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Potential of Pulse Pressure as an indicator for contractility of the heart and successful weaning from Extracorporeal Membrane Oxygenation

Technische Geneeskundig Opdracht (TGO)

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Abstract

Introduction: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is used to offer mechanical circulatory support to patients in cardiogenic shock (CS). However, determining whether patients can successfully wean from VA-ECMO is challenging, due to the complex hemodynamic interaction between the patient and VA-ECMO. Pulse pressure (PP) holds the potential to be a predictor of intrinsic cardiac contractility and could provide guidance in clinical decision-making. The aim of this study is to analyze PP over time and the effects of other hemodynamic factors and VA-ECMO settings to investigate whether the PP can serve as a potential indicator for determining the successful weaning form VA-ECMO.

Method: Data of 88 patients was used by dividing them into subsets based on heart or lung indication and weaning outcome. The absolute pulse pressure (PP) as well as the relative PP are plotted against time to visualize the trends. Relations between PP and heart rate (HR), age and BMI are explored using scatterplots. Subsequently, the effect of these factors on the PP is filtered to evaluate changes in the trends. The same is done for VA-ECMO revolutions per minute (RPM). The increase per 24 hours is calculated to determine when the increase of the PP is at its maximum. To get insight into the significance of the results, the Pearson's Chi-squared test Mann-Whitney U and the Pearson Correlation test are performed.

Results: Based on this report the following results were obtained. The mean relative PP differs between recovered and non-recovered patients. The median of the total change is significantly different for each outcome (p = 0,031). The maximum increase of PP took place on day one for most patients and the mean change in PP per day decreases over time. It was also discovered that for unrecovered patients an increase in heart rate, means a decrease in PP. A significant relation was also found between age and PP (r=0,21and p = 0,05), older patients have a higher pulse pressure. When evaluating the influence of change in ECMO RPM on PP no trend could be observed for both outcomes.

Conclusion: Based on the results it was concluded that successfully weaned patients do on average show a higher relative PP compared to patients who do not wean successfully. When evaluating the PP as an potential indicator for recovery of the heart and therefore successful weaning, a doctor should take the heart rate into consideration. This also applies to the age, since a weak linear relation was found. The BMI and the influence of change of ECMO RPM on PP should not be considered, because no relation has been observed. The chance of showing a maximum increase in PP is highest on day one on VA-EMCO. After day one the chance of showing maximum increase lowers as days on VA-ECMO progress.

Keywords: VA-ECMO, pulse pressure, PP, heart rate, age, BMI, VA-ECMO RPM, weaning, VIS-score, VIS, inotropic, vasoconstrictors, dilatators, ECLS, Veno-Arterial Extracorporeal Membrane Oxygenation

Content

Introduction

Extra corporeal membrane oxygenation (ECMO) is used as cardiac and respiratory support for patients with cardiogenic shock. Cardiogenic shock (CS) is systemic tissue hypoperfusion secondary to an insufficient cardiac output (CO)[1]. Often this is caused by heart failure in which the contractility is inadequate. This will lead to a higher venous- and filling pressure emerging from the remaining blood in the left ventricle (LV) after contraction [2]. The persisting filling pressure weakens the heart muscle even further. As a result, contractility decreases more and thus the systolic pressure drops below 90 mmHg, causing CS [3]. The estimated 30-day mortality of patients with CS is high at approximately 30-40% in present clinical trials [4]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides a solution to patients with cardiogenic shock who are refractory to conventional treatment. VA-ECMO increases tissue perfusion and prevents multi-organ failure by forming a temporary mechanical circulatory support system. The blood is drained from the right atrium or inferior vena cava through a venous cannula, oxygenated and pumped back through an arterial cannula causing a retrograde flow in the aorta.

Since VA-ECMO drains blood from the venous system and returns it to the arterial system, the preload of the right atrium (RA) is decreased (Tsangaris, Alexy et al. 2021). Arterial reinfusion to the systemic circulation is supported by a flow up to 7 L/min. The retrograde ECMO-flow interferes with the blood flow originating from the heart. This leads to an increased mean arterial pressure (MAP)[5]. As the MAP increases, the LV afterload increases, thus the heart must contract stronger to overcome this afterload. If the heart is insufficient to do so, overloading of the LV may occur, this decreases the cardiac contractility further.

Patients on ECMO still have a cardiac output of the heart. The remaining cardiac output collides with the ECMO-flow. The region where this happens is called the watershed region. The point where the watershed lies is dependent on the strength of the heart and the ECMO-flow. As ECMO-flow increases, stroke volume (SV) and PP decrease, while the left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP) increase [6]. If the antegrade flow caused by the output of the LV is relatively high to the retrograde ECMO-flow, the watershed point lies more distal (i.e. closer to the diaphragm), meaning the coronaries are at risk for hypoperfusion [6].

To predict whether a patient is stable enough to wean from VA-ECMO, an estimation of the intrinsic cardiac contractility should be made to determine the cardiac condition. Currently doctors use the left ventricular ejection fraction (LVEF) as an indicator. LVEF is based on echocardiography [7]. However, echocardiography has several limitations. In 1D or 2D echocardiography the exact outlining of the LV cannot be determined; the echocardiography must make several assumptions about the LV-shape to calculate the LVEF. In addition, the quality of the echocardiogram is dependent on the expertise and experience of the echocardiograph technician [8]. Therefore, the LVEF is not a reliable indicator.

So, there is still a lot of uncertainty about whether a patient can wean from VA-ECMO at the start of a weaning trial. To prevent a bad outcome, the patient should be closely monitored, and staff should be ready to intervene when the weaning fails. This results in a large team surrounding the patient, which is very inefficient [9].

To reduce personnel needed and to better decide beforehand whether a patient can wean from VA-ECMO, a different indicator should be used. Several studies have shown that pulse pressure (PP) is a good indicator [10]. VA-ECMO uses quasi-continuous flow, the difference in systolic and diastolic pressure therefore is the result of cardiac contractility [11]. However, PP is not only dependent on contractility, but also on other hemodynamic factors, medication and ECMO-flow. This should be taken into consideration when using the PP as an indicator for intrinsic cardiac contractility. The aim of this research is to predict whether a patient is ready to wean from VA-ECMO based on the PP and therefore the research question is as follows: **How can be predicted whether patients can successfully wean from veno-arterial extracorporeal membrane oxygenation based on monitoring pulse pressure and related parameters?**

Methods

Introduction

In previous studies observations were made based on a cardiovascular computer model [12]. These observations were further assessed in an observational study evaluating six patients. The six patients were evaluated using a methodology to accurately track the PP over time in patients on VA-ECMO and to set up a way to determine the effect of external factors such as the VA-ECMO setting and the use of inotropes and vasopressors.

In this retrospective chart review an evaluation of a larger set of patients is made to evaluate the PP as a reliable indicator for successful weaning from VA-ECMO. Due to the large number of patients, it is no longer possible to observe each patient individually. To obtain an overview, the individual patients are plotted in spaghetti plots and the mean of all the patients is used to visualize the parameters over time. Since the PP fluctuates, a moving average filter is applied on all the spaghetti plots to smoothen the graph. This way it can be analyzed more clearly.

The methodology is extended to evaluate a larger set of patients. The previous methodology focused on the VIS-score, while it might be relevant to look at inotropes, vasoconstrictors and vasodilators separately as well. The methodology is also extended to observe influence of heart rate on pulse pressure. Other correlations that are assessed are those between the PP and age and PP and BMI. Furthermore, the trend of the PP over time is evaluated in multiple ways.

Data request

The patient data is obtained from the Intensive Care Unit (ICU) in the University Medical Centre Utrecht (UMCU). The data from each patient was provided from the moment the patient entered the ICU until the patient was discharged from the ICU or until the patient died. Many parameters are requested for each patient, only a few were included in the analysis.

The data is acquired from MetaVision and anonymized by adjusting the dates and the patientID's. The time intervals of various factors range from minutes to hours. To analyze the data and compare parameters with each other, the intervals were equalized.

Patient selection and characteristics

To conduct a comprehensive study involving a larger patient population, the data is divided into two subsets. These subsets are classified based on patient outcomes, distinguishing between successful weaning and unsuccessful weaning cases.

VA-ECMO is not only used for patients with cardiogenic shock, but also for patients with pulmonary disease or patients who went through lung transplantation. These patients are not on VA-ECMO for cardiac indication. So, it is presumed that based on cardiac health they should be able to wean from VA-ECMO. Therefore, patients with a pulmonary indication should not show an increase in PP. However, due to stress after surgery or other reasons, the heart may not be performing at its optimal potential when these patients go on VA-ECMO. Thus, an increase in PP can still be observed. It may also be the case that some patients, besides having a lung condition, suffer from cardiac disease. Their increase in PP could then be accounted for by an increase in cardiac contractility. Even though these patients show an increase in PP, they could still have an unsuccessful outcome due to their pulmonary indication. The cause of death is not known, so therefore these patients are not taken into consideration when drawing conclusions, this could give a distorted image. Patients with lung indication are thus excluded from analyses that focus on trends. Patients with other indications are excluded from this whole study, since their cardiac condition is unknown. When looking at the relation between age and PP, heart rate and PP, BMI and PP, the lung patients are included, since this is not about the trend of the PP.

The dataset also contains patients with an intra-aortic balloon pump (IABP), which influences the PP strongly. This IABP increases cardiac output by reducing afterload during systolic deflation, creating a vacuum. During diastolic inflation the IABP increases coronary blood flow via retrograde flow. The IABP causes an increased diastolic aortic pressure and a decreased systolic aortic pressure, this potentially causes a decreased pulse pressure. Since this would give distorted information, the patient group with an IABP is excluded from the dataset.

Analysis of PP over time

To determine whether PP is a reliable indicator for weaning from VA-ECMO, the PP is evaluated over time. The PP is measured every minute for each patient and a running median filter is applied to reduce the noise. Since the PP fluctuates to some extent, the PP per hour is calculated by taking the mean of sixty minutes and plotted subsequently. To visualize the PP over time, the PP per hour of patients with a heart indication is plotted in a spaghetti plot. In these plots, a distinction is made between successfully and unsuccessfully weaned patients by color. To create an overview, the mean PP per hour of all the patients in a group is calculated and plotted over time. This will give insight into how the PP over time differs between the successful and unsuccessful weaned groups.

Analysis of relative PP

Besides the absolute values of PP over time, the change of the PP over time is observed. An increasing cardiac condition is assumed to result in an increasing PP, therefore a higher relative PP. This relative PP is more suited to compare multiple patients, since the initial value is equalized.

To calculate the relative PP, the following formula is used:

$$PP(\%) = \frac{PP(t) - PP(0)}{PP(0)}$$

- PP(%) = relative PP
- PP(t) = measured PP at time t (hours)
- PP(0) = initial value of PP

Since the relative PP is entirely dependent on the initial value (PP(0)), it is important to make sure this value is reliable. Therefore, the mean of the first 12 hours is used to disregard the fluctuation of PP in the first hours of VA-ECMO.

Once the relative PP of each hour is calculated for every patient and plotted over time in a spaghetti plot. Besides, a mean relative PP per hour for all patients is calculated and plotted over time. A distinction between successfully and unsuccessfully weaned patients is visualized in both plots, using the colors green and red.

Total percentual change in PP

The total change in PP during a patient's stay on VA-ECMO is also an interesting indicator that is observed. The total percentual change in PP, comparing the last 12 hours to the first 12 hours on VA-ECMO, of the successfully weaned patients and unsuccessfully weaned patients is analyzed by plotting them separately in a boxplot. The medians of the two subgroups are compared using a Mann-Whitney U test to observe if a significant difference is found.

Analysis of PP maximum increase

Day with highest increase of PP

Rilinger et al. mentioned that a low PP in the first 24 hours on VA-ECMO increases the likelihood of unsuccessful weaning. This suggests that the timing of the PP increase may also be significant in predicting the outcome. To explore when PP increases the most, the change in PP per 24 hours is calculated. It is relevant to know when the most increase takes place, because survival rate decreases as patients stay longer on VA-ECMO [11]. If the PP is a reliable marker to predict successful weaning (and subsequently survival), this decrease in survival rate implies that it is unlikely major changes in PP happen in a later stadium. To verify this hypothesis, a graph is made wherein the average daily increase in PP for all cardiac patients is represented by yellow dots. This is called the increment of PP. To make sure the value of the PP at the end of each timeframe is reliable, the mean is taken over the 5 hours following the respective timeframe. Likewise, the mean after the first day (24 – 29 h) is compared to the mean in the first hours (1 – 5 h). In addition, the day on which the PP increases the most is determined per patient. This is illustrated by bars representing the normalized frequency of patients that had the highest increase on that day in the same graph. This is calculated using the following formula:

Besides a review of the overall maximum increase per day. The analysis was also done separately for the different outcomes.

$$Normalized\ frequency\ =\ \frac{Number\ of\ patients\ with\ highest\ PP\ increase\ at\ day\ x}{Total\ number\ of\ patients\ on\ VA-ECMO\ at\ day\ x}$$

Analysis PP and multiple parameters

Analysis of PP and age

Several studies have suggested that the PP increases with age [13]. This can be explained by the decreased compliance, due to tissue aging [14]. The decreased compliance is associated with an increase of PP, with both higher systolic pressures and lower diastolic pressures without a significant change in MAP [15]. Therefore, the PP will increase. To visualize the relation between age and PP, a scatterplot is made. This relation is preferably investigated with PP values of healthy subjects, so the PP value from the last hour on VA-ECMO is taken. To compare the difference between the successful and unsuccessfully weaned patients, both groups are plotted in a different color.

Analysis of PP and BMI

Another parameter that influences the compliance is the BMI. Overweight or obese patients tend to suffer from hyperlipidemia and during progression of atherosclerosis there is an increase in vascular stiffness [16]. However, the increased risk for arterial stiffness among obese individuals is thought to be due primarily to the influence of other associated risk factors [17]. To visualize the relation, the PP in the last hours on VA-ECMO from every patient is used and plotted, in the right color, against the corresponding BMI.

Analysis of PP and heart rate

Although not much research has been done about the influence of heart rate on pulse pressure, the cardiovascular simulation model by Libera has shown that an increase in heart rate is followed by a decrease in PP [18, 19].This could be accounted for by the fact that the PP depends on the stroke volume (SV)[20]. The SV is affected by the preload, and since a higher heart rate causes a shorter diastolic filling time, it is thought that the preload decreases. Because of the lower preload, the heart is not able to fully contract. This is assumed to result in a lower PP. To verify this assumption, the relation between heart rate and pulse pressure is visualized in this report [21, 22].

Both the PP and heart rate have a time resolution of one minute and were automatically extracted from the monitor. To visualize the influence of heart rate, the PP is plotted against the heart rate. The heart rate per hour and the PP per hour are calculated for every patient and visualized in a scatterplot. This generates a lot of bullets in the scatterplot. To give an overview of these points, a heatmap is used. The scatterplot is used to distinguish the recovery and non-recovery patients and to show what group the values originate from.

A decreasing trend when plotting the PP against heart rate is expected, since the hypotheses is that as heart rate increases, pulse pressure decreases. If a relation is found, the relative PP per hour of every patient is used to calculate the mean of all patients, and this is divided by the mean heart rate per hour. The mean PP/mean heart rate is plotted over time and is distinguished by colors based on outcome to check whether there is a stronger relation between outcome and PP, once corrected for heart rate.

Analysis of PP and VA-ECMO RPM responsiveness

Simulation studies have revealed that the PP is also dependent on the interaction with VA-ECMO [12, 18, 23]. To further investigate this principle, clinical data is analyzed. A parameter that influences PP is ECMO-flow, since the retrograde continuous flow causes changes in the hemodynamics. The ECMO-flow is only noted once per hour by the nurses, and it varies between the maximum, minimum and mean flow. The revolutions per minute (RPM) is a value that is set on the VA-ECMO, making it more reliable. A. Florax plotted the PP change against the change in ECMO RPM in a scatterplot and found something remarkable [24]. Only patients who did not successfully wean from VA-ECMO were located on the bottom right quadrant of the scatterplot. This suggests that an increase in RPM results in a decrease in PP. Insight is given by analyzing a larger number of patients into whether a relation is found or that this observation was simply a coincidence.

To determine the relation between PP and ECMO RPM, the change of PP as a result of the change in RPM was calculated. Since the time resolution for ECMO RPM was one hour, the specific time of change was not documented. Therefore, the mean of the PP over the ten minutes before the hour of change, and the mean of the PP over the ten minutes after the hour of change were used. The PP change was plotted against the change in RPM for every patient with a heart indication, creating a scatterplot. The recovery and non-recovery group are visualized with the colors green and red.

Analysis of PP and medication

Most of the critically ill patients receive inotropic and vasoactive medication. This medication influences the PP, making the PP less representative for the contractility of the heart. To evaluate the PP without the effect of the medication, the PP is divided by different scores. The medication doses are known for every minute of the first 72 hours in the ICU and are used to calculate the average doses per hour.

Analysis of PP and VIS

The vaso-inotropic score (VIS) is an indicator to objectively quantify the hemodynamic support. It is the sum of multiple drugs accompanied by different weighting factors [25]:

$$\begin{aligned}\text{VIS} = {} & \text{dopamine } (\mu g/kg/min) + \text{dobutamine } (\mu g/kg/min) + 100 \times \text{adrenaline } (\mu g/kg/min) \\ & + 100 \times \text{noradrenaline } (\mu g/kg/min) + 10 \times \text{milrinone } (\mu g/kg/min) \\ & + 10{,}000 \times \text{vasopressin } (units/kg/min)\end{aligned}$$

Some drugs only influence the vascular tone, constriction or dilatation, others influence contractility and some influence both. Therefore, the VIS score should be taken into account when evaluating the PP to estimate the cardiac condition. The PP per hour is divided by the VIS per hour and plotted for every patient in a separate plot to visualize the PP without the effect of vasoactive and inotropic medication. Before performing the division, the VIS score is normalized by using a scale to prevent dividing by zero when a patient gets no medication. The quartiles (Q1 and Q3) are calculated. When no medication is administered, the value of the normalized VIS score is set at 1, so there is no effect on the PP. The third quartile is given a score of 10 and all values above the third quartile are given a score of 10 as well. This partly filters out the extreme (likely biased) values of VIS. The VIS scores in the interquartile range (IQR) are scaled along the values 1 to 10, by performing the following equation:

$$\text{Normalized score} = \frac{1 + (\text{VIS score} - \text{Q1})}{\text{Q3} - \text{Q1}} \times 9$$

Analysis of PP and inotropes

However, inotropes (IN) and vasoactive drugs differ in their effects and should therefore not be combined when evaluating the PP as an indicator for contractility [26]. To visualize the effect of only the inotropic medication, the PP is divided by the inotropic score. This score already exists and includes the inotropic drugs from the VIS [27]:

$$\begin{aligned}\text{IN} = {} & \text{dopamine } (\mu g/kg/min) + \text{dobutamine } (\mu g/kg/min) + 100 \times \text{adrenaline } (\mu g/kg/min) \\ & + 10 \times \text{milrinone } (\mu g/kg/min)\end{aligned}$$

Inotropic drugs elevate the contractility of the heart. It is expected that it raises the PP, while the heart is not yet recovering [28]. Since most VA-ECMO patients receive inotropes, it is important to look at the effect of these medicine on the PP. Just like the VIS score the values of the IN score are normalized along a scale to prevent division by 0.

Analysis of PP and vasoactive agents

Vasoactive drugs consist of vasoconstrictors and vasodilators. Vasoconstrictors are expected to lower the compliance and thereby increase the PP [20]. Vasodilators, on the other hand, are expected to decrease the PP because of a higher compliance. The constrictors and dilators are separated into two formulas. This way it is possible to look at the relation with the two types of drugs. To determine the formula, the VIS has been investigated. The vasoconstrictors and vasodilators, out of the VIS, are separated and form a score on their own:

$$\mathrm{CS} = 100 \times \text{norepinephrine } (\mu g/kg/min) + 10{,}000 \times \text{vasopressin } (units/kg/min)$$

$$\mathrm{DT} = 10 \times \text{milrinone } (\mu g/kg/min)$$

To filter out the effect of the vasoconstrictors and the vasodilators, the PP per hour is divided by normalized constrictor (CS) scores and dilator (DT) scores. Both are plotted over time for every patient in a separate plot. In those figures, a distinction is made between successful and unsuccessful weaning by color.

Processing the results

Since the hypothesis is that medication changes the trend of PP, the plots are analyzed individually to determine those changes. When analyzing all patients together, by for example taking the mean or making a spaghetti plot, the change in trends cannot be visualized accurately. By looking at the individual graphs for each score, the number of patients is counted where the line of the graph corrected for the medication score gives a better picture than the uncorrected PP. This means that the trend should be steeper for patients with a positive outcome. And for the others, the opposite is true. A percentage is calculated by dividing the obtained number of patients by the total number of patients. This percentage gives insight whether the medication should be considered when evaluating the PP as an indicator for outcome.

This observation is prone to observer's bias. To undermine this bias, Cohen’s Kappa is calculated to view the inter-observer reliability. Cohen’s Kappa gives information on the extent of agreement between observers and it corrects for agreement by chance. In retrospective chart reviews a Cohen’s Kappa of higher than 0.6 is considered acceptable [29]. Cohen’s Kappa was calculated using an online Kappa calculator which can be found at http://justusrandolph.net/kappa/. The fixed-marginal multirater kappa by Fleiss's (1971) was used.

Statistical analysis

In table 1, the categorical variables are presented as median and interquartile range. These are calculated using the statistics module in Python with Pearson's Chi-squared test. Categorical variables are shown as numbers and percentages. To analyze the continuous variables, the Mann-Whitney U test is performed. The P-values are calculated to assess the variables as predictors for successful weaning. The threshold for all tests is $p<0.05$, meaning that once the $p<0.05$ there is a significant difference between the two groups.

The mean of the total change in PP of successfully and unsuccessfully weaned patients is analyzed to see if there is a significant difference. To determine whether there is a significant difference between the two groups, a Mann-Whitney U test is performed. To perform the tests, the scipy library in Python is used.

Several scatterplots are made, visualizing a potential relation between two parameters. To determine whether there is a linear correlation, the Pearson’s correlation coefficient and matching p value is calculated for all the scatterplots. Again, a significance of 0.05 is used. [11]

Results

Patient selection

Flowchart

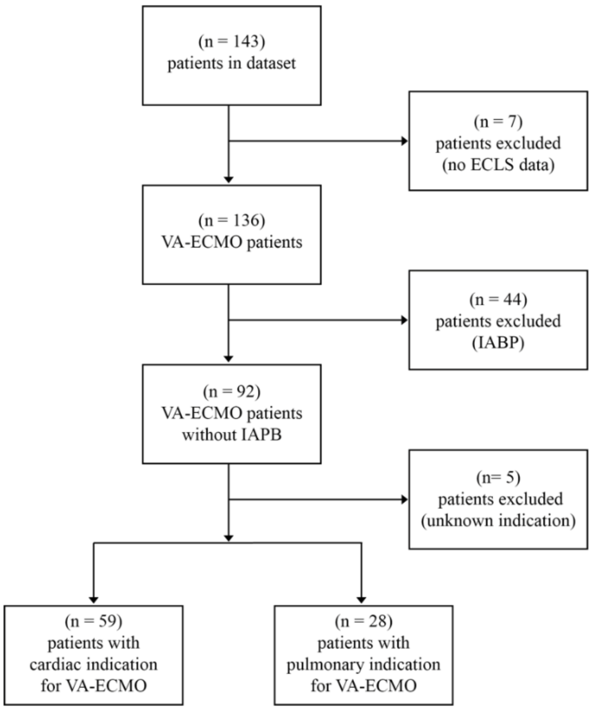


Figure 1: flowchart of patient inclusion

Patient characteristics

	All **(n = 88)**	**Recovery** **(n = 57)**	**Non-recovery** **(n = 31)**	**P-value**
Indication				0,129
Heart	60 (68%)	31 (35%)	29 (33%)	
Lung	28 (32%)	20 (23%)	8 (9%)	
Age (years)	53,5 (43 – 64)	56 (48 – 65)	53 (25 – 64)	**0,019**
BMI	26 (24 – 29)	26 (24 – 29)	26 (22,5 – 28)	0,239
Duration (hours)	102 (53 – 305)	104 (62 – 184)	100 (50 – 193)	0,906

Table 1: Baseline characteristics of the recovery and non-recovery groups. P-values < 0.05 are presented in bold.

There is a significant difference in age between the recovery and non-recovery group. This is explained in more detail in the discussion (p. 28).

Analysis of PP over time

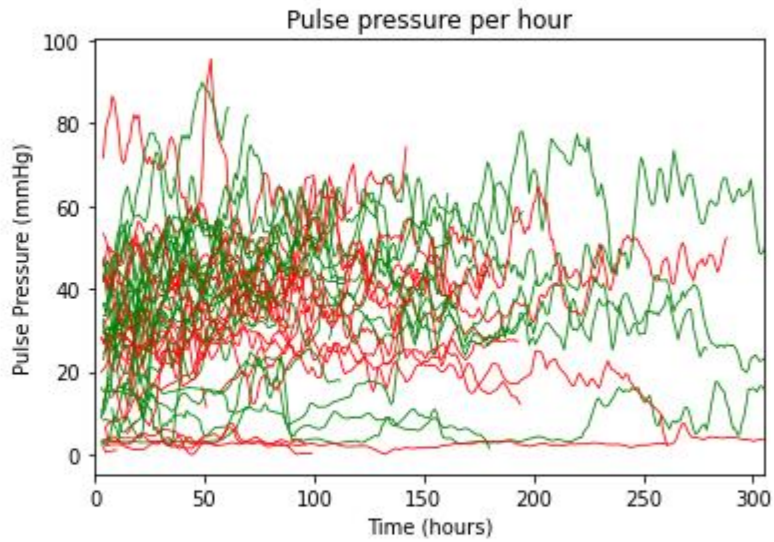


Figure 2: Spaghetti plot of the PP per hour of every patient over time for recovery and non-recovery group.

The PP per hour is used to plot an individual graph for every patient into a spaghetti plot. In the plot it can be seen that the recovered and not recovered patients are intertwined. So, not much can be said about the difference between the two groups for both beginning values and end values. It can be speculated that there is a concentration of recovered patients in the upper left side of the graph. This would indicate that the beginning values of successfully weaned patients are higher overall.

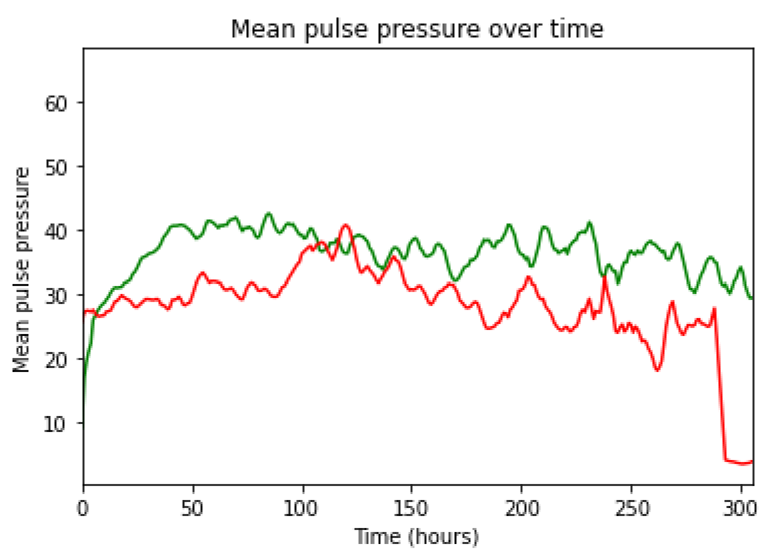


Figure 3: Plot of the mean PP per hour over time.

The mean PP over time does indicate that the recovered patients overall do have a higher PP. The green line starts at a lower PP than the red line and only crosses after around 5 hours. In general, the recovered patients have a higher PP than the non-recovered patients, with an exception around 100-130 hours.

Analysis of relative PP

Relative PP over time

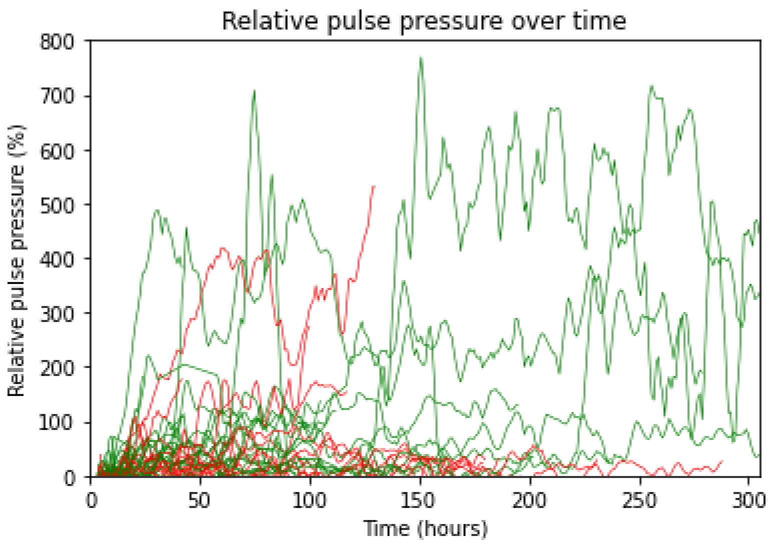


Figure 4: Spaghetti plot of the relative PP per hour of every patient over time

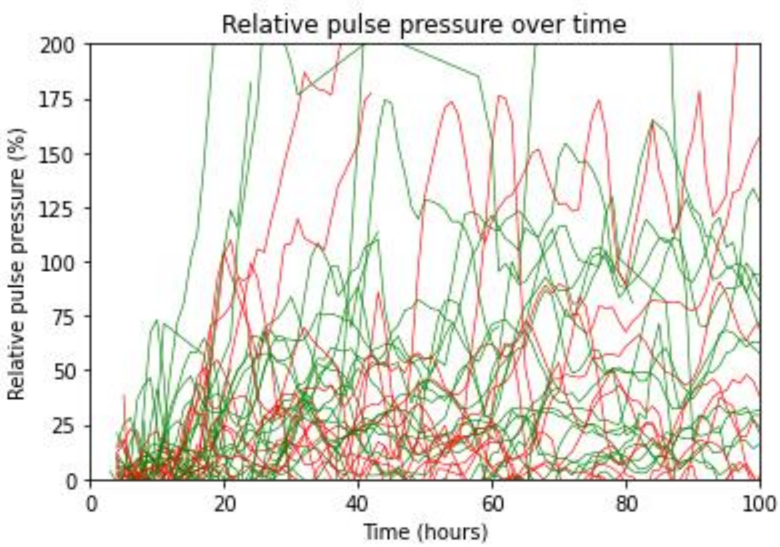


Figure 5: Zoom in of the spaghetti plot to visualize the first period.

At first glance, it could be stated that there is a distinction between the outcomes. Recovered patients overall do have a higher relative pulse pressure. However, some unrecovered patients also increase in pulse pressure steadily over time. Additionally, when zooming in on the patients that are on VA-ECMO for a shorter period of time, no distinction can be made between recovered patients and unrecovered patients.

Mean relative PP over time

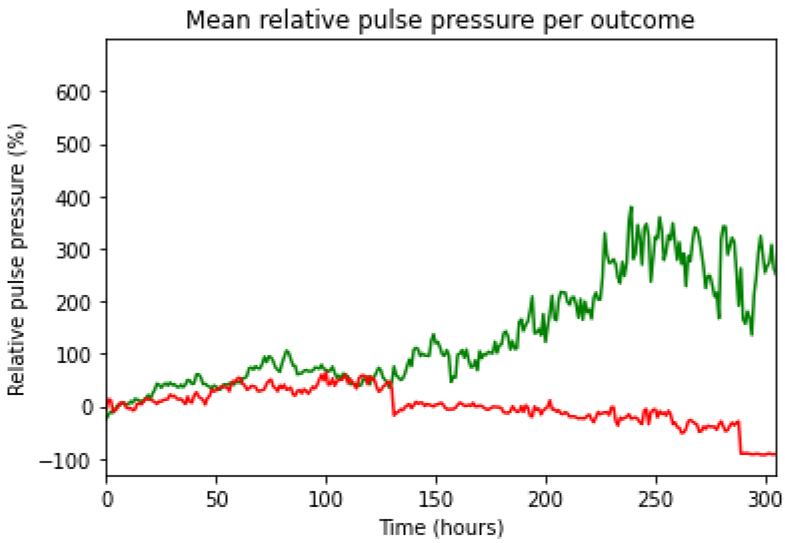


Figure 6: Plot of the mean relative PP over time for recovery and non-recovery groups separately.

Even though the spaghetti plot did not reveal much, the mean relative PP plotted over time does show a relevant distinction. The green line, representing the recovered group, lies above the red line. This indicates that on average the recovered group increases more in PP over time. In the beginning the difference between the recovered patients and unrecovered patients is less obvious, but from about 130 hours the gap increases between the red and green line.

Total percentual change in PP

	All (n = 88)	**Recovery (n = 57)**	**Non-recovery (n = 31)**	**P-value**
Total change of PP (%)	17 (-0,3 – 101)	34 (8,8 – 101)	1,6 (-9,7 – 31)	**0,031**

Table 2: Difference in total percentual change in PP between recovery and non-recovery group.

Statistical analysis on the difference between recovery and non-recovery group shows a significant difference in the percentual change of PP. Recovered patients have a median total change of 34%, while non-recovered patients show a median total change of 1,6%. This analysis only uses the difference between the PP in the last hours of VA-ECMO with respect to the PP in the first hours. It is shown that there is a significant difference between the percentual change of the two subsets, with $p= 0{,}0314 < 0{,}05$. It is remarkable that the lower IQR of the non-recovery group has negative values, meaning that unrecovered patients decrease in PP on VA-ECMO.

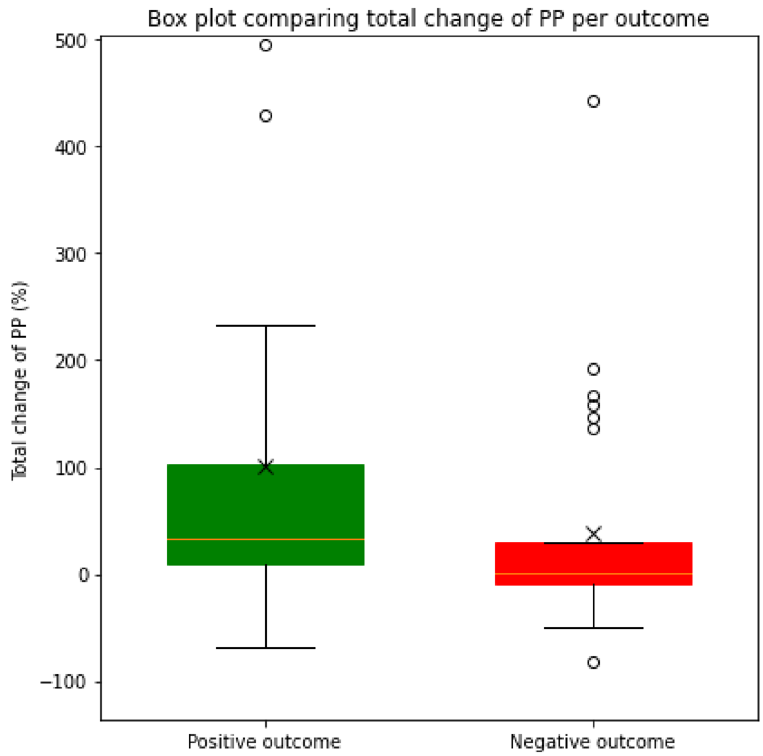


Figure 7: Box plot of percentual change of PP between first and last hours of VA-ECMO of recovery and non-recovery group.

In this graph, the spread of the dataset is visualized per group based on outcome. This spread is wider for the successfully weaned group. One outlier, lying around 850% total change is not included in this plot, since it limits the visibility of the other points. In the appendix a more detailed insight is given on the fourth quartile of the negative outcome.

Analysis of PP derivative

Day with highest increase of PP

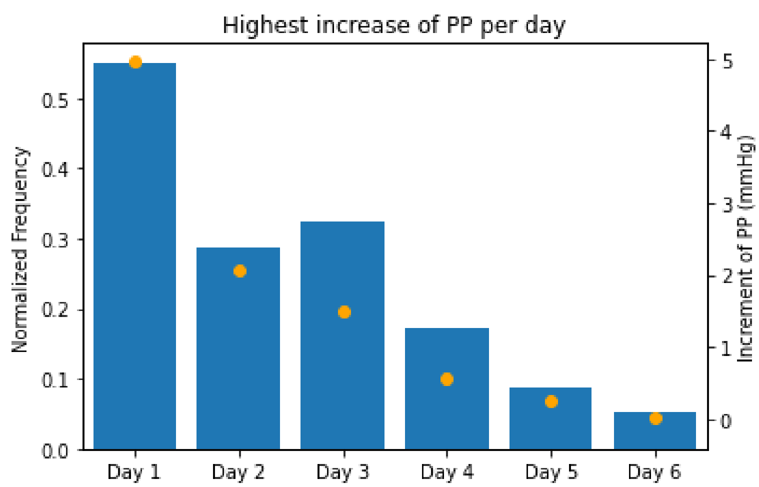


Figure 8: Bar chart of normalized frequency of patients with the most increase of PP on a certain day with in yellow the mean absolute increase per day.

The blue bars represent the frequency of patients with the highest increase on a specific day. 55% of the patients show the highest increase of PP on the first day on VA-ECMO. On day 6 only 5% of patients had their highest increase. The yellow dots represent the mean increasement of PP for all patients on that day. On day one an average increase of 4.9 mmHg takes place, while on day six this is minus 0.16 mmHg. Meaning on average the PP decreases. This demonstrates that on a daily basis, the average increase is diminishing.

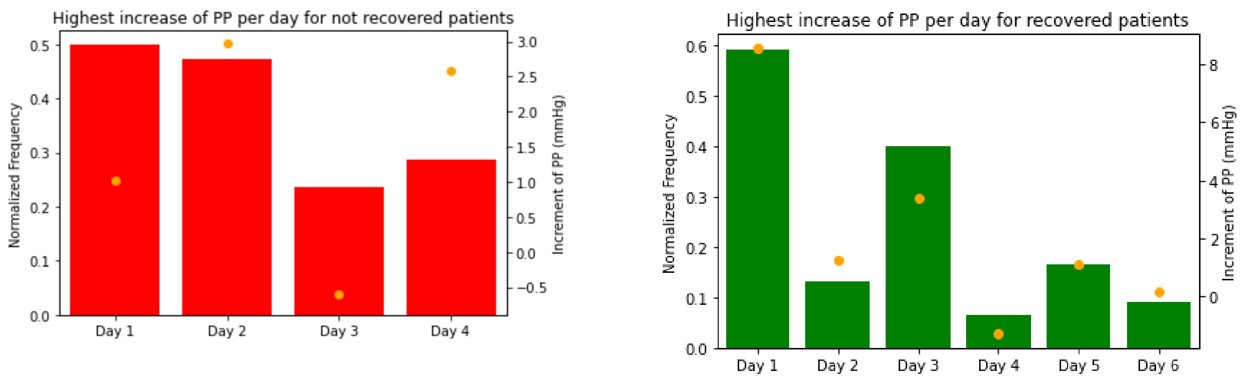


Figure 9&10: Bar chart of normalized frequency of patients with the most increase of PP on a certain day with in yellow the absolute increase per day. Separate for the different outcome subgroups.

Patients who recover from VA-ECMO overall show a higher increase in PP in the first day. The increment of recovered patients being 8.53 mmHg on day one and for unrecovered patients 1.01 mmHg. On day two the mean increment of PP for unrecovered patients is 3.39 mmHg, this is still not close to the maximum the recoverd patients reach (8.53 mmHg). It is also noticeable that for the unrecovered patients the normalized frequency does not show great fluctuations. While for recovered patients on day one 59% of patients show their maximum increase and after which this it diminishes greatly. Lastly it is important to note that no unrecovered patients show a maximum increase after day four.

Analysis PP and multiple parameters

Multiple corrections are made, trying to filter out the effect of confounders on the PP when evaluating it as an indicator cardiac condition. The patients are plotted together in a spaghetti plot or a scatterplot, reviewing the overall trend of weaned patients and not weaned patients.

Analysis of PP and age

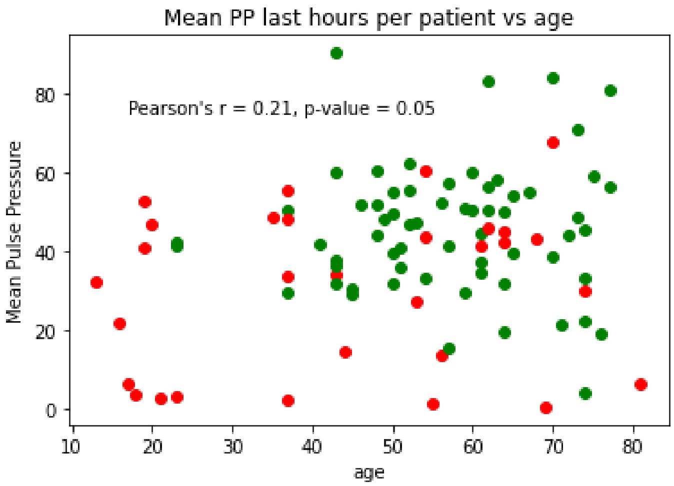


Figure 11: Scatterplot of the PP of the last hours on VA-ECMO against age.

In the scatterplot that visualizes the PP against the age, there is a visible trend that the PP rises with age. This relation is significant, since the p-value of Pearson's correlation coefficient is 0.05. It is also notable that the successfully weaned patients are most represented in the upper right quadrant of the graph, while the unsuccessfully weaned patients are represented more in the lower left quadrant. Unsuccessfully weaned patients tend to have a lower end PP, so they will lay underneath the other patients. The mean PP increases once a person gets older.

Analysis of PP and BMI

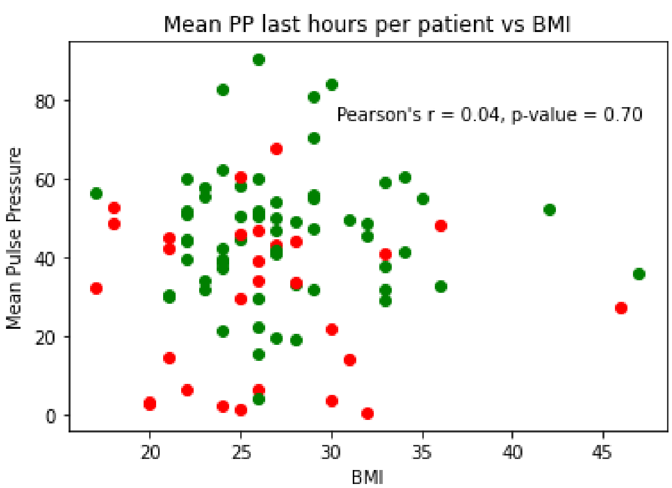


Figure 12: Scatterplot of the PP of the last hours on VA-ECMO against BMI.

This scatterplot shows a Pearson Correlation Coefficient of r = 0,04, meaning there is a very minor rise. This rise is not significant (p = 0,70) and could therefore be a coincidence.

Analysis of PP and heart rate

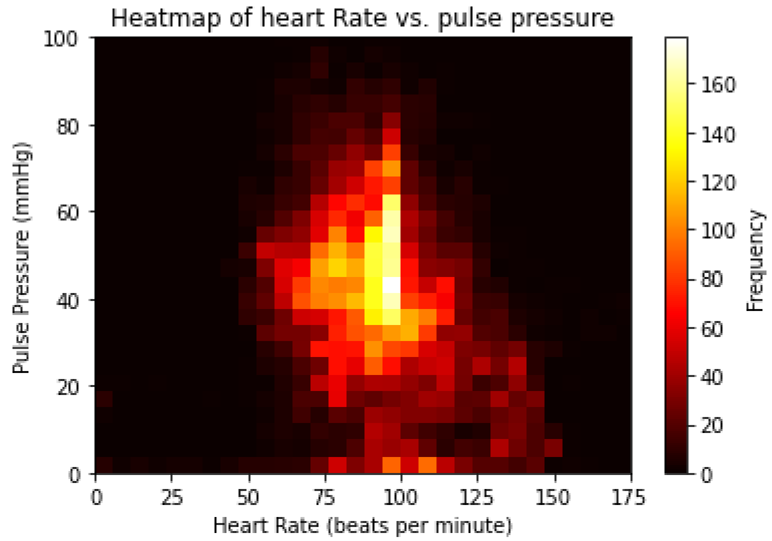


Figure 13: Heatmap of heart rate against PP

The relationship between heart rate and pulse pressure is shown in the heatmap. This shows that most patients have heart rates around 100 with varying pulse pressures. At higher heart rates, lower pulse pressures are observed. This can be seen in the lower right corner. The lower heart rates show fluctuating pulse pressures just like the PP does around the average heart rate.

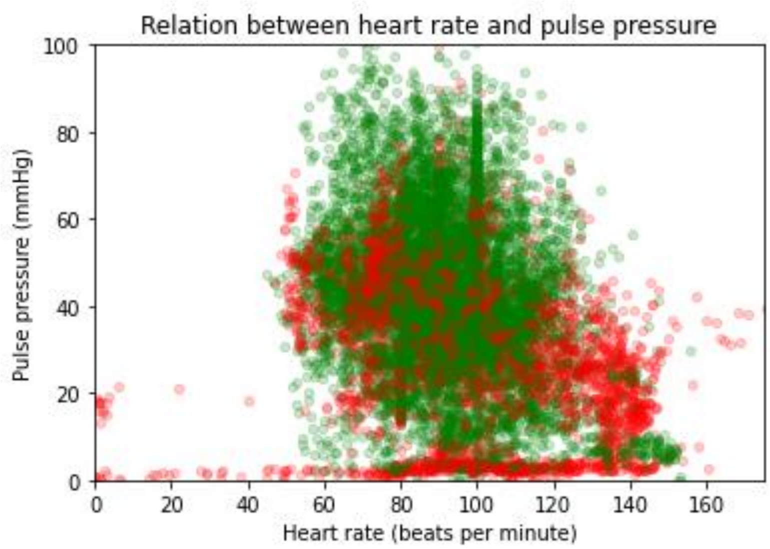


Figure 14: Scatterplot of PP against heart rate for recovery and non-recovery group.

Overlapping the scatterplot with the heatmap indicates that the lower right corner is mostly made up of patients who did not recover. The relation between heart rate and pulse pressure seems to only be caused by patients who do not recover from VA-ECMO.

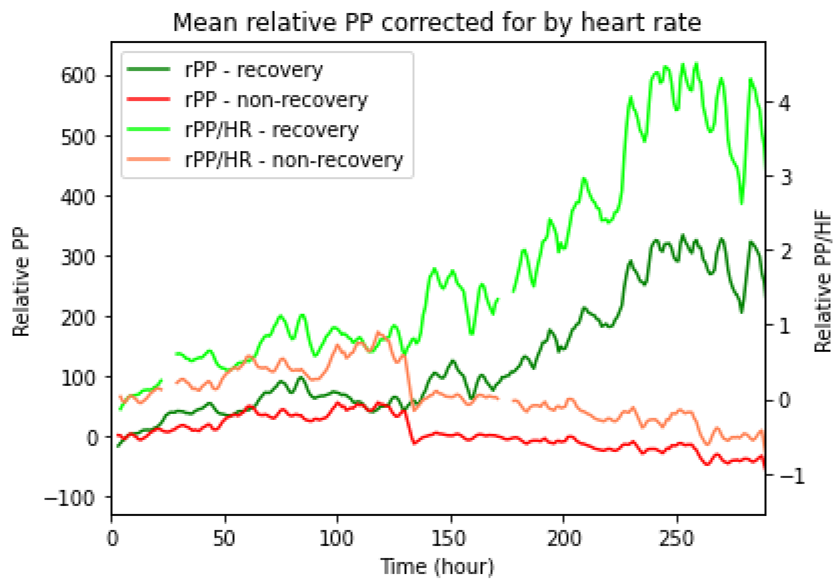
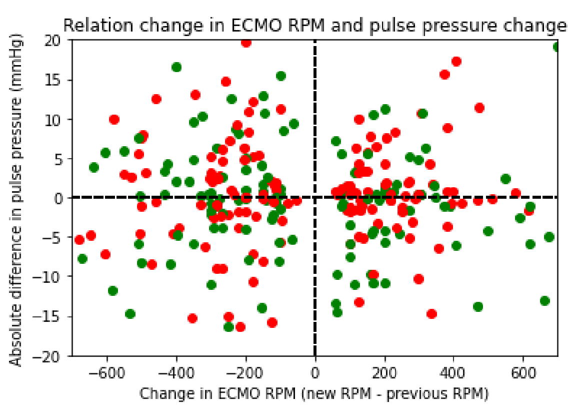


Figure 15: Plot of mean relative PP divided by heart rate per hour for recovery and non-recovery group.

In this graph the relative PP is graphed together with a corrected PP for HR. After the correction was made, a difference in trend is observed. The lime graph shows a higher increase than the green graph. This trend is especially seen after hour 130, but even in the earlier hours, the corrected graphs can better be distinguished than the original PP.

Analysis of PP and ECMO RPM responsiveness



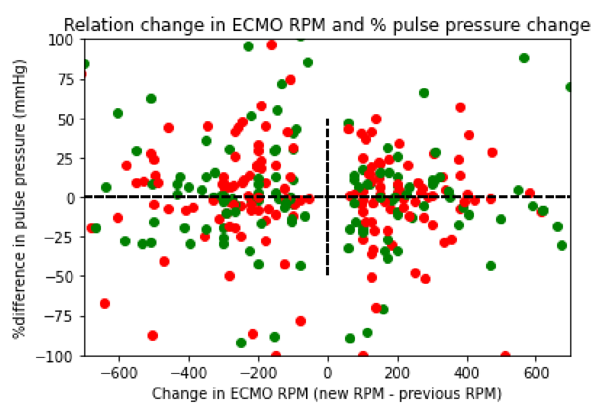


Figure 16: Scatterplot of absolute change in PP after a change in RPM for recovery and non-recovery patients.

Figure 17: Scatterplot of relative change in PP after a change in RPM for recovery and non-recovery patients.

The change of the PP in the 10 minutes after the hour of RPM change is plotted in a scatterplot. The recovery and non-recovery patients are evenly spread. In contrast to the results of A. Florax, the bottom right quadrant does not only consist of non-recovery patients. In every quadrant, successfully and unsuccessfully weaned patients are represented.

Analysis of PP and medication

A dataset is obtained, containing information about seven types of medication for each patient on VA-ECMO. The mean PP per hour is used to calculate the different medication scores. 20 patients received little to no medication in the first 72 hours on ECMO and are therefore excluded from this analysis. First the inter-observer reliability is calculated.

	COHEN'S KAPPA + 95%-CONFIDENCE INTERVAL.
CS	0.69 (0.49, 0.89)
DT	0.87 (0.67, 1.00)
IN	0.77 (0.60, 0.90)
VIS	0.54 (0.39, 0.69)

Table 3: Cohen's Kappa

To observe inter-observer reliability the Cohen's kappa was calculated. Above 0.6 is considered reliable in retrospective chart reviews. The inter-observer reliability of the CS, DT and IN are sufficient. However, the VIS Cohen's kappa is only 0.54.

	N total	**N +**	**N -**
VIS	39	10 (25%)	13 (33%)
IN	26	7 (27%)	13 (50%)
CS	29	9 (31%)	7 (24%)
DT	25	4 (16%)	11 (44%)

Table 4: Number of patients per medication type with change in trend. (N total = total number of patients that received medication of this type, N + = number of patients with trend in alignment with outcome, N - = number of patients with trend in contrast with outcome)

Analysis of PP and VIS

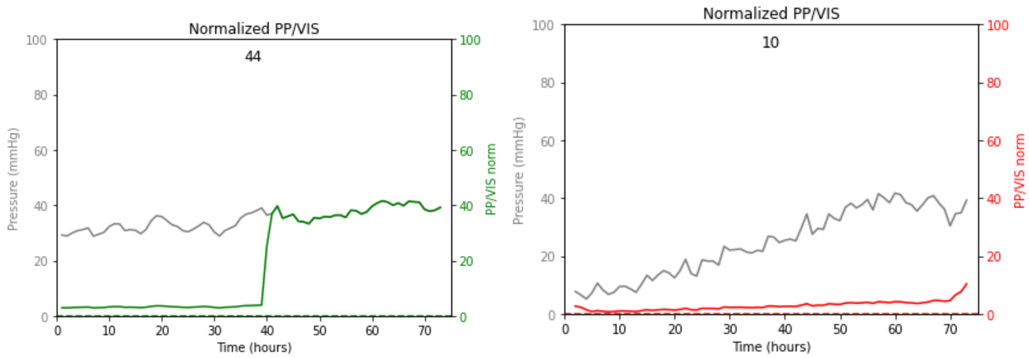


Figure 18: PP per hour/ normalized VIS per hour plotted over time in line with outcome

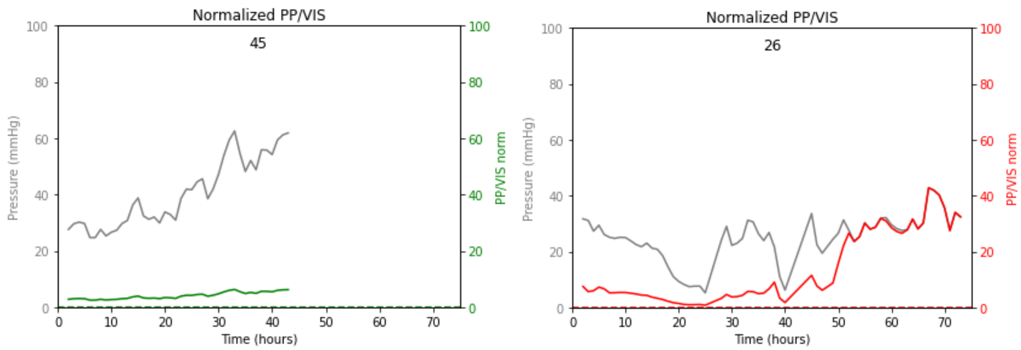


Figure 19: PP per hour / normalized VIS per hour plotted over time not in line with outcome

When plotted over time, the trend of the PP divided by the normalized VIS score differs a lot for each patient. In the upper two graphs the division by the normalized VIS score results that are in line with the outcome. The PP of patient 44 shows almost no change. However, the VIS score in the first 40 hours is high and decreases to a negligible value after 40 hours. In the earlier stages the heart was supported by a lot of medication, while in the end, the heart was not supported anymore, but the PP remained the same. With patient 10 the opposite is true. The PP rises over time, but after dividing by VIS score, the trend decreases.

In contrast, there are also cases in which filtering the effect of medication showed a trend that is not in line with the outcome. Like in figure X, the rise in PP is minimal after division by VIS score. This would indicate that the patient is not ready to wean from VA-ECMO, even though the patient recovered. Besides, figure X shows an increasing trend when looking at the PP divided by the normalized VIS score, but, despite this trend, they have failed to wean.

After analyzing each patient individually, multiple cases like the ones illustrated above are observed. The trend aligns with the outcome in ten patients. This is 25% of the patients who received medication, while in 13 patients the trend does not align with the outcome (33%). In the other patients the trend after dividing by normalized VIS did not change. The graphs of all patients are shown in the appendix.

Analysis of PP and inotropes

With inotropes the results are comparable to the VIS score. In some cases, the division by the normalized IN score altered the trend in a manner that better reflected the outcome compared to the unfiltered PP. This happened in 7 patients (27%) that received inotropic medication. However, there were even more patients by whom the effect of inotropes changing the trend resulted in an incorrect representation of their outcome. They account for 50% of the patients that received inotropes. Again, the plots can be seen in the appendix.

Correction for vasoconstrictive agents

The correction for vasoconstrictors was the only one that had trends displaying more correct than incorrect representations of the outcome. A total of 29 patients received vasoconstrictors. There were 9 cases (31%) in which the trend aligned with the outcome and 7 (24%) in which it did not. Yet, there were no major changes visible, except for one patient, shown in figure 20. The rest is shown in the appendix.

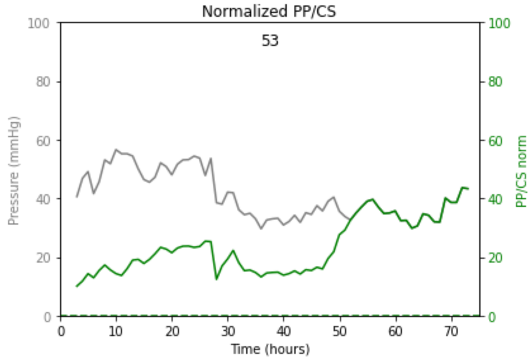


Figure 20: PP per hour/CS per hour plotted over time with a clear change in trend resulting in a better reflection of outcome.

Correction for vasodilator agents

The corrections by the normalized dilator scores showed a significant difference, particularly concerning the number of patients that show a trend that is not in alignment with the outcome. In 11 patients (44%) the trend did not reflect the outcome well and in only 4 patients (16%) it did. In figure 21, the trend of the PP/DT increases, since only the first 30 hours dilators were given. However, the patient did not successfully wean.

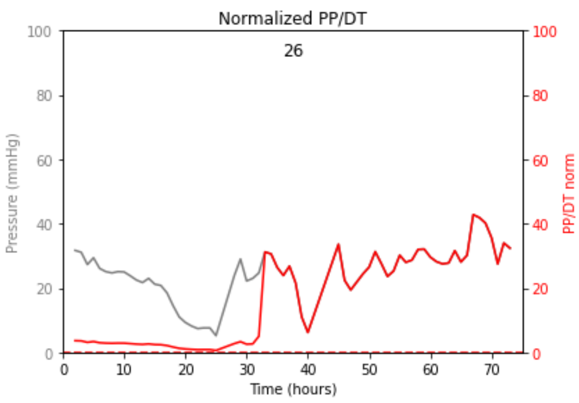


Figure 21: PP per hour/DT per hour plotted over time with a clear change in trend resulting in a worse reflection of outcome.

Discussion

The aim of this study was to analyse the PP over time and get insight into several factors influencing the PP. This discussion is divided into four parts. The first sections will discuss the methodology. The second section will present the observations that were made in de results. The third part will sum up some limitations that were encountered in this research, and lastly some recommendations are made for future research.

Methodology

Study design

This report is based on a retrospective chart review [29]. In general, these study outcomes are not as reliable as for example randomized controlled trials. For example, the recruitment of patients was by convenience sampling, the patients may not be representative of the whole population, therefor this study is prone to selection bias [30].

Bias

The bar chart illustrating the moment of highest increase reveals that a significant proportion of patients experience the greatest rise in PP within the initial 24 hours of being on VA-ECMO. The frequency of patients depicted in the chart has been normalized to the number of patients undergoing VA-ECMO during that specific timeframe. Patients who did not stay on VA-ECMO were excluded; however, it is important to acknowledge that patients who had short durations of VA-ECMO support (slightly longer than 24 hours) may introduce some distortion to this frequency representation. Almost all of these patients show the highest increase at the first day and therefore raise the frequency. Since only 14 patients were on VA-ECMO for 24 hours, it is still feasible there is a relation between time on VA-ECMO and maximum increase of PP.

Timeframe plots

After hour 305 there were only 3 patients left on VA-ECMO. When analyzing the trend in a spaghetti plot or when evaluating the average after 305 hours, the conclusion would have been drawn based upon 3 patients. This is not representative for the whole patient group and the general population. Since, on average a patients in on VA-ECMO for a time between 106 hours and 276 hours (Rillinger 2021). The analysis is therefore stopped at 305 hours.

ECMO RPM

As well as in A. Florax her report the ECMO RPM was used instead of the ECMO-flow. This might influence the conclusion of this study, since the effect of ECMO RPM on ECMO-flow differs quite a lot in each patient. The ECMO RPM is a setting on the machine and does not tell anything about the interaction with the body. ECMO-flow is the retrograde flow and therefore this would be more accurate. The expectation is that the PP of recovered patients is less influenced by an increase in ECMO RPM, since their cardiac output is greater. This would mean the PP of recovered patients would decrease less when ECMO RPM increases than in patients who do not recover and therefore do not have a sufficient cardiac output.

Medication response

The VIS-score, inotropic score, dilatator score and constrictor score give an indication of the amount of medicine that is given to a patient. However, it is important to keep in mind that individuals all react differently on medication and the effect on pulse pressure differs. Moreover, the obtained data only contains seven types of medication: Dopamine, Dobutamine, Milrinone, Norepinephrin, Epinephrin, Adrenalin and Vasopressin. By conducting a detailed examination of the medication files, it is possible to identify other specific medications that the patient received. These medications may have an impact on PP and therefore could distort the information about the recovery of the heart. Examinating the files ensures that the potential confounding effects of all the medications are appropriately considered, leading to more reliable conclusions regarding heart recovery.

Score scaling

By using a scaling factor for medication, some information is lost. The lower threshold is the first quartile Q1. This means that values below this threshold are set to 1, which is the same as when no medication is administered. Similarly, values above Q3 are set to a maximum value as well. On one hand, this filters out excessive values. On the other hand, this may undermine the effects of heavy medication and give a distorted image of the recovery of the heart.

Results

High PP

Another interesting aspect is the height of the maximum pulse pressure when plotted over time. Some patients have an ending point of around 90 mmHg. However, a pulse pressure above 60 mmHg is considered wide and could be accounted for by cardiovascular disease [31]. This cardiovascular disease does not increase significantly over the time a patient is on VA-ECMO. However, when looking at the endpoint of PP it might be interesting to take this into consideration to quantify the influence of cardiovascular disease on pulse pressure.

Age and PP

When evaluating the influence of age on PP and outcome, a significant p-value was found. Meaning that the age of recovered patients was significantly higher than that of unrecovered patients. When analyzing the patient group, it was noted that out of the 12 patients under 30, 5 were on VA-ECMO for a palliation indication. The significant difference may have been strongly influenced by this. Therefor for future analysis patients with a palliation indication should be excluded from the research.

While a significant relation between PP and age was found. It is important to note that this might not be the result of an increased contractility. With age comes an increase in arterial compliance and an increased arterial compliance is associated with an increased PP. It is thus likely that that is the cause of the higher PP [32], The value of PP seems higher for elderly people, but this doesn’t state that their cardiac condition is at that level. This is something that should be taken into consideration when a doctor decides whether a patient can wean from VA-ECMO. However, the points of the recovered patients are mainly located in the high age and high PP region, indicating that a high PP appears to be an indication of successful weaning despite the age.

Heart rate

Even though the heart rate was found to be of influence on PP, it might be relevant to evaluate the change in trends of the individual plots, oppose to taking the mean. By taking the mean relevant information is lost about the influence of a change in heart rate.

Medication plots

Some plots were easy to analyze a difference in trend. However, in some patients this was not clear. For example, in figure 23 in the appendix. The patient received vasoconstricting medication during his stay on VA-ECMO. During his time on VA-ECMO he had a stable pulse pressure. Shortly before 72 hours, he got off the medication. So, his total change in PP/VIS in the 72 hours is the same as his normal PP. But in the middle, he did receive a lot of medication, meaning his PP was largely influenced by the medication and that would indicate he actually had a decreasing trend. This makes it hard to interpret. Since the VIS-score fluctuates more than the other scores, it is difficult to interpret. That was also seen, when looking at inter-observer reliability, with a Cohen’s Kappa of 0.54, meaning it was not reliable.

Limitations

This study had several limitations. In the analysis of the patient data, several patients were excluded. This decision was made since necessary data were missing or were abnormal values. If the patients were included, a distorted image would have been shown.

Another limitation was the lack of information on medication. The information about the medication was only provided for the first 72 hours a patient was in the ICU. Since some patients were on VA-ECMO for a longer period, the effect of the medication on the PP in the last hours is not investigated. Moreover, some patients started with VA-ECMO after 72 hours, resulting in an empty plot when looking at the medication.

Recommendations

In future research it is advisable to also take into consideration the change in PP over time in patients with an IABP. Especially since the IABP provides information on the compliance in the arteries. This gives more accurate data on compliance than using the age and BMI as was used in this report. Compliance is of high influence on afterload and thus on PP. Using the information provided by the IABP, PP could be corrected for compliance.

The aim of this study was to get a better understanding of the influence of several factors on PP and to evaluate the PP over time. This could be used to potentially design a new parameter for clinical decision making. This parameter could be the pulse pressure corrected for by important hemodynamic influences, medications, heart rate and the VA-ECMO settings. However, this parameter should still be evaluated over time, to indicate recovery of the heart.

Conclusion

This analysis of pulse pressure of VA-ECMO patients shows that there is no clear distinction in pulse pressure and relative pulse pressure when evaluating patients in a spaghetti plot. The graphs of recovered patients and unrecovered patients are completely intertwined. However, the mean relative PP does show that on average patients who wean successfully from VA-ECMO have a higher increase in PP over time. This is further supported by the analysis of total change of PP for the time a patient is on VA-ECMO, a significant difference was found. This means the relative PP is a valid indicator for recovery of patients on VA-ECMO.

In this report it was also analysed at which day the increase in PP took place on average. It was analysed that most patients increase most in PP at day one. The chances of rising in PP are getting lower as the days progress. Besides, the absolute value of change in PP decreases per day. The plots for the recovery and non-recovery group show that the first day increase is higher in the recovered group. The non-recovered group displays a more evenly distributed pattern of the day with the maximum increase. Besides, the absolute increase of PP remains lower, and the PP values tend to decrease after day six. Comparing the two groups, the first three days could play a part in predicting whether the patient will recover from VA-ECMO.

No correlation between PP and BMI was found. However, a weak linear correlation between PP and age was found, meaning that the PP slightly increases with age.

The main conclusion that can be drawn based upon the scatterplot and heatmap of the age is based on the bottom right part of the map, indicating that as heart rate increases, the pulse pressure is decreasing. When evaluating the PP as an indicator for weaning, doctors should take this into consideration. The trend also changed for the corrected heart rate.

Even though in previous reports interesting discoveries were made between the relation of ECMO-rpm and PP, we found no new relation when looking at the change of PP after a change in ECMO-rpm was made. In the scatterplot green and red dots were mixed. This means that a change in ECMO- rpm has a random effect on the change in PP for recovered patients as well as unrecovered patients.

From the evaluation of the PP after filtering for medication scores, it is concluded that the constrictor and inotropic medication have different effects on the patients. In some cases, the trend aligns with the outcome, while in others the deviation contradicts the trend. It is shown that the CS and IN score are not suitable potential parameters to consider in decision-making about weaning from VA-ECMO. However, PP divided by the DT showed that most of the filtered PP were not in line with the outcome. This is in alignment with the expectations, since dilators increase the compliance, thus decreasing PP without reflecting a decline in cardiac condition. A rise could therefore be the result of loss of the suppressive effect of dilators on the PP. Lastly, the VIS score has a Cohen’s Kappa of less than 0.6, meaning the observations are not reliable.

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Appendix

Details of box plot

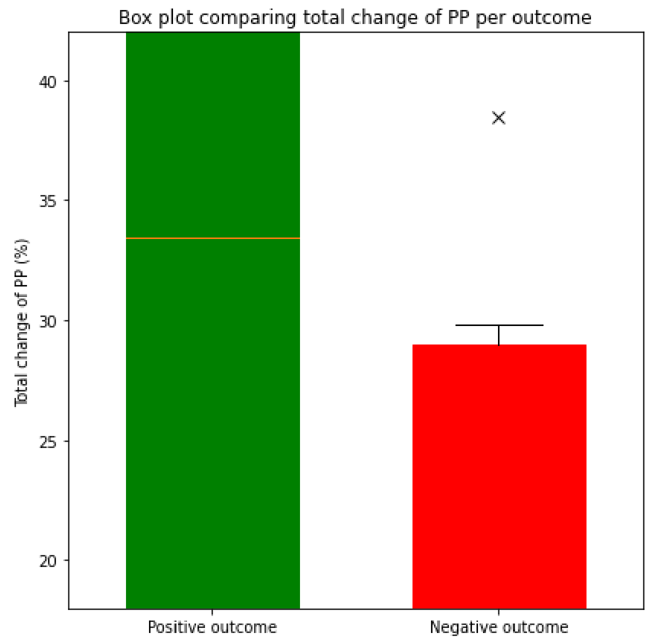


Figure 22: Box plot of percentual change of PP between first and last hours of VA-ECMO of recovery and non-recovery group, zoomed in on Q4 from the non-recovery group.

Example of unclear effect of CS on trend

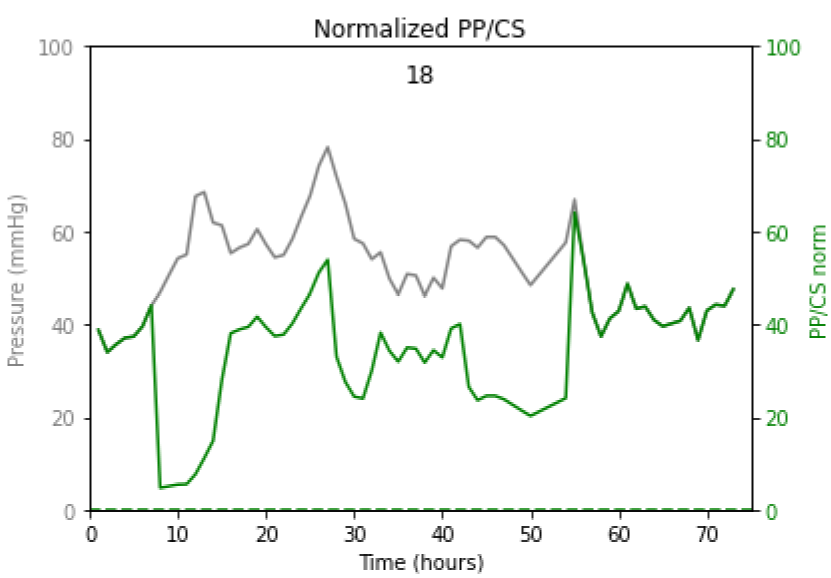
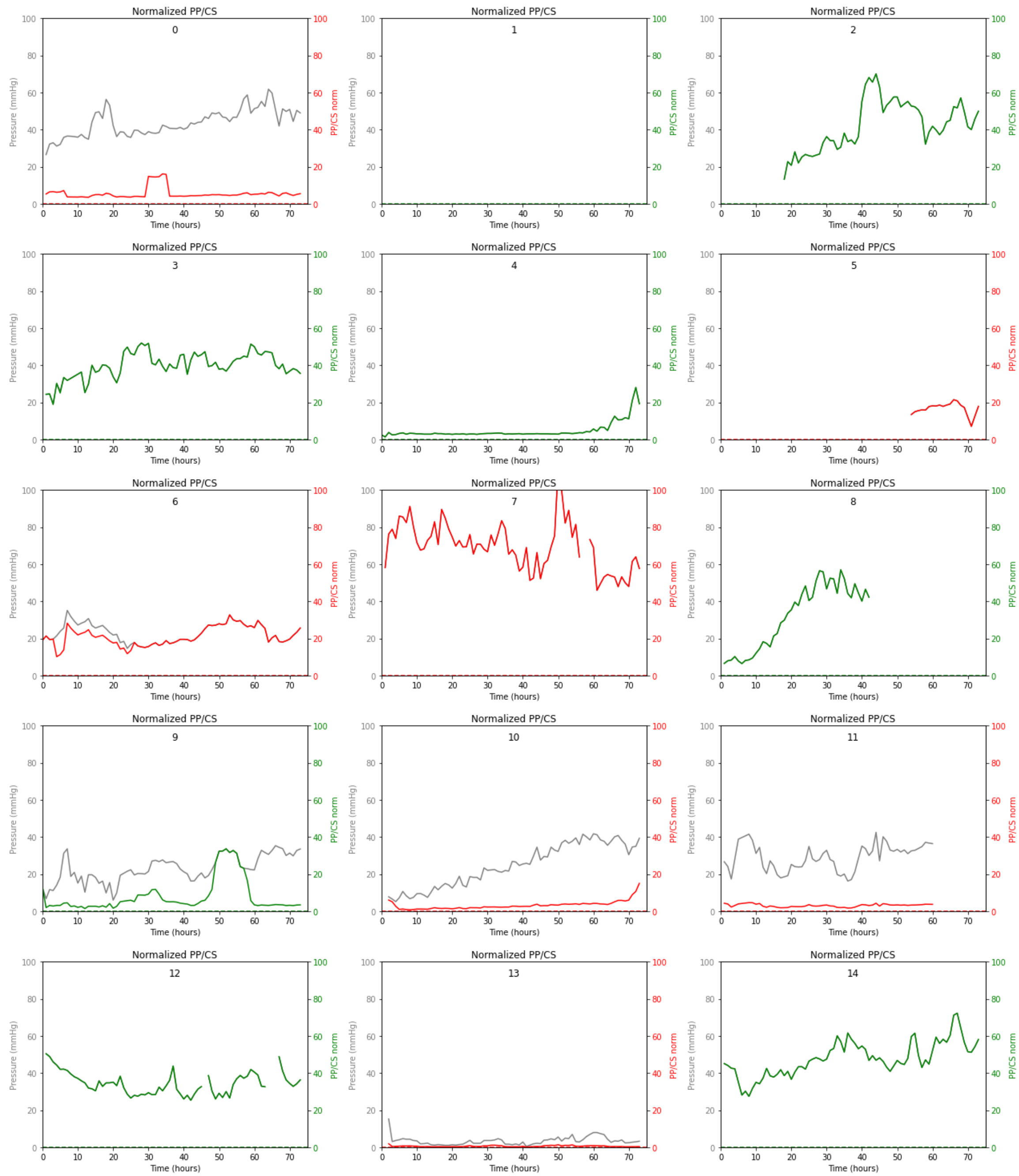
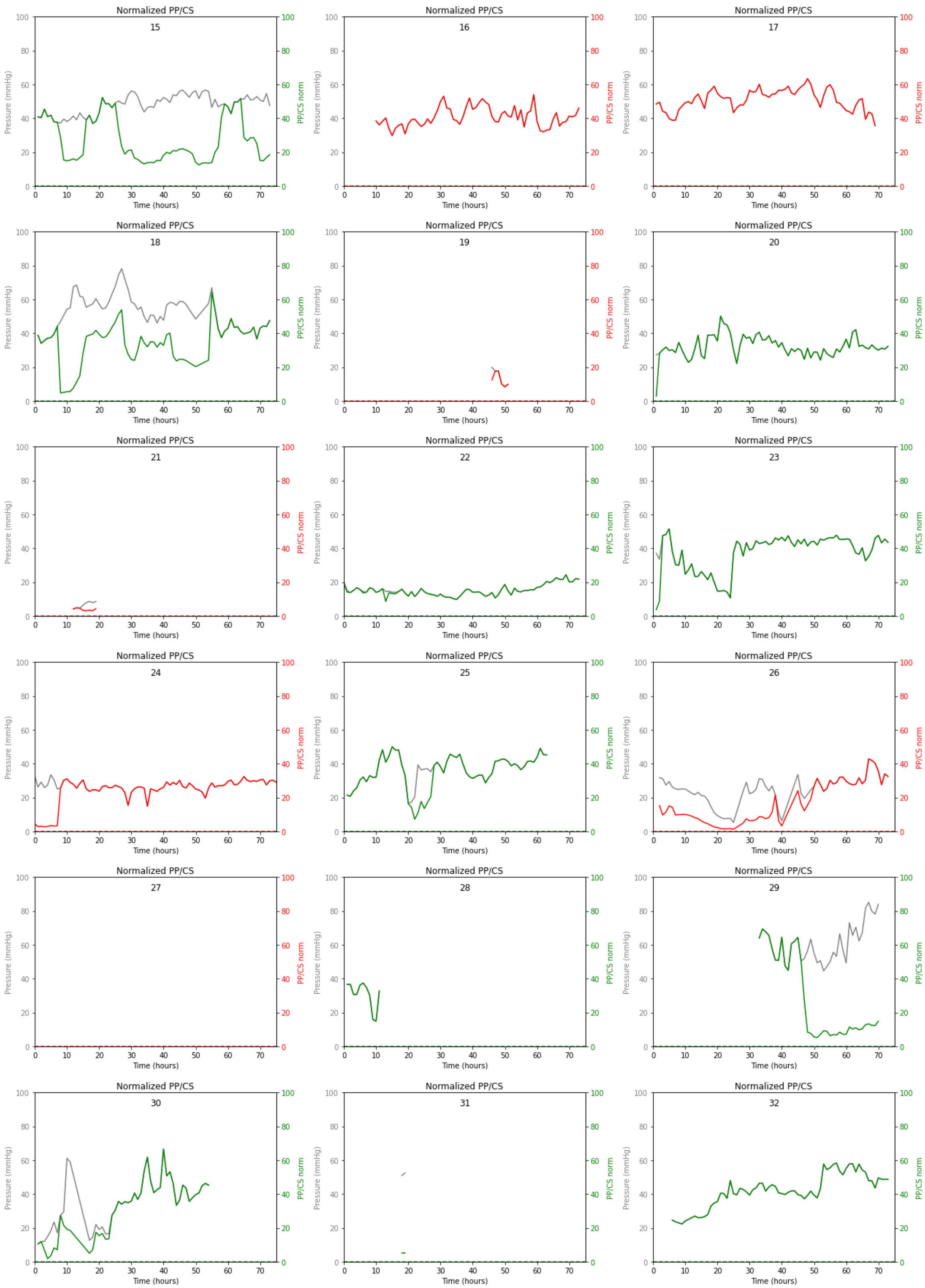


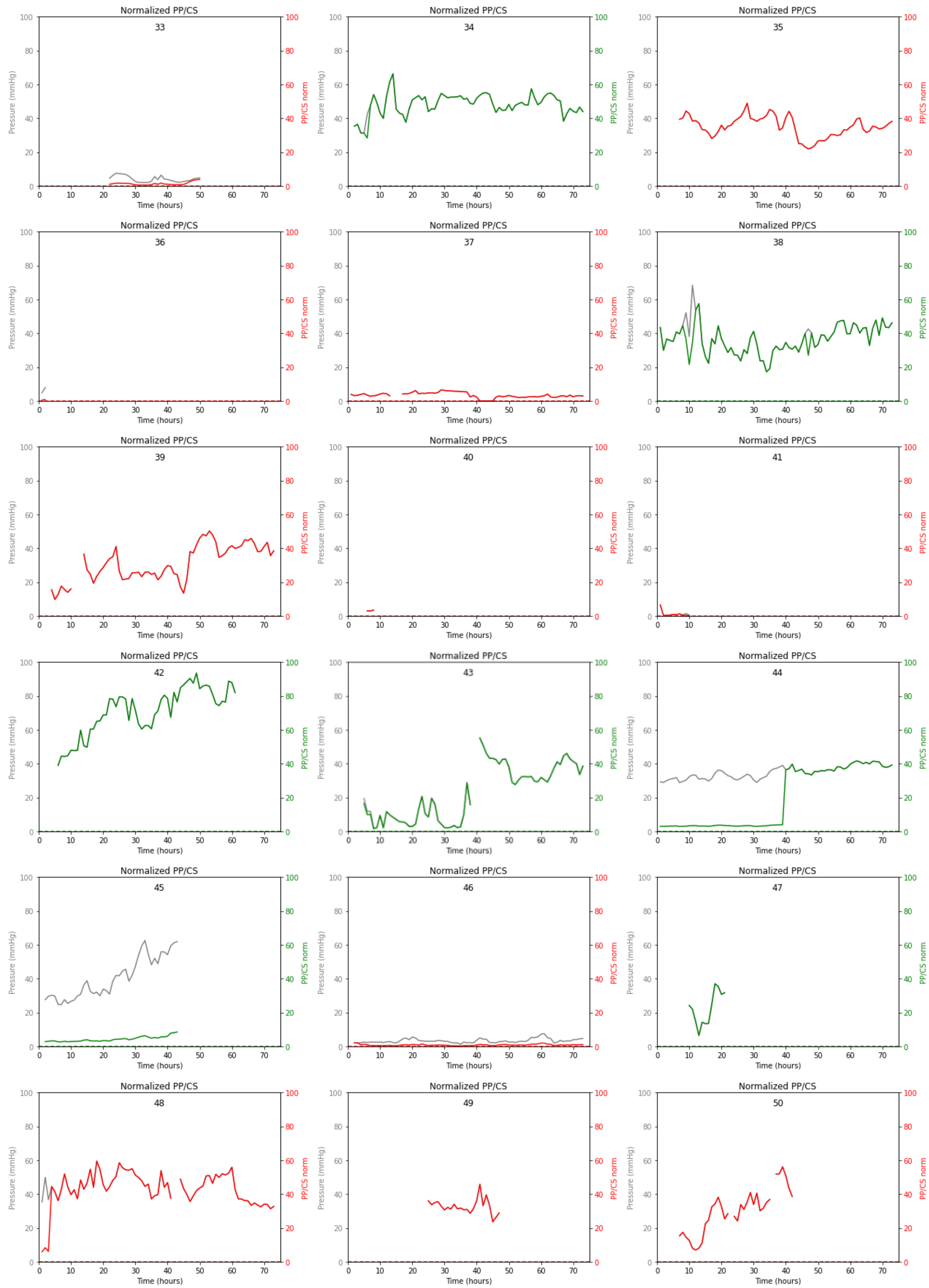
Figure 23: Unclear plot on the change in trend between PP/CS and PP.

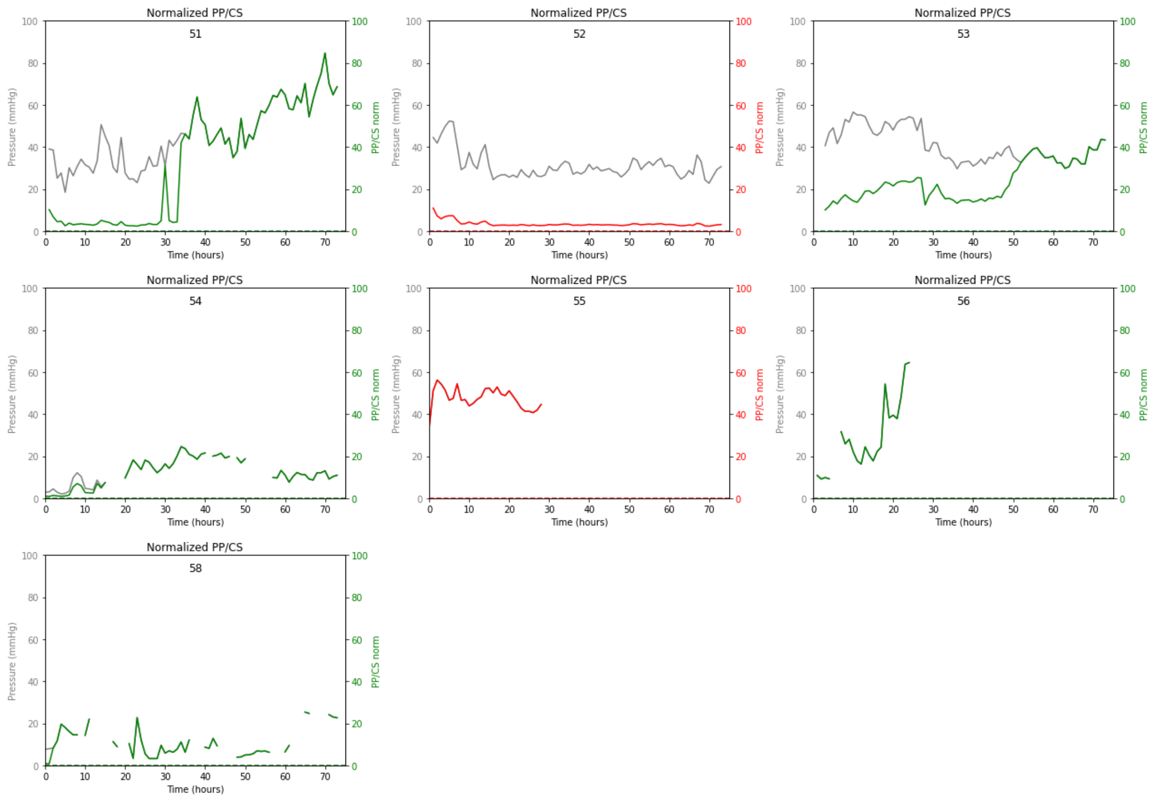
Medication plots

CS

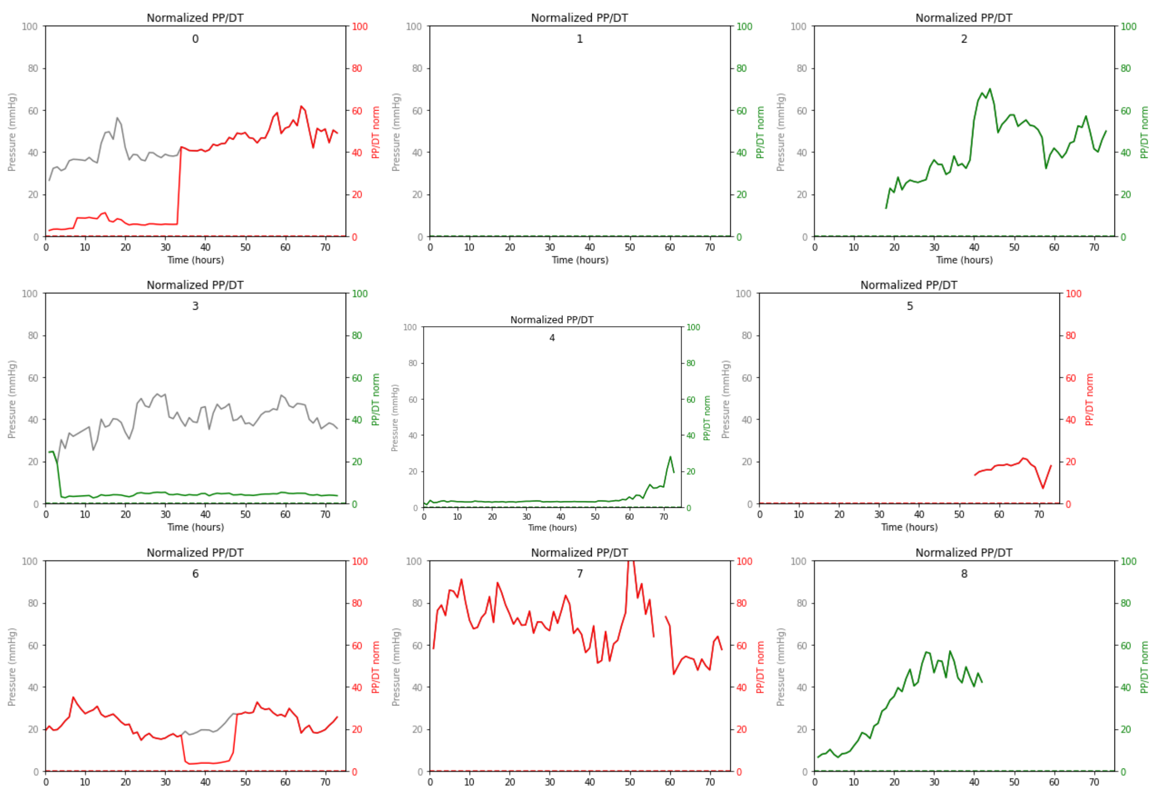


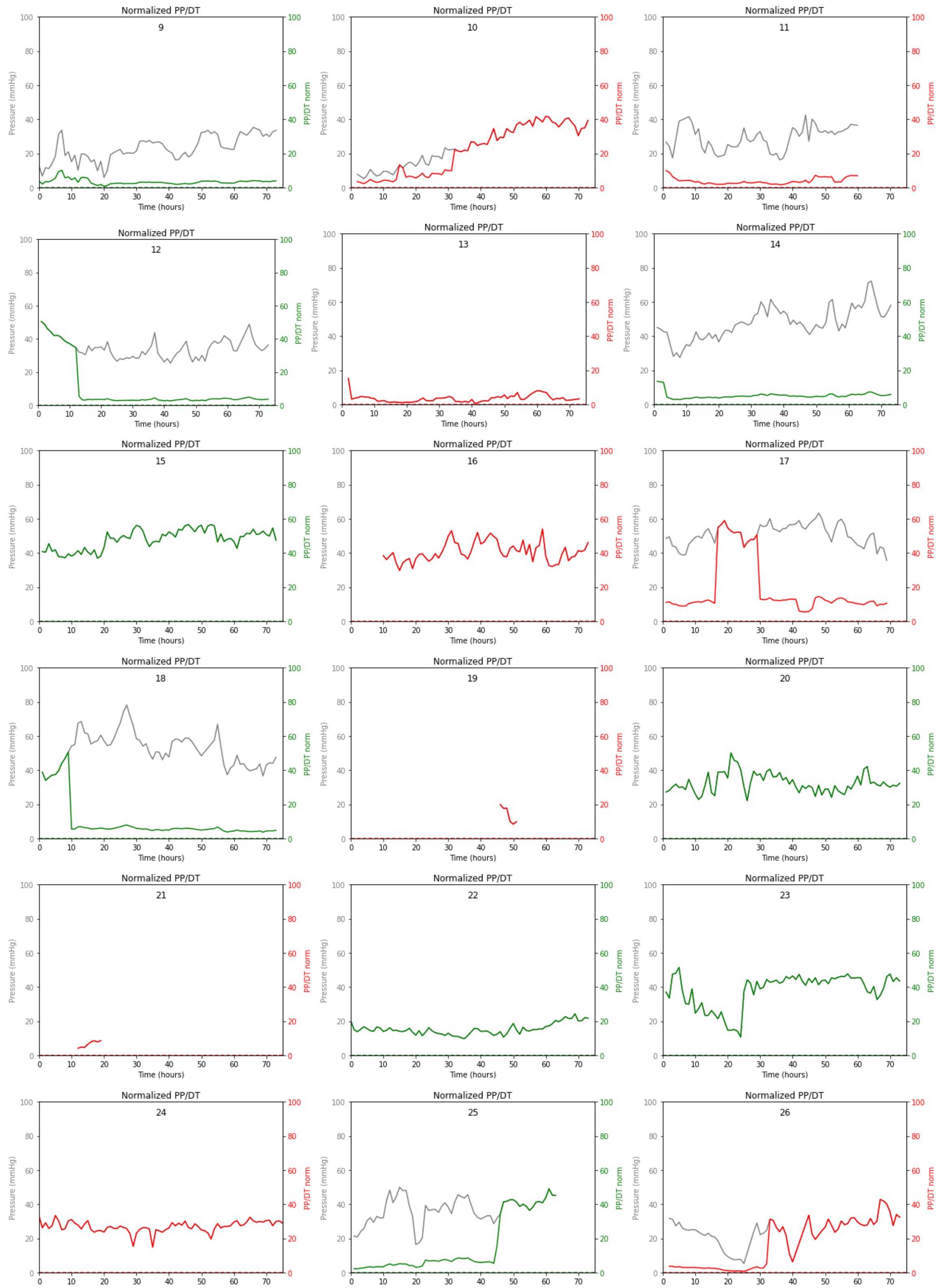

Normalized PP/CS
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
Pressure (mmHg)
PP/CS norm
Time (hours)

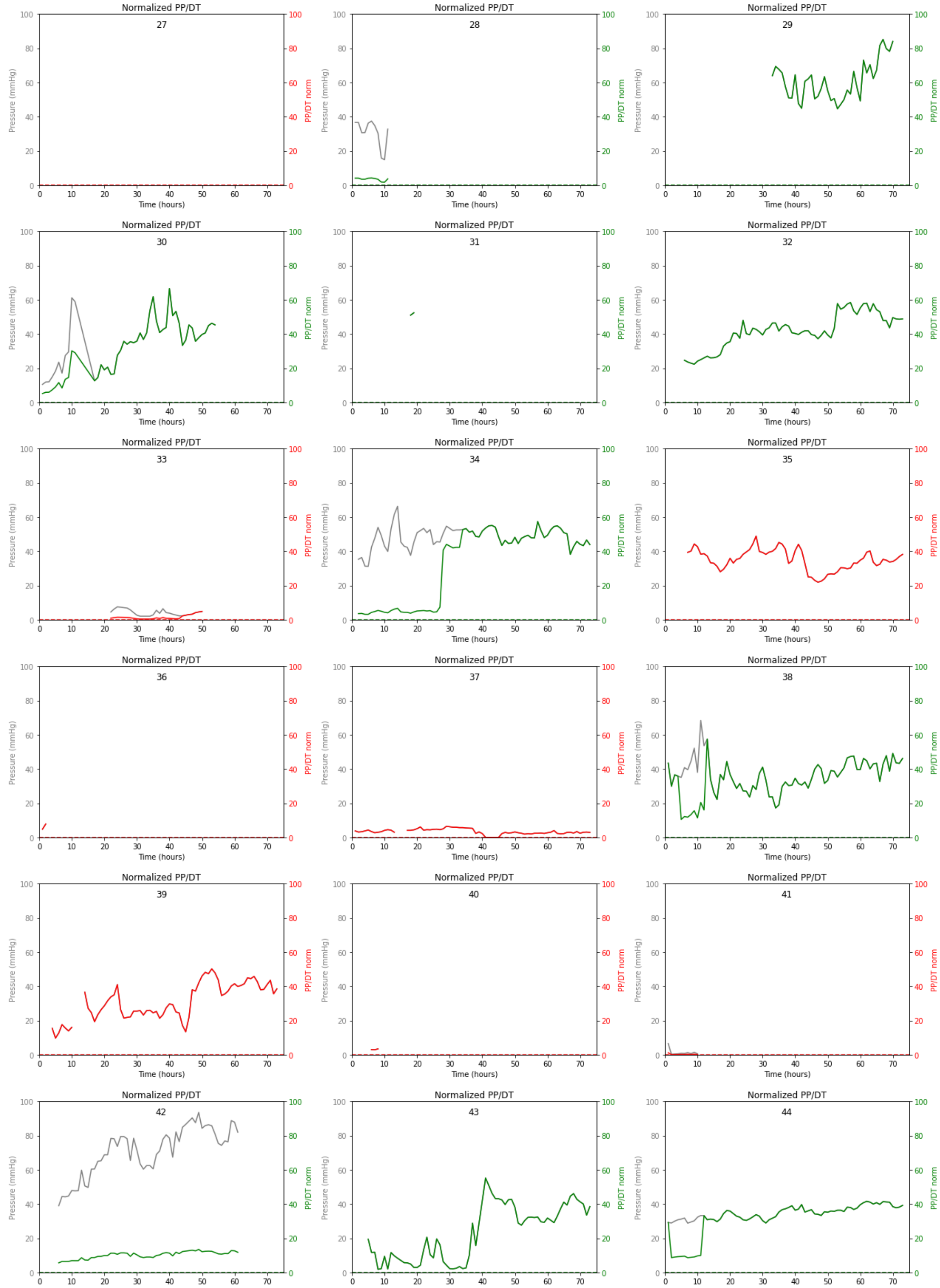

Normalized PP/CS
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
Pressure (mmHg)
PP/CS norm
Time (hours)

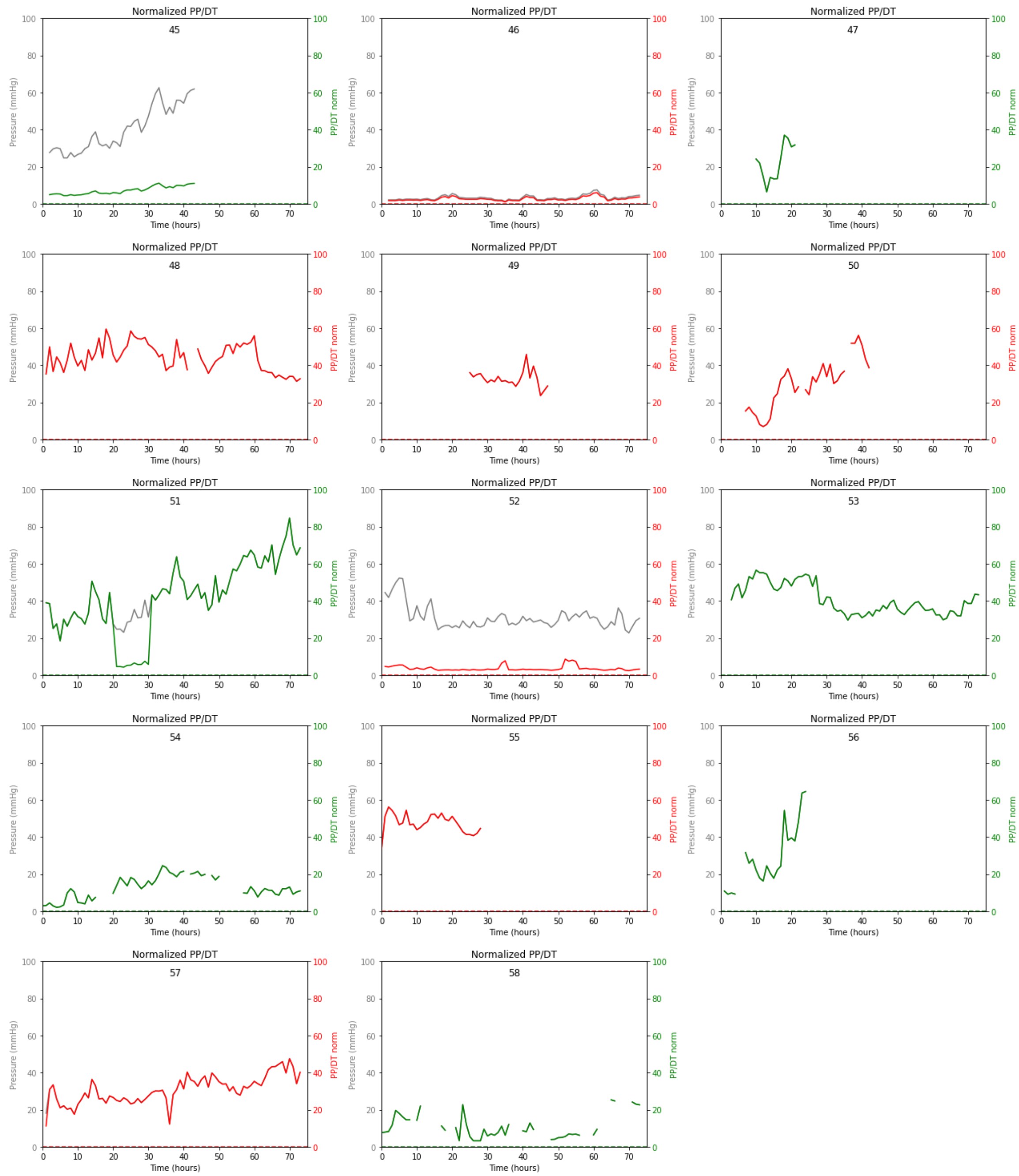

Normalized PP/CS
51
52
53
54
55
56
58
Pressure (mmHg)
PP/CS norm
Time (hours)

DT

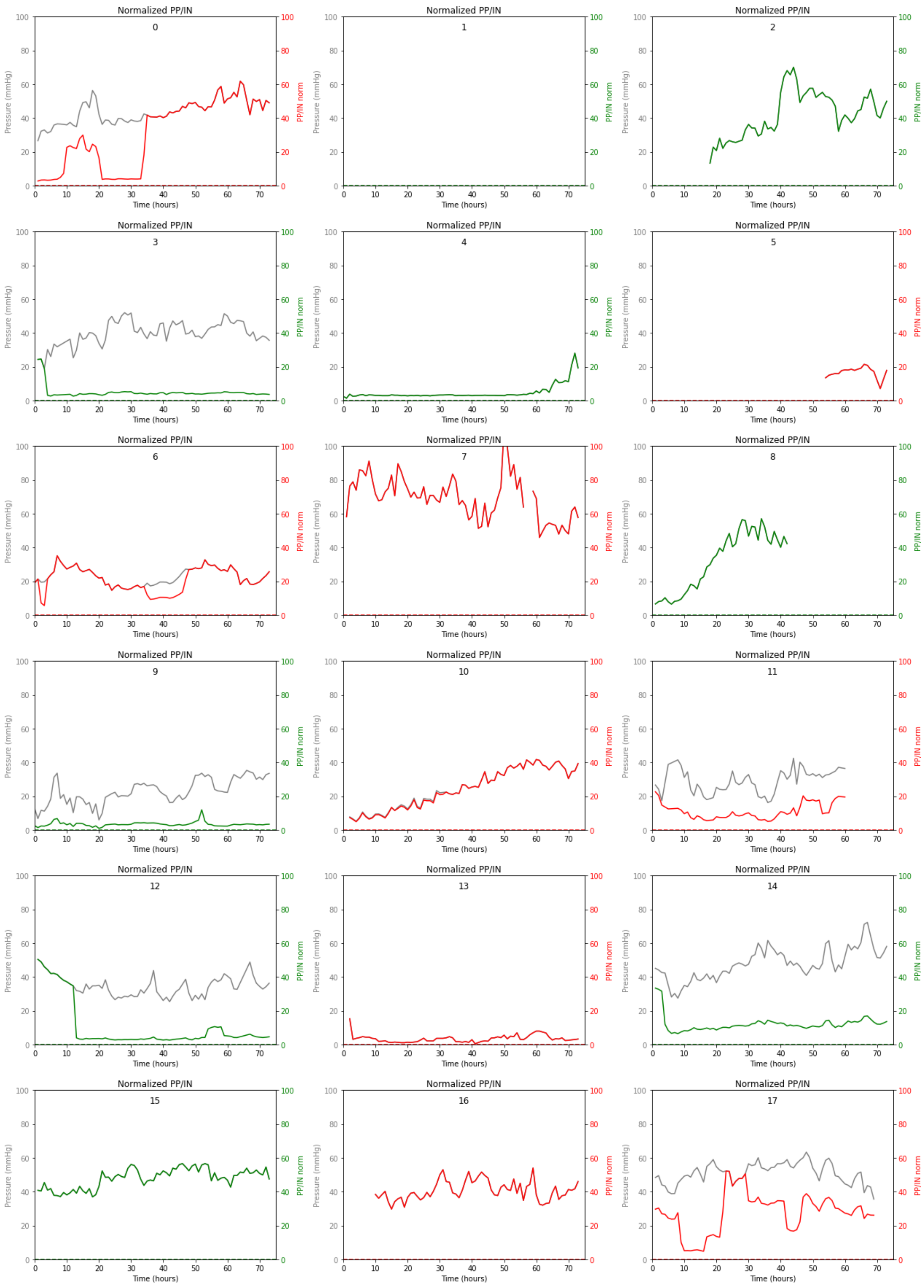

Normalized PP/DT
0
1
2
3
4
5
6
7
8
Pressure (mmHg)
PP/DT norm
Time (hours)

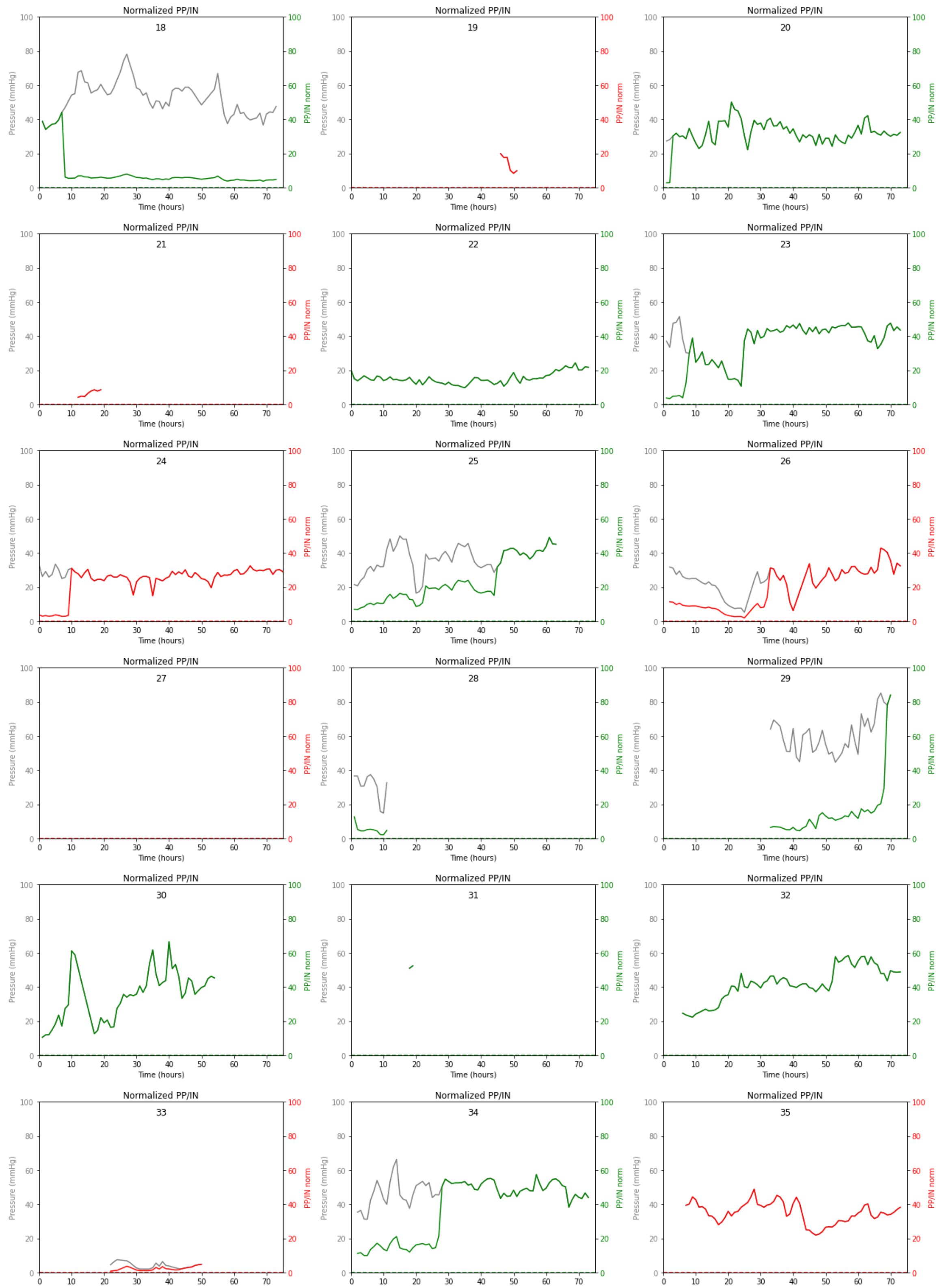

Normalized PP/DT
9
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
10
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
11
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
12
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
13
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
14
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
15
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
16
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
17
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
18
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
19
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
20
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
21
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
22
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
23
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
24
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
25
Pressure (mmHg)
PP/DT norm
Time (hours)
Normalized PP/DT
26
Pressure (mmHg)
PP/DT norm
Time (hours)

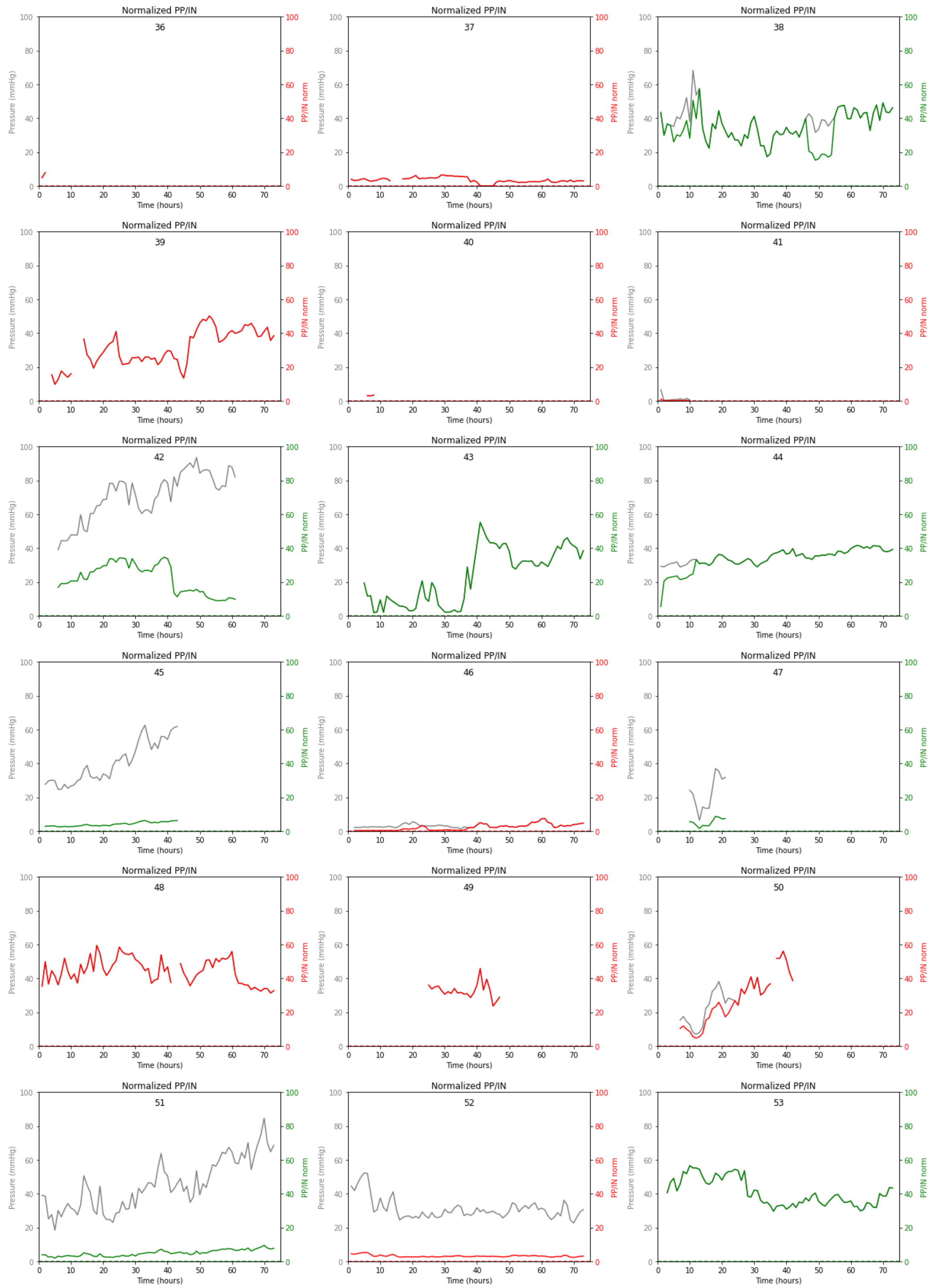

Normalized PP/DT
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
Pressure (mmHg)
PP/DT norm
Time (hours)

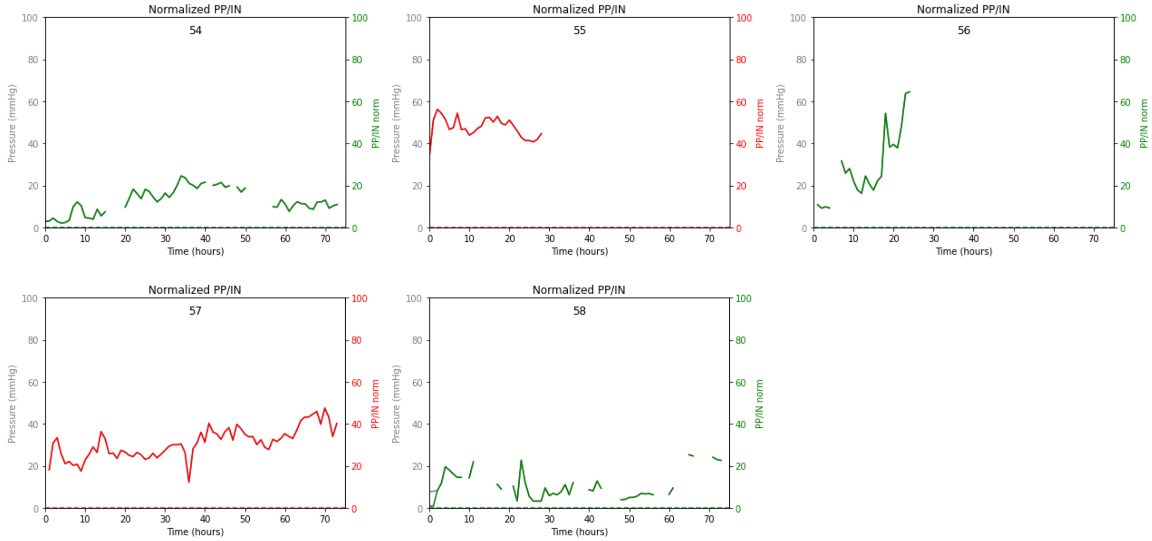

Normalized PP/DT
45
46
47
48
49
50
51
52
53
54
55
56
57
58
Pressure (mmHg)
PP/DT norm
Time (hours)

IN

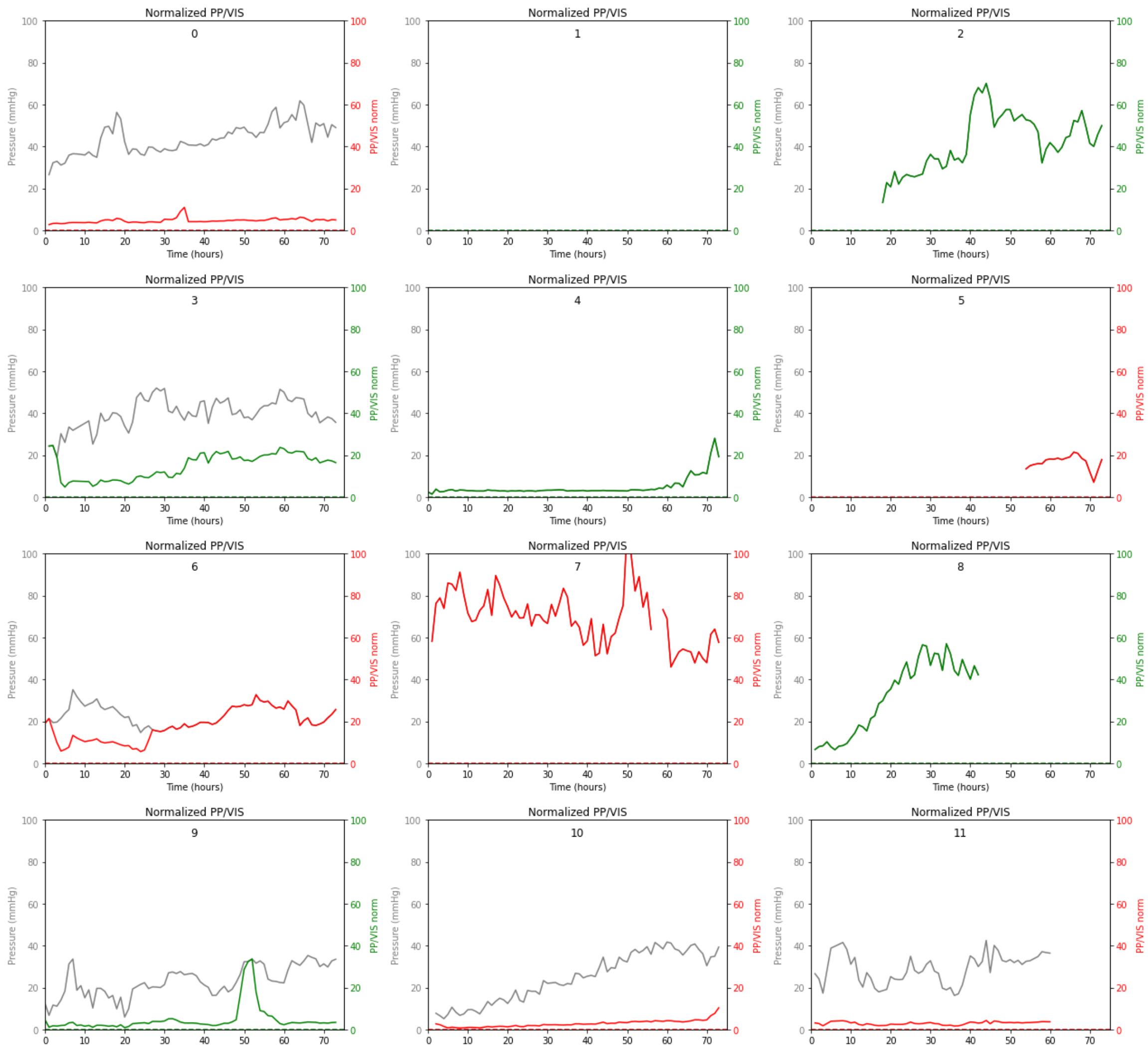

Normalized PP/IN
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Pressure (mmHg)
PP/IN norm
Time (hours)

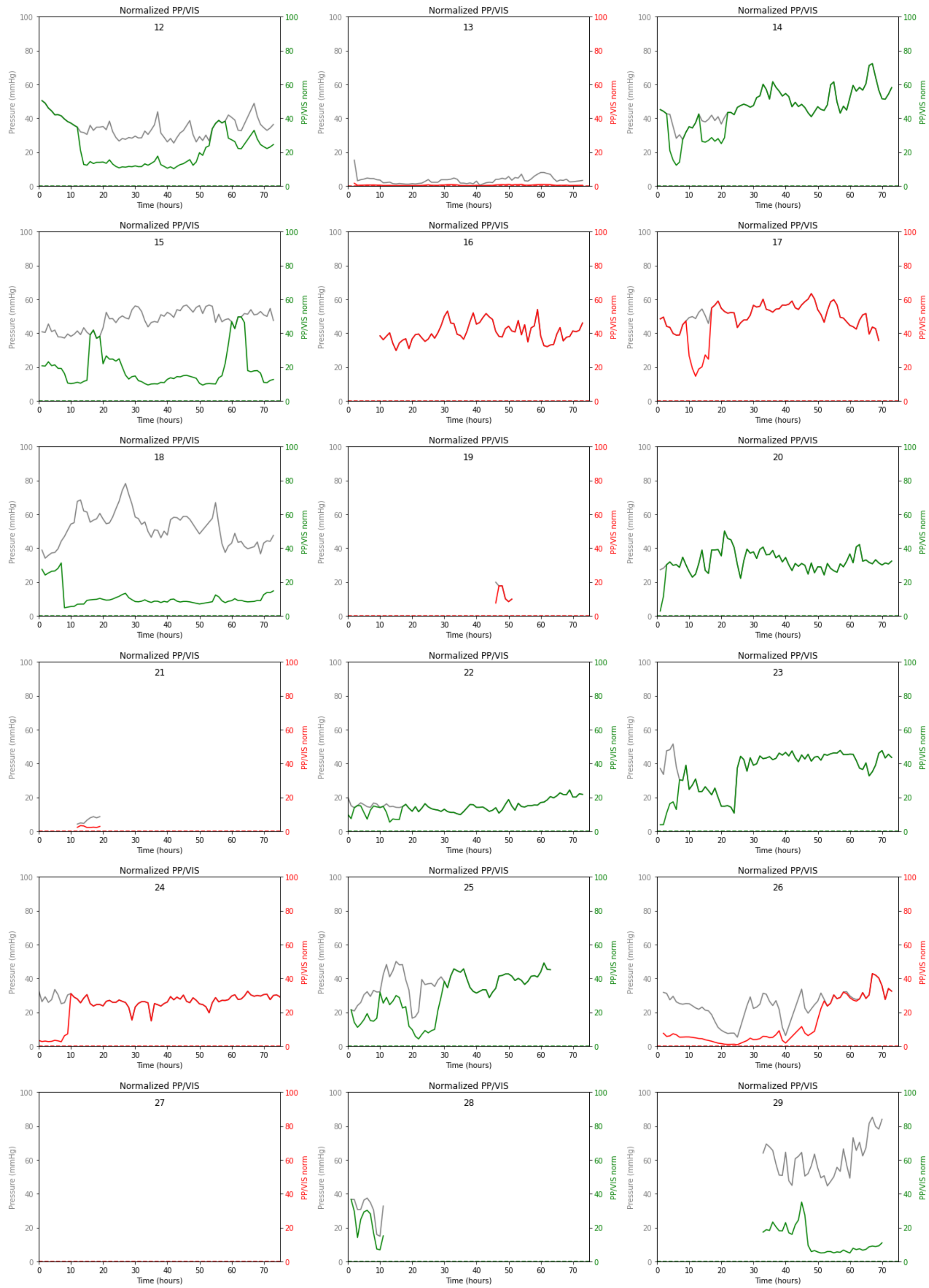

Normalized PP/IN
18
Normalized PP/IN
19
Normalized PP/IN
20
Normalized PP/IN
21
Normalized PP/IN
22
Normalized PP/IN
23
Normalized PP/IN
24
Normalized PP/IN
25
Normalized PP/IN
26
Normalized PP/IN
27
Normalized PP/IN
28
Normalized PP/IN
29
Normalized PP/IN
30
Normalized PP/IN
31
Normalized PP/IN
32
Normalized PP/IN
33
Normalized PP/IN
34
Normalized PP/IN
35
Pressure (mmHg)
PP/IN norm
Time (hours)

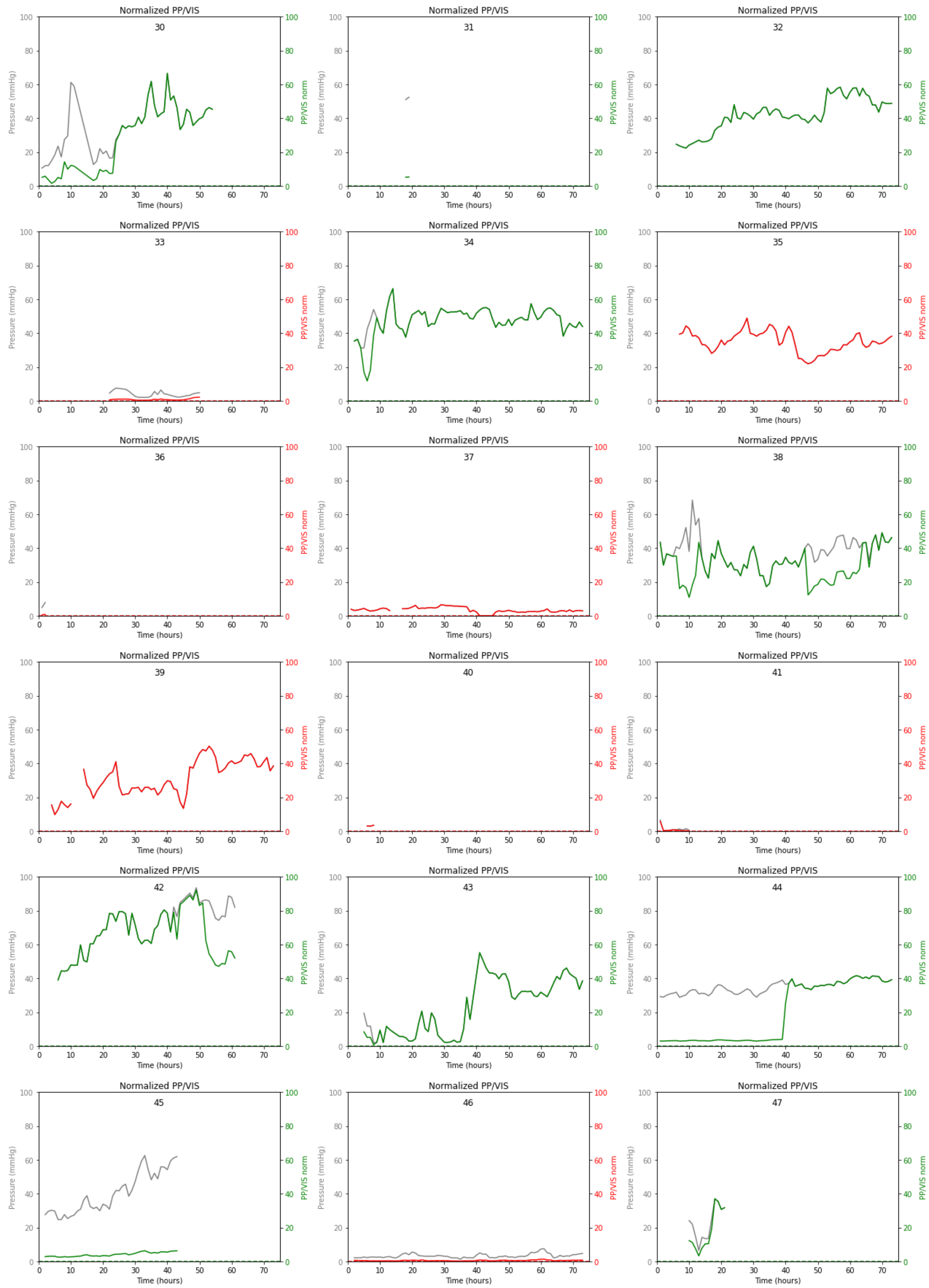

Normalized PP/IN
36
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
37
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
38
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
39
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
40
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
41
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
42
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
43
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
44
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
45
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
46
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
47
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
48
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
49
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
50
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
51
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
52
Pressure (mmHg)
PP/IN norm
Time (hours)
Normalized PP/IN
53
Pressure (mmHg)
PP/IN norm
Time (hours)

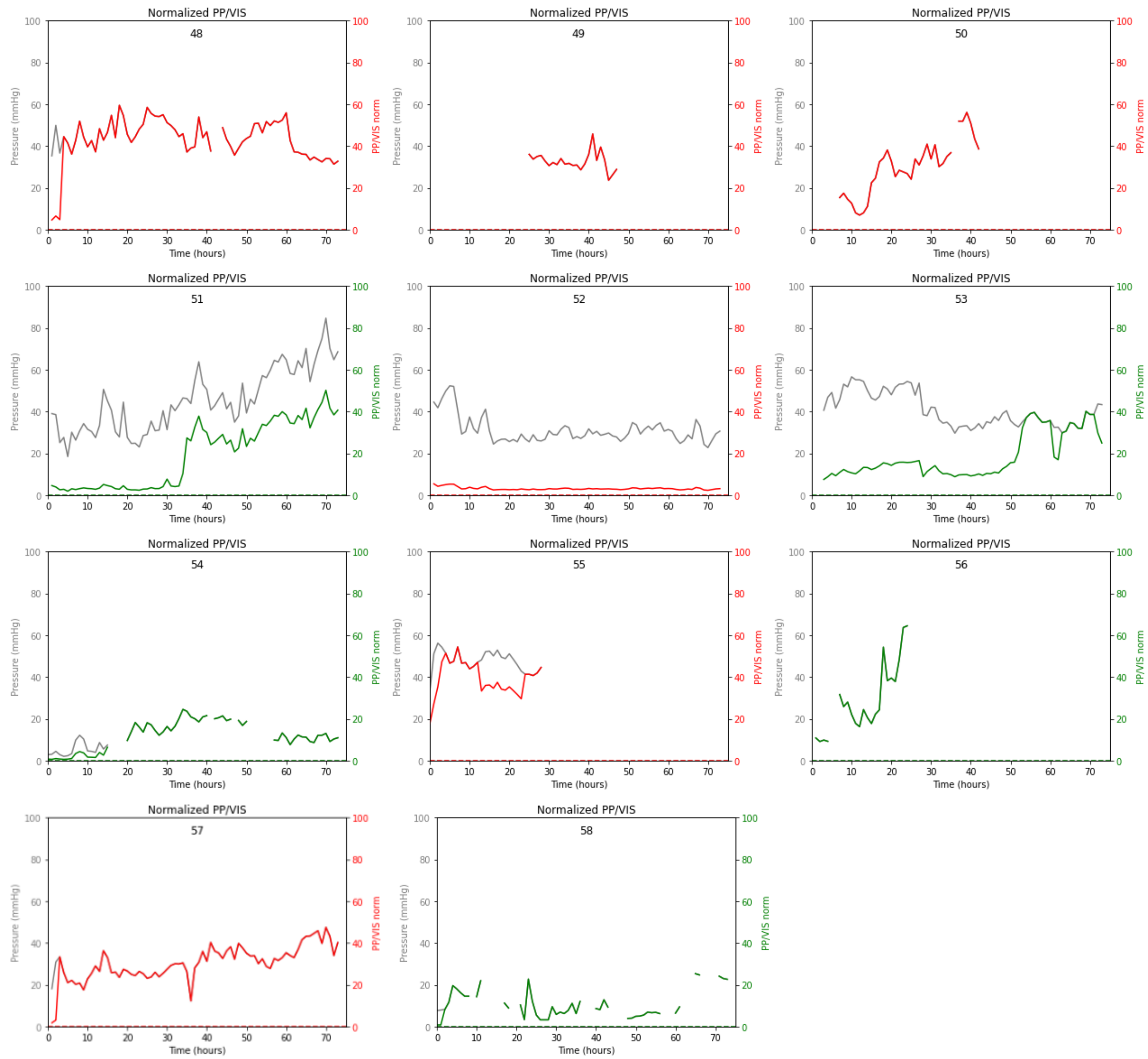

Normalized PP/IN
54
55
56
57
58
Pressure (mmHg)
PP/IN norm
Time (hours)

VIS


Normalized PP/VIS
0
1
2
3
4
5
6
7
8
9
10
11
Pressure (mmHg)
PP/VIS norm
Time (hours)


Normalized PP/VIS
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
Pressure (mmHg)
PP/VIS norm
Time (hours)


Normalized PP/VIS
30
Normalized PP/VIS
31
Normalized PP/VIS
32
Normalized PP/VIS
33
Normalized PP/VIS
34
Normalized PP/VIS
35
Normalized PP/VIS
36
Normalized PP/VIS
37
Normalized PP/VIS
38
Normalized PP/VIS
39
Normalized PP/VIS
40
Normalized PP/VIS
41
Normalized PP/VIS
42
Normalized PP/VIS
43
Normalized PP/VIS
44
Normalized PP/VIS
45
Normalized PP/VIS
46
Normalized PP/VIS
47
Pressure (mmHg)
PP/VIS norm
Time (hours)


Normalized PP/VIS
48
49
50
51
52
53
54
55
56
57
58
Pressure (mmHg)
PP/VIS norm
Time (hours)