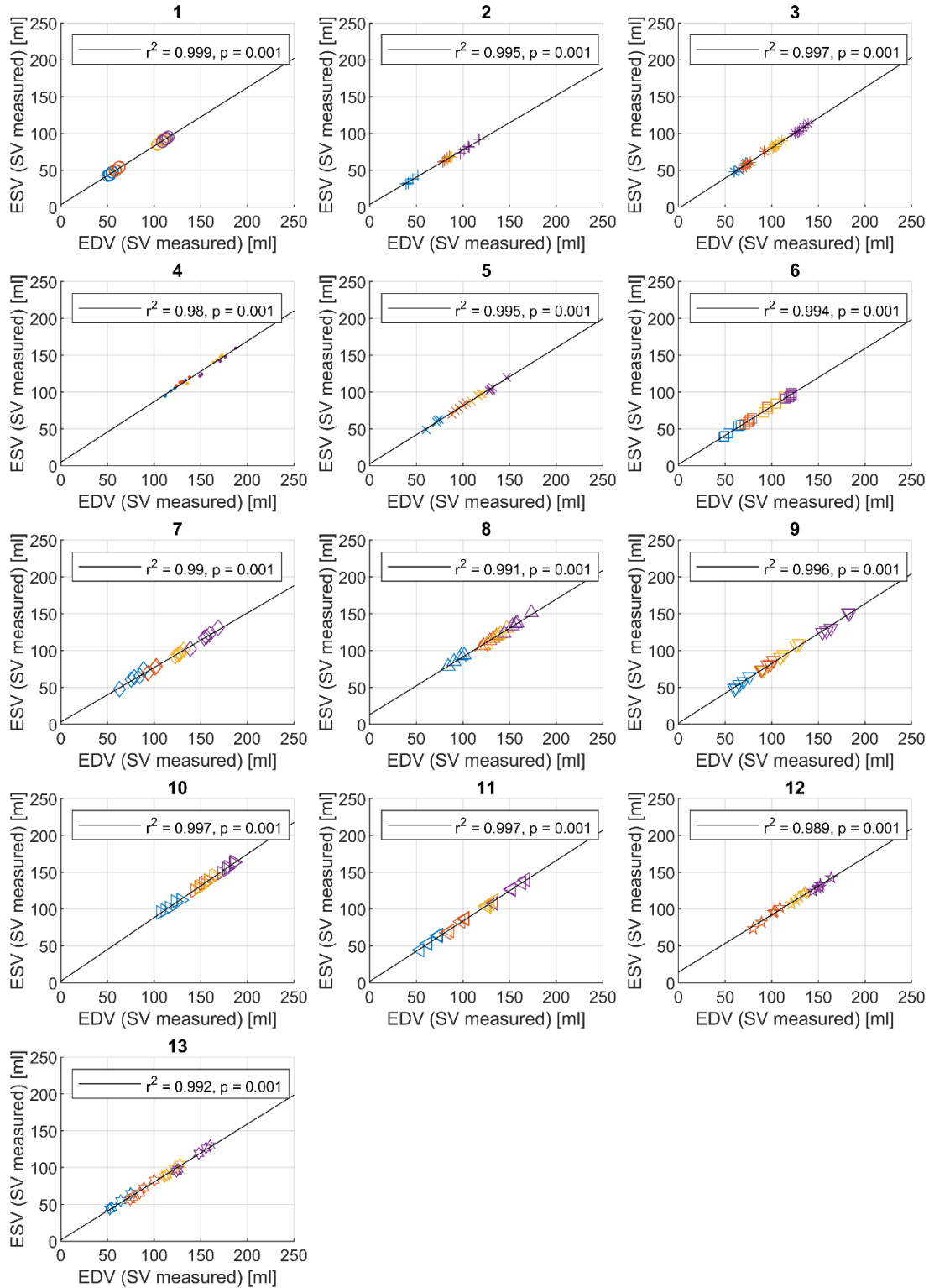
SUPPLEMENTARY FIGURE E5 - RV ANALYSIS – EDV VS. EDV (SV CALCULATED FROM TD)



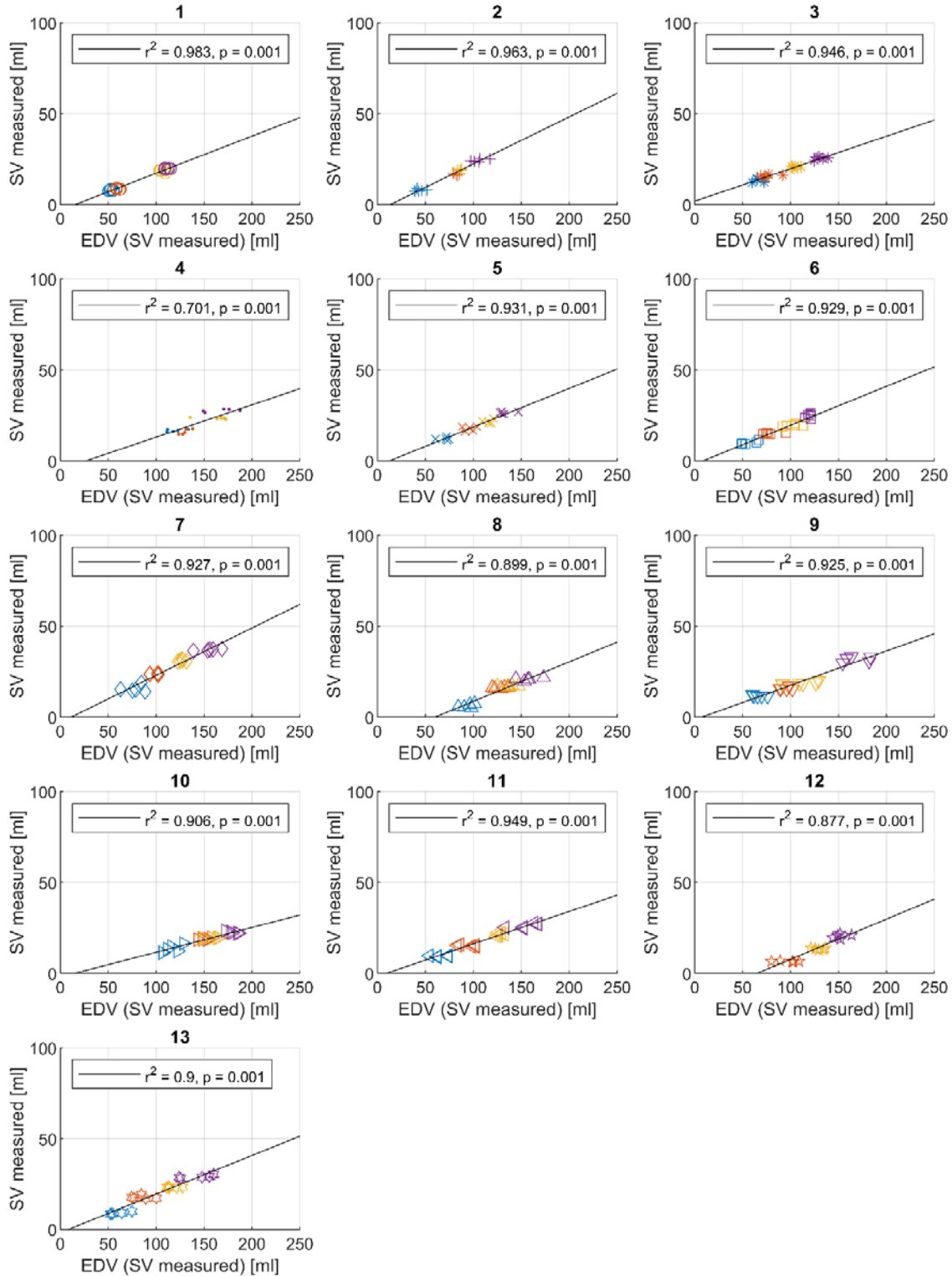
SUPPLEMENTARY FIGURE E6 - RV ANALYSIS – EDV VS. SV (SV CALCULATED FROM TD)



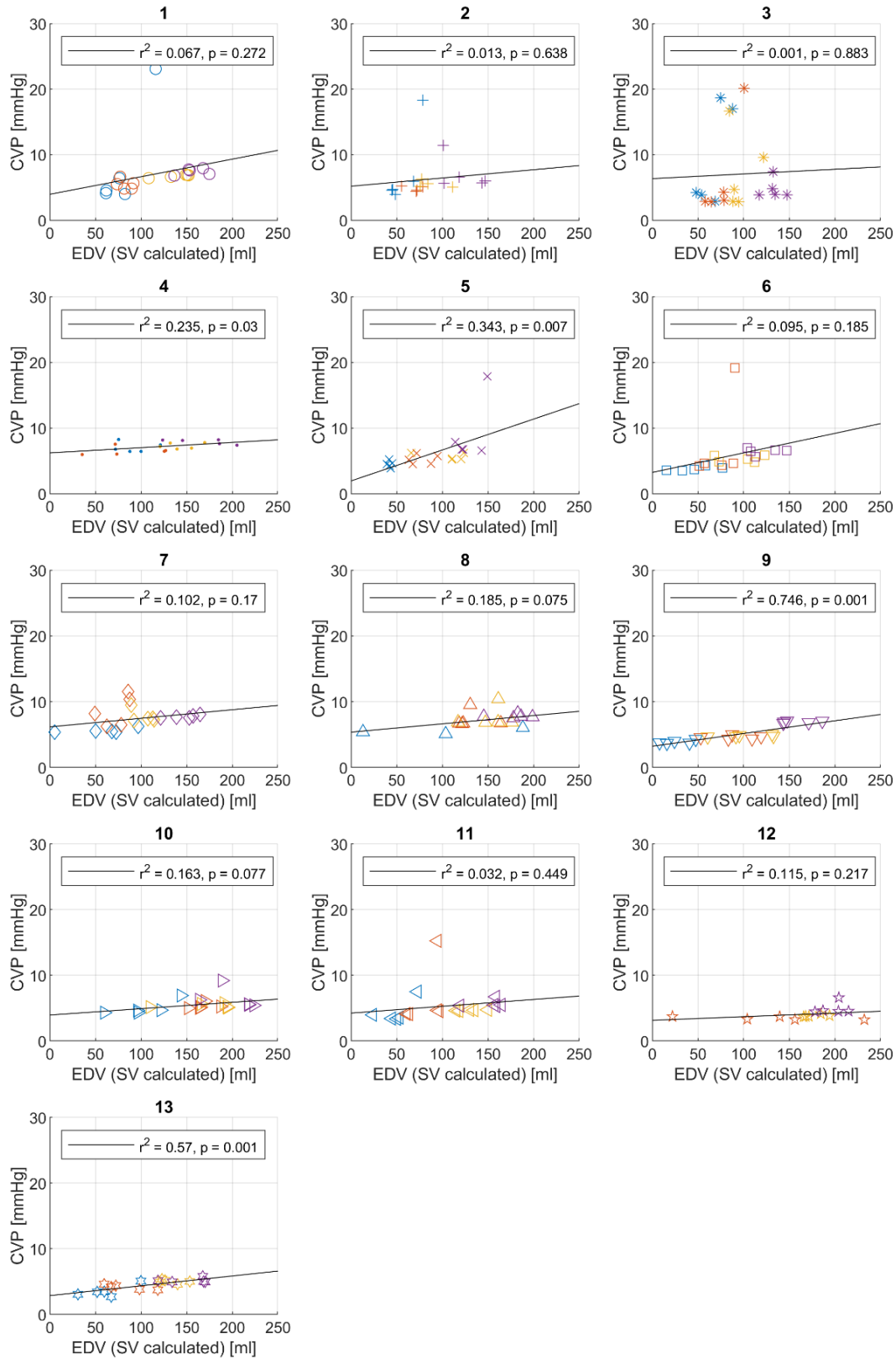
SUPPLEMENTARY FIGURE E7 - RV ANALYSIS – EDV VS. ESV (SV MEASURED BY FLOW PROBE)



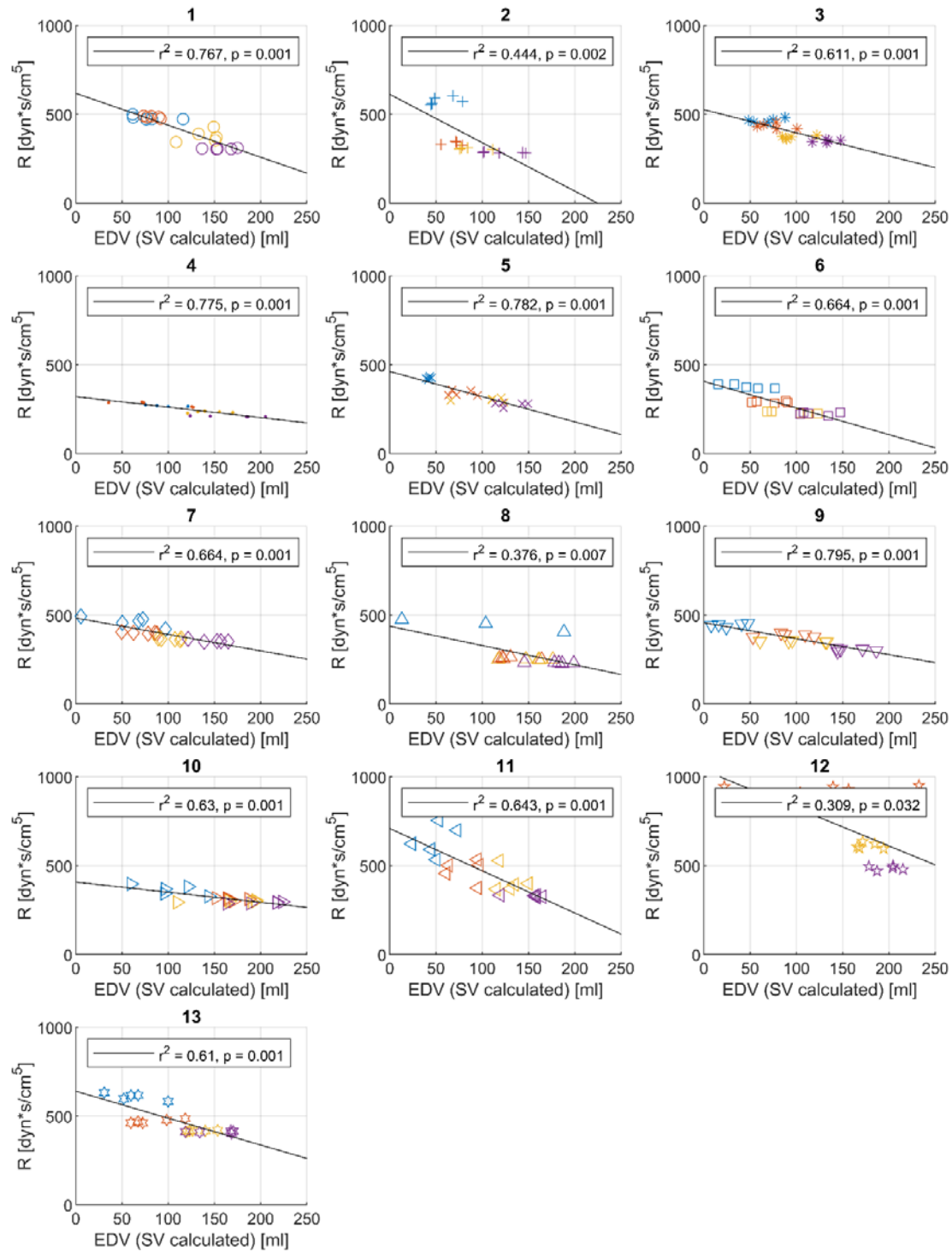
SUPPLEMENTARY FIGURE E8 - RV ANALYSIS – EDV VS. SV (SV MEASURED BY FLOW PROBE)



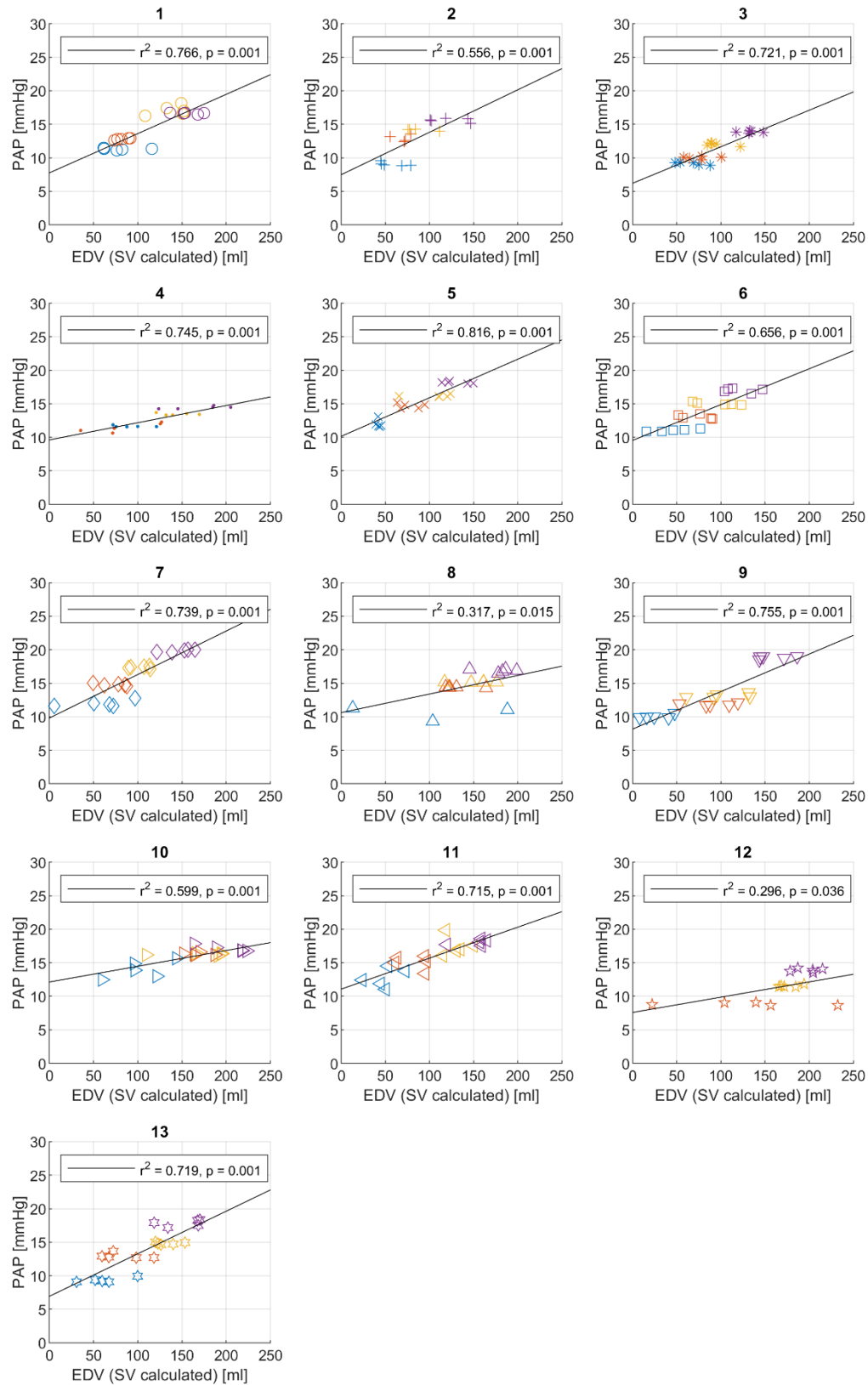
SUPPLEMENTARY FIGURE E9 - RV ANALYSIS – EDV VS. CVP



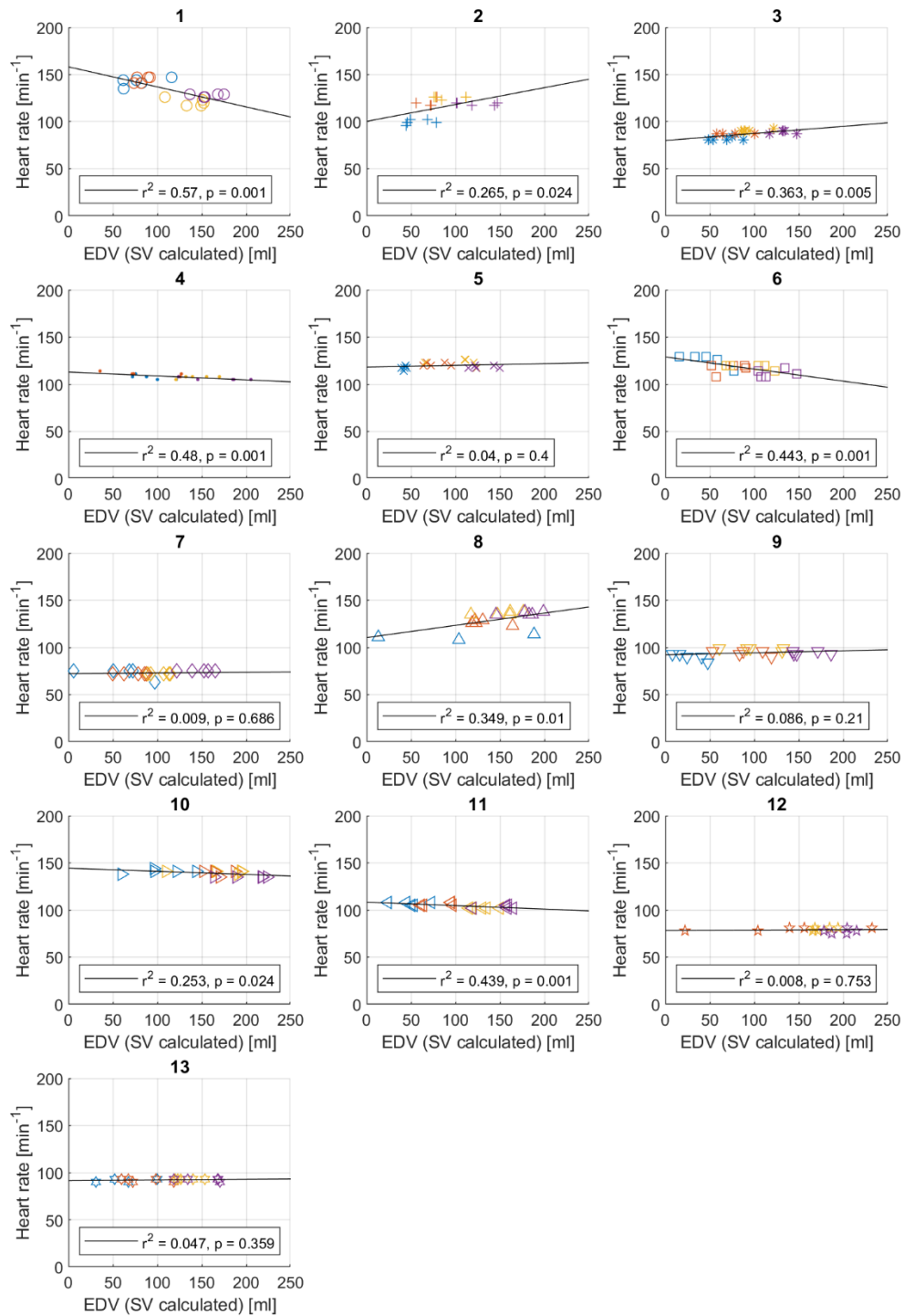
SUPPLEMENTARY FIGURE E10 - RV ANALYSIS – EDV VS. PULMONARY VASCULAR RESISTANCE



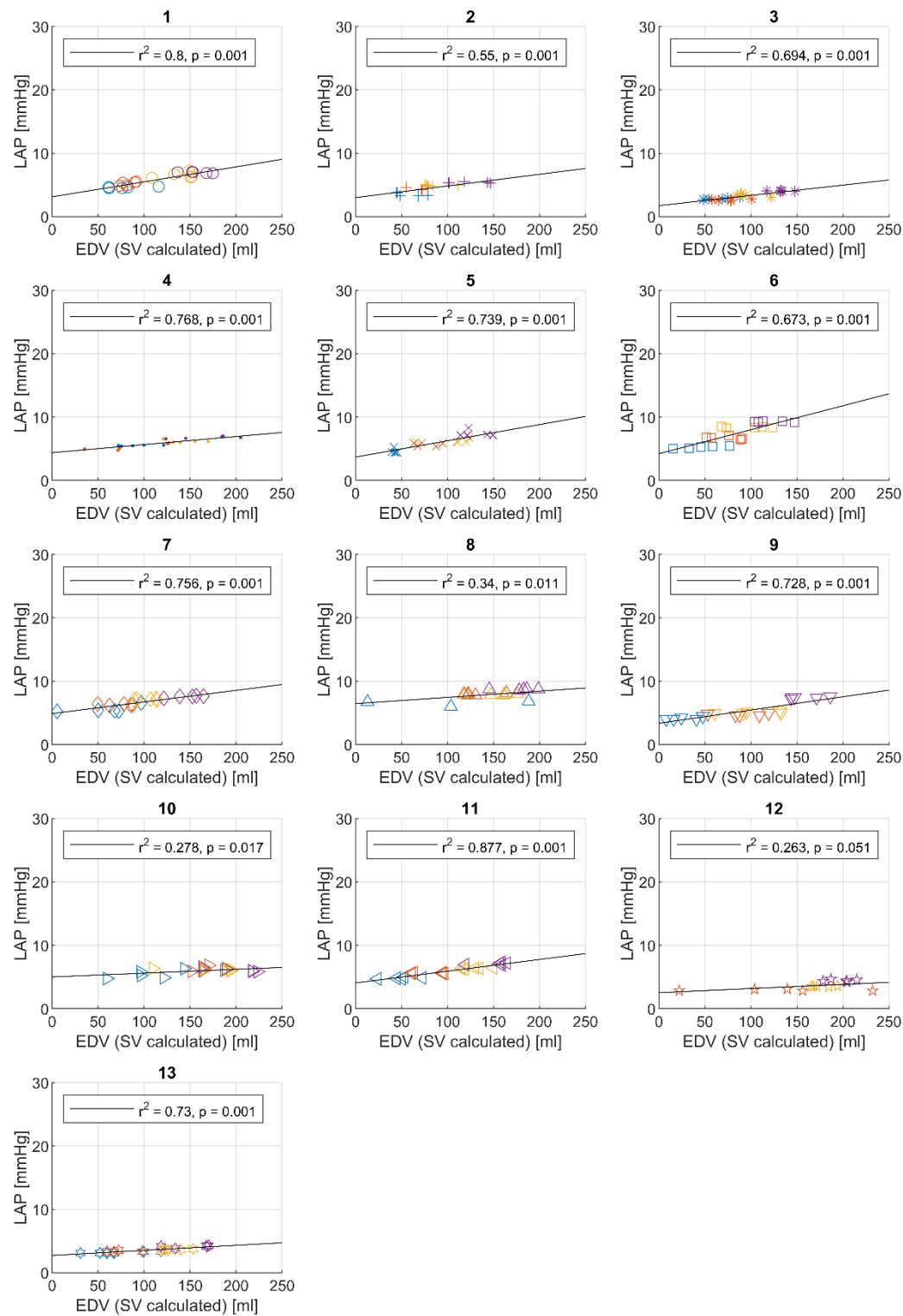
SUPPLEMENTARY FIGURE E11 - RV ANALYSIS – EDV VS. PAP



SUPPLEMENTARY FIGURE E12 - RV ANALYSIS – EDV VS. HEART RATE



SUPPLEMENTARY FIGURE E13 - RV ANALYSIS – EDV VS. LEFT ATRIAL PRESSURE



3 SUPPORTING INFORMATION: STEP-BY-STEP CALCULATIONS USING MATLAB

This MatLab Script is a step-by-step calculation of cardiac output as well as right ventricular ejection fraction using thermodilutions signals at the ECMO and in the pulmonary artery after an injection of 10ml cold saline into the right atrium. The purpose of this script is to give a step-by-step insight into how the calculations are actually performed. This script was then automated to calculate the data from all included injections.

DATA LOAD

First, the data is loaded. We use the last animal of the experimental series in this example.

```
clear
AnimalNumber = "P16";
load(strcat(AnimalNumber, "\", AnimalNumber, "_Data.mat"))
```

Additionally we load the already calculated constants.

```
load('Scripts/Thermodilution/TD_Constants.mat')
```

DEFINE MARKER AND SAMPLE TIMES

We now define the marker of the injection. In this example script, we only extract one marker. In this example, this marker corresponds to the 3/5 injection at 3 liters min⁻¹ of ECMO flow.

```
Marker = "T_V3_3";
```

Next we define extract the sample points from the data library, corresponding to the marker.

```
Start = ds.Marker.Sample(ds.Marker.Name == Marker)
```

```
Start = 436682
```

We will analyze 30 seconds after the marker was set.

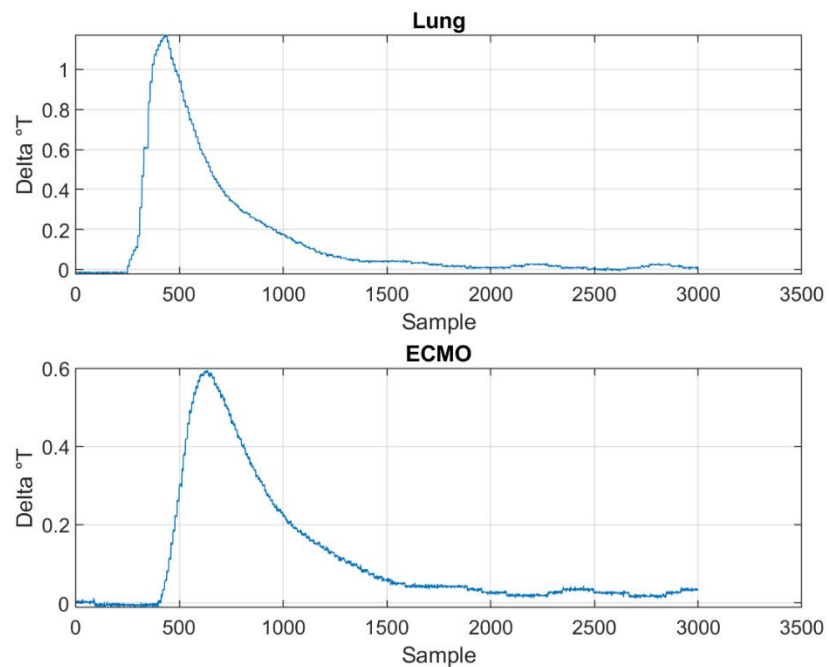
```
Time = 30;
End = Start+Time*100 % The sample rate is 100 Hz.
```

End = 439682

PLOT THE THERMODILUTION CURVE FOR ECMO AND LUNG

```
figure()
    subplot(2,1,1)
    plot(ds.Data.deltaBT1(Start:End))
    title('Lung')
    xlabel('Sample')
    ylabel('Delta °T')
    grid on

    subplot(2,1,2)
    plot(ds.Data.deltaBT2(Start:End))
    title('ECMO')
    xlabel('Sample')
    ylabel('Delta °T')
    grid on
```



CALCULATE INJECTION VOLUME FROM ECMO CURVE

We now calculate the injection volume from the ECMO injection. We use the already calculated constants from the constant function.

We define the following variables:

```
% Define ECMO Data
XData = ds.Data.deltaBT2(Start:End);
% Define Area Under the Curve
AUC = trapz(XData)
```

AUC = 331.0977

```
% Define Bodytemperature
BodyTemperature = mean(ds.Data.BT(Start:End))
```

BodyTemperature = 37.2064

```
% Get Constant Coefficient and Intercept
Coefficient = Constants(13).Coefficient.ECMO
```

Coefficient = 0.0971

```
Intercept = Constants(13).Intercept.ECMO
```

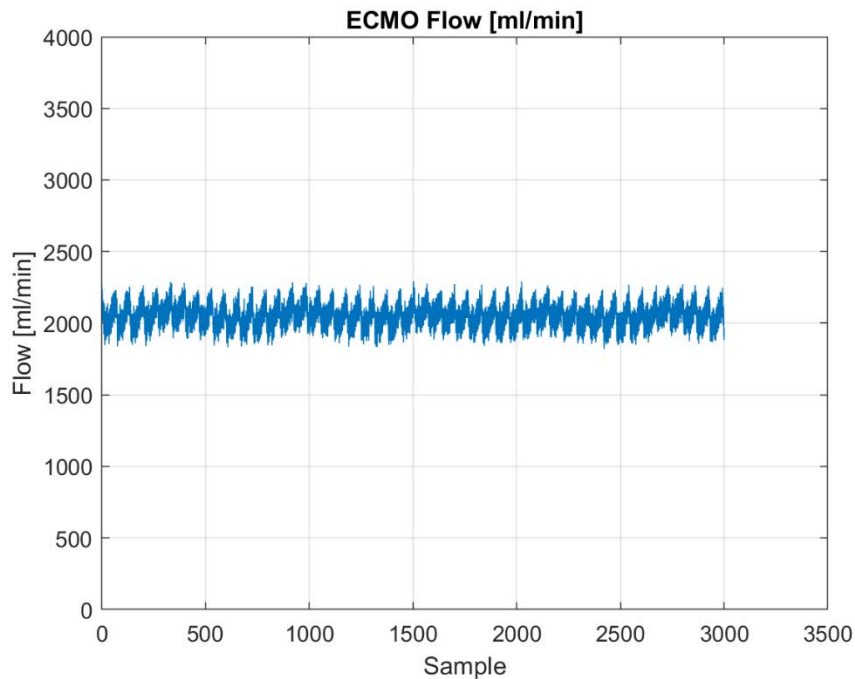
Intercept = 4.3856

Now we need to define the injection temperature, which for this injection was 1.2 °C.

```
InjectionTemperature = 1.2;
```

Next we plot and then define the measured blood flow at the ECMO.

```
figure()
plot(ds.Data.ECMOFlowPuls(Start:End))
title('ECMO Flow [ml/min]')
ylabel('Flow [ml/min]')
xlabel('Sample')
grid on
ylim([0 4000])
```



```
YData = mean(ds.Data.ECMOFlowPuls(Start:End))
```

```
YData = 2.0494e+03
```

Now we use the already defined constants to build an equation system, which we solve for Injection Volume.

```
% Define variable
syms InjectionVolume
% Define equation
eqn = YData/1000 == InjectionVolume .* (Coefficient .* InjectionVolume +
Intercept)...
      .* (BodyTemperature - InjectionTemperature)./AUC
```

```
eqn =
```

$$\frac{2307390468405709}{1125899906842624} = \frac{2533725249826919 \text{ InjectionVolume} \left(\frac{3497755208932481 \text{ InjectionVolume}}{36028797018963968} + \frac{4937750651386135}{1125899906842624} \right)}{23298931460175308}$$

```
% solve equation
sol = (solve([eqn],[InjectionVolume]));
% Get Solution, defined as the maximum of possible solutions.
```



```
InjectionVolumeECMO = double(max(vpa(sol)))
```

```
InjectionVolumeECMO = 3.9514
```

We now define the injection volume for the lung as 10 - the injection volume at the ECMO.

```
InjectionVolumeLung = 10 - InjectionVolumeECMO
```

```
InjectionVolumeLung = 6.0486
```

CALCULATE PULMONARY BLOOD FLOW USING CALCULATED INJECTION VOLUME AT THE LUNG

```
% Define lung data
XData = ds.Data.deltaBT1(Start:End);
% Define area under the curve
AUC = trapz(XData)
```

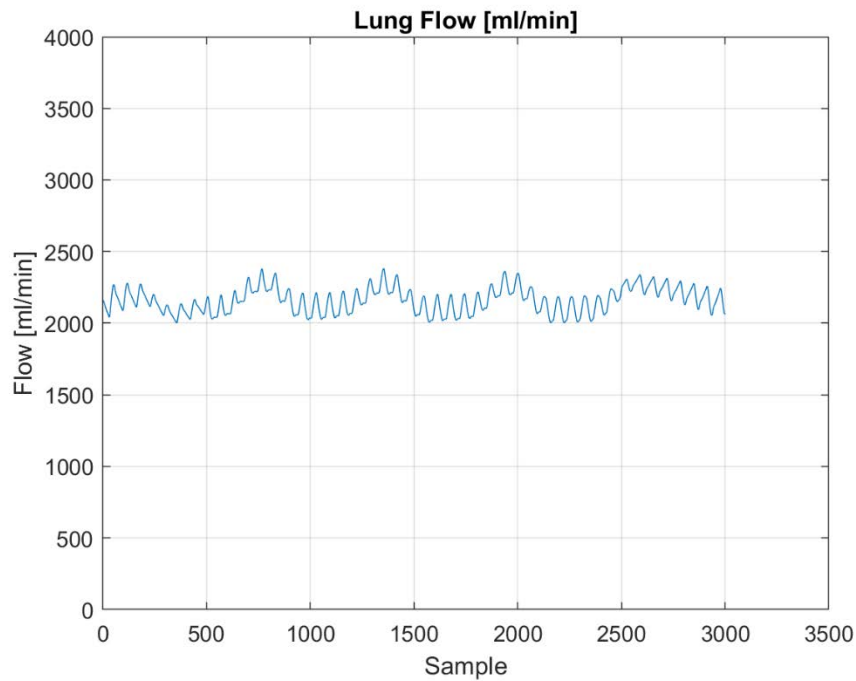
```
AUC = 454.1869
```

```
% Calculate Pulmonary Blood Flow
CalculatedPulmonaryBloodFlow = InjectionVolumeLung .* ...
    (Coefficient.*InjectionVolumeLung + Intercept) .* ...
    (BodyTemperature - InjectionTemperature)./AUC*1000
```

```
CalculatedPulmonaryBloodFlow = 2.3845e+03
```

Plot and average measured pulmonary blood flow from data set.

```
figure()
plot(smoothdata(ds.Data.PulmFlowPuls(Start:End),"movmean",1000))
    % There is a moving average of 10 seconds = 1000 samples applied to the
data
title('Lung Flow [ml/min]')
ylabel('Flow [ml/min]')
xlabel('Sample')
grid on
ylim([0 4000])
```



```
MeasuredPulmonaryBloodFlow = mean(ds.Data.PulmFlowPuls(Start:End))
```

```
MeasuredPulmonaryBloodFlow = 2.1669e+03
```

Calculate the difference between calculated and measured blood flow [ml/min]

```
DifferenceBloodFlow = MeasuredPulmonaryBloodFlow - CalculatedPulmonaryBloodFlow
```

```
DifferenceBloodFlow = -217.6317
```

```
PercentageError = DifferenceBloodFlow./MeasuredPulmonaryBloodFlow.*100
```

```
PercentageError = -10.0435
```

For this sample, there is a 10% error (overestimation) from true pulmonary blood flow.

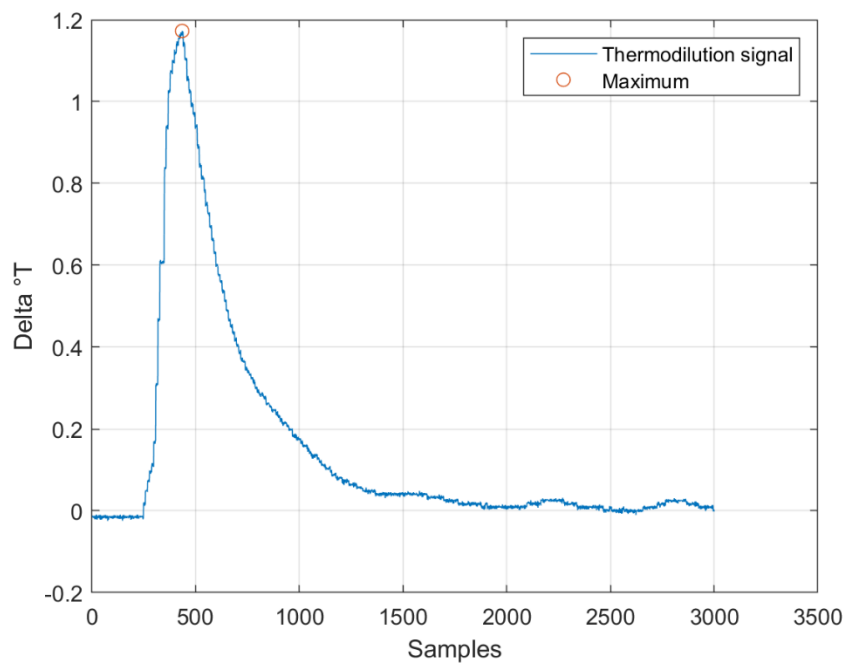
CALCULATION OF EF AND STROKE VOLUME

```
% Define thermodilution signal at the lung
XData = ds.Data.deltaBT1(Start:End);

% Find Maximum of Signal
[val,locs] = max(XData);
```

We define a new curve starting from the maximum point of the signal.

```
figure()
plot(XData)
hold on
plot(locs,val,'o')
grid on
legend('Thermodilution signal','Maximum')
ylabel('Delta °T')
xlabel('Samples')
```



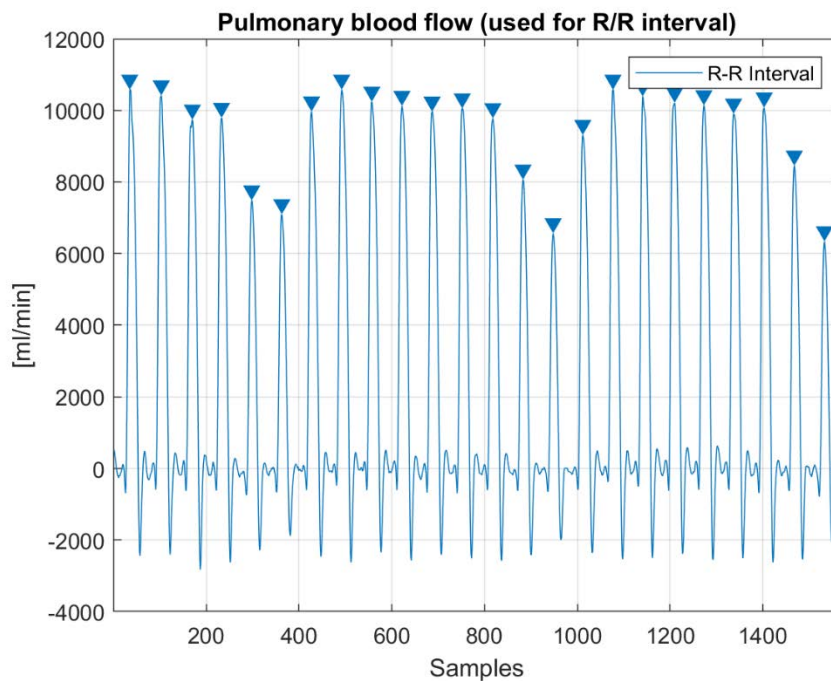
```
% Define new signal starting from maximum
NewStart = Start + locs;
```

```
NewEnd = Start + 20*100;
```

We now define new data. We have no ECG record available, therefore the R/R interval /heart cycle is derived from the pulmonary flow curve.

```
% Define New Data
T = ds.Data.deltaBT1(NewStart:NewEnd);
Flow = ds.Data.PulmFlowPuls(NewStart:NewEnd);

% Plot the data and find peaks in pulmonary blood flow signal
figure()
    findpeaks(Flow, 'MinPeakHeight',1000, 'MinPeakDistance',30)
    [pks,locs] =
findpeaks(Flow, 'MinPeakHeight',1000, 'MinPeakDistance',30);
    title('Pulmonary blood flow (used for R/R interval)')
    legend('R-R Interval')
    ylabel('[ml/min]')
    xlabel('Samples')
```



Now we fit an exponential model to the decay of the thermodilution curve.

```

% Fit Exponential Model
% Define X
    x = 1:1:length(T);
    x = x.'; % Transpose Vector
% Define thermodilution signal as Y
    y = T;
% Perform exponential fit
    f = fit(x,y,'exp1')

```

f =

General model Exp1:

$f(x) = a \cdot \exp(b \cdot x)$

Coefficients (with 95% confidence bounds):

a = 1.151 (1.147, 1.155)

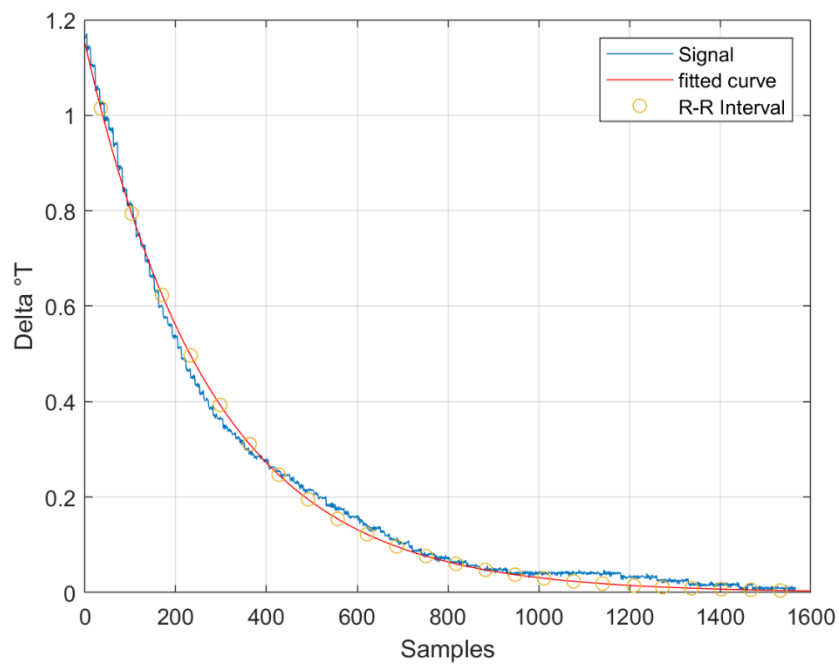
b = -0.003605 (-0.003624, -0.003586)

We now plot "locs", which represents the R-R Intervals in terms of samples, on the exponential fit.

```

figure()
    plot(T)
    hold on
    plot(f)
    scatter(locs,f(locs))
    legend('Signal','fitted curve','R-R Interval')
    grid on
    xlabel('Samples')
    ylabel('Delta °T')

```



Last, we calculate Ejection fraction as $EF = 1 - RF$, where RF is the ratio of $\Delta T(n+1) / \Delta T(n)$.

```

for i=1:(length(locs)-1)
    T1 = f(locs(i));
    T2 = f(locs(i+1));

    RF(i) = T2/T1;
    EF(i) = 1 - RF(i);
end

```

RF

RF

RF = 1×23

0.7826 0.7854 0.7968 0.7911 0.7911 0.7940 0.7911 ...

Ejection fraction EF

EF = EF .* 100

EF = 1×23

21.7415 21.4589 20.3180 20.8905 20.8905 20.6048 20.8905 ...

We now calculate the mean of all EF calculated. [%]

```
EF = mean(EF) % [%]
```

EF = 20.9268

4 SUPPLEMENTAL REFERENCES

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