

A technical and data analytic approach to pressure-volume loops over numerous cardiac cycles

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ABSTRACT

Cardiac pressure-volume (PV) loop analysis is the reference standard for studying the cardiovascular implications of clinical perturbations (eg, heart failure, aortic occlusion, hypovolemia) and is a benchmark for comparisons with noninvasive alternatives (eg, ultrasound, magnetic resonance imaging). Historically, most PV loop analyses were of individual cardiac cycles for which the options to analyze PV loops using off-the-shelf software were limited, and home-grown analysis software often lacked peer review or code-sharing. Our aim was to describe a start-to-finish implementation of PV loops for determination of hemodynamic parameters in swine, to provide technical advice for vascular access and proceduralization, and to describe data capture, curation, preprocessing, and analysis of raw PV time data. We have provided a novel data analytic method to programmatically analyze raw PV loop data beyond single cardiac cycles and real, raw swine PV loop data and the accompanying MATLAB (MathWorks, Inc, Natick, Mass) code as an example of how to process and analyze raw data directly. (*JVS—Vascular Science* 2022;3:73-84.)

Keywords: Data analysis; Pressure volume loops; PV loops; Swine cardiovascular research

Pressure-volume (PV) loop analysis has emerged as a comprehensive approach for understanding ventricular systolic and diastolic function.^{1–3} Thus, the end-systolic and end-diastolic PV relationships (ESPVRs and EDPVRs, respectively) and PV loop morphology can be used to quantify pump function, including preload, afterload, contractility, and the changes associated with pathophysiology such as heart failure, hypovolemia, and iatrogenic changes such as aortic occlusion or the testing of support devices (eg, intra-aortic balloon pumps or ventricular assist devices). This application is well established and has been used across disciplines clinically, translationally, and in the basic sciences for decades.^{4–7}

PV loop relationships are known as the reference standard for assessing cardiac parameters.^{1,2} PV catheters are, however, invasive and require central instrumentation. In contrast, other alternatives such as thermodilution or ventriculography can be less invasive and still accurate, although designed to focus on cardiac output and its associated measures only.⁵ Using this technology

and analyzing the data acquired from it have a high barrier to entry. The catheters used to obtain PV loop data require deep knowledge of the anatomy of the organism of study and facility with arterial and venous access, catheter placement and troubleshooting, and data collection, curation, and analysis once the data have been obtained. Cingolani and Kass⁸ and Abraham et al⁹ have described how to implement and analyze the PV relationship analysis in mice. For any laboratory or individual interested in implementing PV analysis in mice, their reports would be instrumental.^{8,9} However, limited resources are available for the practical implementation in swine or other large animals, including no detailed information on where or how to obtain access, or how to place, initialize, and troubleshoot the PV catheter. At present, the best resource for this is the manufacturers' literature.¹⁰ However, their methods are not peer reviewed, and the data can only be analyzed using the limited tools they have provided (eg, analyzed only every second or millisecond or averaged using their method vs other smoothing options). Where comparable, these options require manual removal of artifact data, which might be reasonable for a small number of animals but will not be feasible for a high-throughput laboratory or long experiments with thousands or millions of cardiac cycles. Furthermore, most resources for data analysis of PV data have focused on single beat cardiovascular parameter analysis.^{1,3,7,9} Scant resources are available for the practical implementation or formal data analysis of raw PV data, including how to preprocess, interpolate, or provide robust time series analysis. Multiple beat PV loops (ie, "averaging" of a PV loop over numerous cardiac cycles) would allow for small cardiovascular perturbations (eg, respiratory variations or changing resuscitative fluid

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volumes altering the preload minutely) to be smoothed out appropriately compared with either doing so post hoc manually or by selecting individual “representative” loops, which might or might not be truly representative. The learning curve for practical implementation of this in a laboratory setting is steep, and limited resources are available to guide a novice researcher in building such a protocol. Thus, failure or misadventure could result in the unnecessary waste of a precious large animal resource.

Our goal was to describe, from start to finish, a practical method for obtaining PV data from swine and how to approach formal PV data analysis once the data have been obtained that does not use proprietary software. We have provided a novel data analytic method for high fidelity PV loop data cleaning and averaging PV loops over numerous cardiac cycles. We have provided actual raw PV data from an animal obtained in our laboratory, detailed data science method, and sample code that can be used to clean and analyze the provided data. These data could act as a resource for any large animal laboratory seeking to use PV loop data in experiments or to examine PV loop trends for longer periods or as a starting framework for an approach to PV loop data analytic practices.

METHODOLOGIC OVERVIEW

The University of Maryland, Baltimore, institutional animal care and use committee approved all the animal studies conducted using PV catheters, which conformed to the National Institutes of Health guidelines for ethical animal research.¹¹ These methods have been used across multiple studies and in both real-time “bedside” animal assessment and for postprocedure formal data analysis. In the present report, we have specifically provided data from one 55-kg male Yorkshire swine (*Sus scrofa*) acquired as a part of another trial (raw PV data are provided in [Appendixes 1-4](#)) as a practical example to facilitate reproducibility with our provided code ([Appendix 4](#)); available at: https://figshare.com/projects/PV_Loop_Data_Analysis_Raw_PV_Loop_Recordings_and_Matlab_Code/122878.

Before experimentation, this animal had undergone our typical preparation pathway. We have provided the protocol as benchmark for animal preparation to obtain PV loop data, although some experiments using PV loops will require modification in accordance with the experimental goals. Our protocol includes housing the animals in communal pens under veterinary supervision with free access to food and water for ≥ 72 hours to allow for acclimatization, with 12 hours of preoperative fasting. We typically sedate the animal with Telazol (tiletamine and zolazepam; 5 mg/kg) plus xylazine (2 mg/kg) via intramuscular injection and then proceed with orotracheal intubation after isoflurane by face mask. The animals are usually placed on a warming blanket set to

37°C and mechanically ventilated to maintain an end-tidal carbon dioxide pressure of 30 to 45 mm Hg and a target of a fraction of inspired oxygen of 40%, adjusted appropriately according to the serial arterial blood gas values. During most studies, the animals will be monitored with electrocardiography, temperature probes, pulse oximetry, and real-time arterial pressure tracings using vascular access sites as needed.

Animal instrumentation and monitoring

Our laboratory uses PV loops in conjunction with other monitoring devices. The findings from the noninvasive and support monitoring as described provide a typical framework for our approach to animal preparation.

Most of our protocols require the routine recording of basic animal data, including the weight, sex, and baseline blood resistivity (see the section “PV loop data capture”). We typically obtain central venous access in the external jugular, internal jugular, or femoral vein under ultrasound guidance using the Seldinger technique.¹² Depending on the nature of the protocol, we will obtain multiple access site or use additional monitoring methods. In the present report, we have specifically discussed the use of the PV loop catheter. We have, however, reported detailed information of the vascular anatomy of swine, which differs from that of humans.¹²

PV loops are generated using a micromanometer-tipped catheter (Transonic Corp, Ithaca, NY) and computed using the admittance method¹⁰ (see the “PV loop data capture” section). These data are recorded in milliseconds. The PV loop data are captured as pressure vs volume vs time data using LabChart (ADInstruments, Sydney, New South Wales, Australia). We have previously reported up-to-date lists of all the actual devices, equipment, and reagents (with their product numbers) from several trials using these catheters to facilitate equipment ordering and reproducibility.^{13–15}

Technical application of PV loop catheters

PV loop catheters come in a range of sizes and, as such, the proper vascular access will facilitate placement of the catheter. The catheter used in our laboratory for animals ranging in weight from 25 to 80 kg has a 5F diameter, and we use a percutaneous, modified-Seldinger technique.¹⁶ Placement of a 7F catheter will facilitate passage of the PV loop catheter with ease, with preservation of a portion of the lumen for taking blood samples around the catheter if needed. Alternatively, the PV catheter could be inserted through a 6F diameter sheath. We subsequently place the PV loop catheter into the apex of the left ventricle under direct fluoroscopic guidance.

Continuous electrocardiographic monitoring should be observed after catheter placement, because contact of the catheter with the aortic valve or coronary artery can provoke abnormal cardiac electrical activity, which will typically resolve with retraction of the catheter into the aortic arch or advancement of the catheter into the left

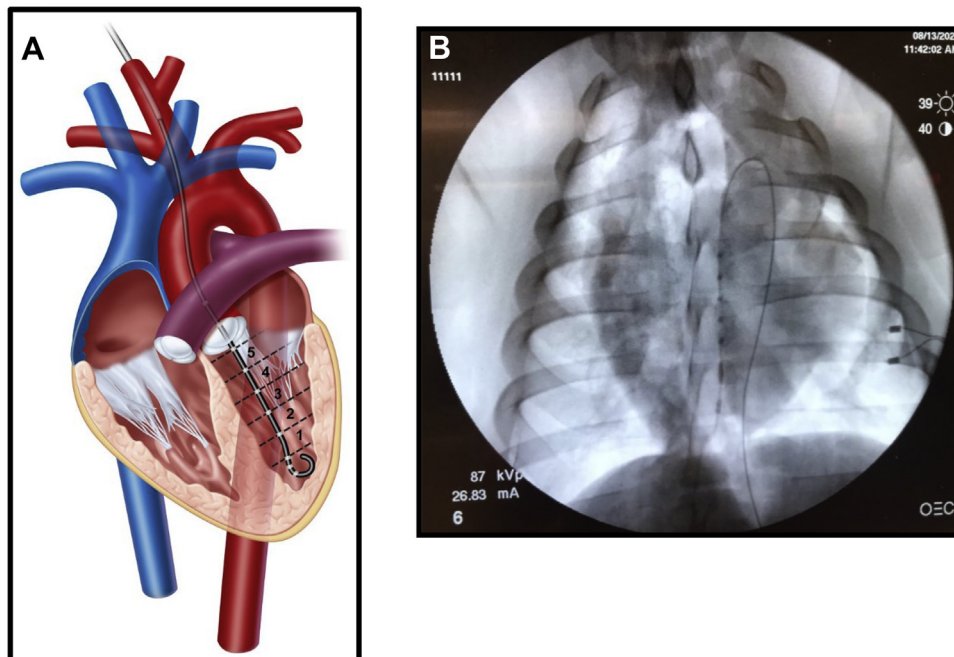


Fig 1. Placement of the micromanometer catheter used to generate the pressure-volume (PV) loops. **A,** Cartoon of PV loop placement showing a left ventricular micromanometer catheter in place, with conceptual delimitations of segmentation. The PV catheter entered the aortic arch from the carotid artery, which is a preferred access point for setup. **B,** Anteroposterior fluoroscopic image of the chest showing a micromanometer catheter in situ within the left ventricle (LV), placed through a 7F sheath in the left femoral artery, which can be more challenging than carotid or brachial artery access for placement, but it is possible.

ventricle. In our experience, the optimal access point for catheter advancement is via the right brachial artery or either of the bilateral carotid arteries. Each of these access points originates from the brachiocephalic trunk, which will naturally steer the catheter into the ascending aortic arch. In contrast, the left brachial artery originates from the left subclavian artery, and catheters will tend to steer naturally down the descending aorta, although cardiac placement is possible.¹² Our laboratory has never experienced carotid dissection or stroke secondary to retrograde carotid access. Stroke is theoretically unlikely even in the event of an embolus owing to the rete mirabile in swine and favoring of the vertebral artery, unlike in humans and nonhuman primates.^{12,17} However, for studies specifically interested in examining cerebral perfusion or carotid blood flow, we avoid carotid access in favor of brachial access to avoid confounding of left vs right uptake or a delay in transit.^{18,19} The femoral arteries are also acceptable access points for the PV catheter. However, advancing the catheter around the aortic arch can require basic endovascular troubleshooting to navigate the arch and avoid the left subclavian artery.

A cartoon representation of typical PV loop placement in the left ventricle (LV) is shown in Fig 1, A. The typical orientation with access from the carotid artery is shown in Fig 1, A. Fluoroscopically confirmed placement in the

LV but originating from the left femoral artery is shown in Fig 1, B. As described, the latter is more challenging for catheter placement. However, because of the experimental parameters, it will sometimes be required and is possible, as shown.

PV loop data capture

The PV data were measured using the ADV500 Pressure Volume Measurement System (Transonic Corp) and the admittance method and collected using PowerLab (ADInstruments).^{10,16} A 5F variable segment length catheter was used. The catheter has seven volume electrode options to allow for optimal segment selection. To prepare for the experiment, all catheters must have been hydrated in saline for 20 to 30 minutes before the experiment and subsequently zeroed using the pressure balance controls in the ADV500 Pressure Volume Measurement System (Transonic Corp).

Blood resistivity is measured in ohm cm using a calibration probe that is connected to the ADV500 system.^{20–22} Although Transonic has suggested not changing the resistivity,¹⁰ we have found it to vary during hemorrhage as hematocrit evolves, possibly because the blood viscosity changes during hemorrhage and fluid resuscitation and viscosity and resistivity are known to be correlated.^{20,21} For our experiments, resistivity is measured using the calibration probe, and the value is inserted into

the ADV500 system to be used to measure the PV parameters. After hemorrhage, the blood is sampled again, and resistivity is measured again using the same method. Our experiments have tended to involve a single hemorrhage event and a single resuscitation event. These events are known to alter blood resistivity^{20,21}; thus, we resampled the resistivity with each of these events.

The location of the catheter in the ventricle is important for data collection. As discussed, the location can be confirmed fluoroscopically. However, it can also be confirmed with the phase values. The signal should have a mean value of $<10^\circ$ and a periodic shape. During PV catheter placement, a PV loop should begin to be generated, and a segment can then be selected. At the first segment, electrodes 1, 2, 3, and 4 will be active (Fig 1, A). At times, the shape of the curve will not be physiologic because the calculated volume will be too low owing to the electrodes having been placed too far from the valve. On segment 2, electrodes 1, 2, 4, and 5 will be active and, depending on the size of the heart, will also lead to low-volume signals. During segment 3, electrodes 1, 2, 5, and 6 will be active and will usually lead to accurate physiologic volumes and PV loops in adult swine. With segment 4, electrodes 1, 2, 6, and 7 will be active and, at times, might be too long for the left ventricle, depending on the heart size. Once the optimal segment has been selected according to the calculated volumes and PV morphology, a baseline scan should be run using the ADV500 system, which will provide a calculated heart rate from the catheter. If the heart rate matches the rate calculated from the aortic root pressure, the baseline scan can be accepted, and the data are ready to be collected.

PV loop data analysis

LabChart (ADInstruments) permits real-time monitoring of hemodynamic parameters and instruments. This allows for real-time clinical reactions to changes in animal physiology and is instrumental for performing experiments. Raw pressure and volume data directly off the instrument can be displayed in real time, as can the LabChart-computed hemodynamic parameters that result from the raw data. Many laboratories, including ours, use these data directly during experiments. However, limitations exist to this for postexperiment data analysis, which led to our development of code to analyze the raw data ourselves. One limitation has been that the data were not being cleaned or preprocessed before analysis. That is, the computer does not know when the data are poor quality (eg, during catheter positioning or placement adjustment or during changes in the animal's position). It will not always be clear post hoc which data are high fidelity and which are not if notes were not taken. Specifically, at times, the LabChart software will produce pressure tracings

that are negative. Such tracings obviously represent bad data. However, at other times, physiologically possible results will occur that could also be poorly captured data. This process is further limited because several methods are available to compute the hemodynamic parameters, and it is not clear how the parameters are derived from the back end by the software. Further limitations exist to data analysis, time series analysis, and graphic presentation using the unprocessed data. The extent of these limitations will, at times, be unclear because of the proprietary nature of the software. Furthermore, single beat analysis can be useful for quickly changing hemodynamic states or when performing the experiment. Single beat analysis has been the focus of much prior research and is supplied by LabChart. PV loop analysis for longer periods by deriving "average" PV loops representing the hemodynamic state for seconds or minutes has not been well described.

Formal data analysis. For formal data analysis, our laboratory has preferred, in most situations, to use raw pressure and volume data over time to compute the hemodynamic parameters ourselves, instead of using the parameters computed by LabChart, because the latter could have been based on bad data or poorly computed given the undefined method used in LabChart. From these raw PV data, we preprocess the findings by removing the inappropriate or low-fidelity data. The hemodynamic parameters can be then computed in reproducibly and reliably and analyzed directly. We have found that raw 5-ms time steps of pressure and volume data pulled from LabChart will provide adequate time granularity without an unnecessary data size burden. These data we export as a comma separated file (.CSV format), which we import into MATLAB, 2020a (MathWorks, Inc, Natick, Mass) for formal analysis, although the use of other software would be reasonable.

Automated data cleaning. Our laboratory has used various methods for data cleaning. It is trivial to programmatically or manually remove negative data readings and obvious artifact, if needed. It is, however, much more difficult to use an algorithmic approach to remove "bad PV loops" within the data. In Appendix 1, we have expanded and detailed on our data cleaning strategy. In brief, the challenge for PV data cleaning is that the relationship is a time dependent two-dimensional cyclic function. The two parameters are coupled according to cardiovascular physiologic principles that evolve together over time during an experiment; thus, we have not found examining either in isolation to be sufficient.

The core of our solution lies in taking raw PV data, importing the data to MATLAB, and then cleaning the data. Thus, we translate the center of the PV loop to the origin, convert the data from Cartesian to polar coordinates, and examine the converted theta-radian relationship (instead of the PV relationship; Supplementary Fig 1). Once reduced to this format, we can construct

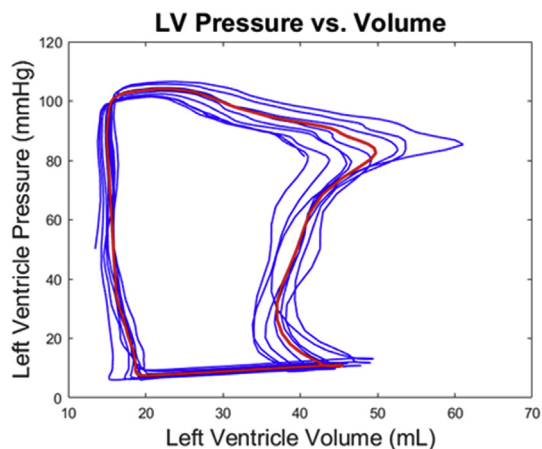


Fig 2. Left ventricle (LV) pressure vs volume over time, with continuous pressure-volume (PV) loops (*blue*) plotted, along with an interpolated PV loop (*red*), representing the average PV loop from the time period.

rules about the progression of the loops in these terms. These rules come in the form of constraints on the length of each PV loop relative to its neighbor loops and the forward progression of theta in time around the loop (Supplementary Fig 1). Other data cleaning solutions could also be feasible, including computer vision and machine learning applications, depending on the goals of the analysis. However, in general, we have found this to be an unnecessary complexity.

Computation of hemodynamic parameters using PV loops. LabChart and other software will typically analyze each PV loop, which corresponds to one cardiac cycle, for hemodynamic parameters such as stroke work, heart rate, and measures of preload, afterload, and contractility over time. These hemodynamic parameters can then be averaged and provided for a specific time period or analyzed serially. However, we are often interested in finding an average PV loop for a time period instead of the average hemodynamic parameters for a specific period of time. We developed a method of smoothing to average the minor artifacts or hemodynamic changes that can occur from loop to loop (Appendix 2). Smoothing allows one to compute the hemodynamic parameters on the interpolated loop that is representative of a time period. As major experimental changes occur, these can be recomputed, and, via this mechanism, robust hemodynamic parameters can be computed for analysis (Fig 2 and Supplementary Fig 2, with an interpolated PV loop [*red*] representing the average of several cardiac cycles during a 5-second period).

The mathematical derivation of these average PV loops are provided in Appendix 2. The MATLAB code used to generate them from the example data is included in Appendix 4. In brief, a user provides the raw PV data over time and a segment-of-interest of the PV data for

interpolation. These are imported into MATLAB, converted to polar coordinates, and interpolated. The data are then converted back to Cartesian coordinates and can be plotted and analyzed (Fig 2). However, this is not a true “average” PV loop obtained by taking the mean values but is, instead, interpolated over time. Once in this format, we prefer to plot this in MATLAB directly. However, it is also possible to export these curve data and plot them using other graphing software, depending on investigator preference.

With an average loop derived, these raw, but cleaned and interpolated, PV data can be used to compute the mean hemodynamic parameters. The mathematical derivation of these parameters from a single PV loop has been well described in previous studies.^{1–3} The practical implementation, however, has been lacking. In Appendix 3, we have provided an overview of how we implement this algorithmically. An interpolated PV loop is shown in Supplementary Fig 3, with previously reported algorithms (Supplementary Fig 3, A) and our adaption (Supplementary Fig 3, B) for finding the critical points along the PV loop needed to compute the ESPVR and EDPVR and their associated parameters. Once these have been derived, computation of the hemodynamic parameters is possible using the MATLAB code provided (Appendix 4). Thus, with the ESPVR and EDPVR already calculated, the end-systolic and end-diastolic volume will be immediately available. This allows for calculation of a stroke volume easily. The heart rate will be equal to the number of PV loops per minute; thus, the cardiac output can be easily computed. Stroke work is the area inside the loop and is also easily computed using the MATLAB function polyarea. The measures of contractility (end-systolic elastance) are related to the slope of the ESPVR, which, because these have already been defined, is easily provided. Other measures of cardiac function, depending on the study design, can also be computed, including the augmentation index, the slope of the EDPVR, and the relationship of any of these parameters with time.

CLINICAL APPLICATION

PV loop catheters are invasive; they require major vascular access and placement of rigid catheters into the heart, which is associated with risk and requires sedation. This risk is usually prohibitive, especially for critically ill individuals. However, PV loops can provide reference standard biomechanical pump information from the heart. PV loops have, therefore, become the reference standard for less-invasive options as these have become more prevalent. When magnetic resonance imaging was used to noninvasively assess cardiac output, the magnetic resonance imaging findings were compared with those computed from the PV loop for validation.²³ When echocardiography has been used to determine the LV functional parameters, these should

be compared with the PV loop as the reference.²⁴ Practically, cardiac output or stroke work cannot be computed in these clinical scenarios from a single PV loop—but this is how PV loops have been used for decades. Single beat estimations ignore small temporal changes. In contrast, multiple beat analysis, such as we have described, has greater similarity to the clinical application of LV functional assessment. Multiple beat analysis can smooth the effects of respiratory variation, or average the effect of changing the vasoactive infusion or intravenous fluid rates in the same way that an ultrasound scan might average the stroke volume or inferior vena cava compression over numerous beats. The method we have described might provide a new reference standard for the validation of noninvasive cardiac assessments closer to how these are used clinically or even a new reference option for invasive measurements that experience the same temporal variations (eg, right heart catheter).

STUDY LIMITATIONS

In the present study, we have provided an overview of PV loop analysis in swine and a novel method for assessing PV loops over numerous cardiac cycles, which, to the best of our knowledge, has not been previously established. The present study, however, was not without limitations. We chose swine because this is the species our laboratory is most familiar with, and because it is used by many cardiovascular research laboratories despite the dearth of literature on how nonproprietary PV loop analysis is being performed. As our laboratory was beginning this work, we relied on experimental designs from mice or extrapolated from secondary sources,^{3,8,9} because they were not available for swine. Also, the literature base is limited for this method for other large animals, such as sheep and nonhuman primates. However, that was beyond the scope of our report. Our laboratory also has less experience with juvenile swine weighing <25 kg, although a 6F diameter sheath for vascular access can be used for all animals in the provided weight range of 25 to 80 kg and the discussed method applies, in our experience, uniformly across this group. The only major exception based on animal size is the choice of PV catheter segment selection as described in detail in our report. Furthermore, we believe (data not shown) that these analyses are likely being performed at serious laboratories around the world using home-grown code and methods, as we have done ourselves. However, most of these have remained siloed within their laboratories and have not been peer reviewed or reported, which motivated our study and the report of our code.

CONCLUSIONS

PV loop analysis provides “gold” standard reference data for cardiac function and can be used to analyze the evolution of hemodynamics over time. The learning

curve for using this technology in large animal research, however, is high. In addition to familiarity with the animal model of choice, it requires knowledge of vascular access, cardiovascular anatomy and physiology, the use of data systems to capture and store raw data, and comprehensive data analytic skills to clean, process, and describe the data.

In the present report, we have provided a practical technical and data analytic approach for using a PV catheter to obtain these data in swine. Although technology does exist to monitor these parameters in real time, this has limitations in practice during postexperimental analysis of the data, and sophisticated signal processing and data analytic solutions are lacking. Therefore, we have provided practical strategies for placing a PV catheter in the animal and the implemented code for automated preprocessing and analysis of raw PV data.

Matthew Holt provided paid medical illustration services for the rendering of Fig 1.

AUTHOR CONTRIBUTIONS

Conception and design: DS, JE, HA, NE, JM

Analysis and interpretation: DS, HA, JM

Data collection: JE, HA, NE, EL, SS

Writing the article: DS, JE, NE, JM

Critical revision of the article: DS, JE, HA, NE, EL, SS, JM

Final approval of the article: DS, JE, HA, NE, EL, SS, JM

Statistical analysis: DS

Obtained funding: Not applicable

Overall responsibility: JM

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APPENDIX 1.

Data processing

Raw pressure-volume (PV) over time data are extracted from LabChart (ADInstruments, Sydney, New South Wales, Australia) as described. Depending on the study protocol and experiment, noise will often be present within the data. This noise could be totally unrelated to changes in physiology and could have resulted from the operator moving the instruments, access sheath, or animal. These, and any other outside factors, can cause artifacts. For small time-segments or noncontinuous analysis, data cleaning can be performed manually. However, any serious time series analysis or modeling would require algorithmic data cleaning to remove nonphysiologic PV loops from the data.

The data cleaning process has several challenges. First, analyzing PV loops is a two-dimensional cyclic evolution of coupled data. Studying pressure or volume in isolation would be inappropriate. Furthermore, depending on the experiment, the loops will evolve and what might initially be an inappropriate loop could become appropriate or vice versa.

We have found, however, no rigorous approaches to applying data analytical strategies to this specific problem in the literature. After considering several approaches, including computer vision and machine learning, we ultimately applied an ensemble rule system to converted polar coordinate data. This uses the “rules” created by the cardiovascular system and helps to determine which data are legitimate.

In our experiments, we have generally had ample data and preferred to remove all possibly inaccurate data even at the loss of some accurate data. Therefore, we have analyzed the data in increments of the “entire loop”; thus, regardless of whether an entire loop or only part of a loop is considered “bad” (as defined below), we remove the entire loop.

The computational strategy is as follows:

- Translate the PV loop to be centered at the origin, saving the translated PV loops old center, because it will be needed to convert back to the Cartesian coordinates
- Convert the centered loops x - y coordinates to the polar coordinates
- Divide the continuous PV loop data into the individual loops as defined by the radius and angle in the polar coordinates (setting theta to 0 for defining a new loop), where each loop represents one cardiac cycle
- Determine the appropriate progression and length of the loop, using the constraints created to identify inappropriate PV loops
 - Remove loops with nonphysiologic morphology
 - Reconstruct the data into Cartesian coordinates and make the data continuous
- Proceed with analysis of the cleaned data

When viewed in polar coordinates over time, outlier loops will be identifiable ([Supplementary Fig 1, Left](#)). Each cardiac cycle was plotted as a single, colored line, showing the progression of theta over time within a single cardiac cycle. The physiology is related to certain properties that this progression should follow. First, the length of each curve along the x -axis is how long each cardiac cycle takes and is, therefore, directly related to the heart rate. Clearly, two of the plotted loops (*blue* and *purple* curves marked with a *double star*, which are apparent outliers) have a time noted that was about twice as long as the other loops. This was an artifact, and these were removed programmatically. Practically, we relate the length of each loop to its neighbor loops and remove any outliers. Second, during the cardiac cycle, theta should only progress forward (ie, the cardiac cycle does not reverse), the loop might pause in time at critical points in the curve but, generally, should not reverse itself. It is not truly monotonic (even aside from the discontinuity at 2π radians), but it is very nearly so, especially at the beginning and end of the cycle. Using this principle, we can programmatically remove the remaining outliers in this example, such as the *red* curve with the *single star* shown in [Supplementary Fig 1](#). In practice, we set a 10% rule: that is, the loop should not, within the same cardiac cycle, reverse theta by $>10\%$. Again, this is because theta should only progress clockwise. Loops that meet this will be filtered out. After data cleaning and removal of artifact loops, we have the image shown in [Supplementary Fig 1, Right](#), which we can reconstruct into Cartesian coordinates and make continuous. In our laboratory’s experience and experiments, it has generally been acceptable to have a high specificity threshold (ie, it is acceptable to filter out some good PV loops to ensure that no bad loops were included). For other experimental conditions, other rules could be necessary, depending on the data quality requirements.

APPENDIX 2.

Pressure-volume loop analysis and determination of hemodynamic parameters

After cleaning raw pressure-volume (PV) data, the next goal is usually to determine what the “average” PV loop shape is for a time period of interest. This allows for the computation of hemodynamic parameters over a period of time instead of a single PV loop (which represents one cardiac cycle).

We again resort to polar coordinates. In brief, we convert the raw xy (pressure vs volume) centroid position, which is the mean pressure and volume, and remove this from all the raw data, which thereby centers the data on the origin. Next, we convert these translated data to polar coordinates. Finally, moving around the unit circle, we can interpolate the center radius stepwise around the

circle for however many loops were included. Several raw PV loops, plotted in polar coordinates (*blue*) with a central “average” PV loop (*red*) traveling through the middle of the paths created by the numerous PV loops, are shown in [Supplementary Fig 2](#). Note that this is not a true average, because it was interpolated along the circle. Depending on the experiment of interest, the interpolation strategies could theoretically differ.

APPENDIX 3.

Determination of hemodynamic parameters from constructed pressure-volume loops

Once an average pressure-volume (PV) loop has been generated for a specific time period, the next goal will often be to determine the values for the hemodynamic parameters from the loop, such as stroke work, volume, and measures of preload, afterload, or contractility, among others. This involves determining the locations in PV space of certain points along the curve, such that these can be computed. It is not always clear how LabChart (ADInstruments, Sydney, New South Wales, Australia) computes these, and, when analyzing their representations of these points, they do not always appear correct (data not shown).

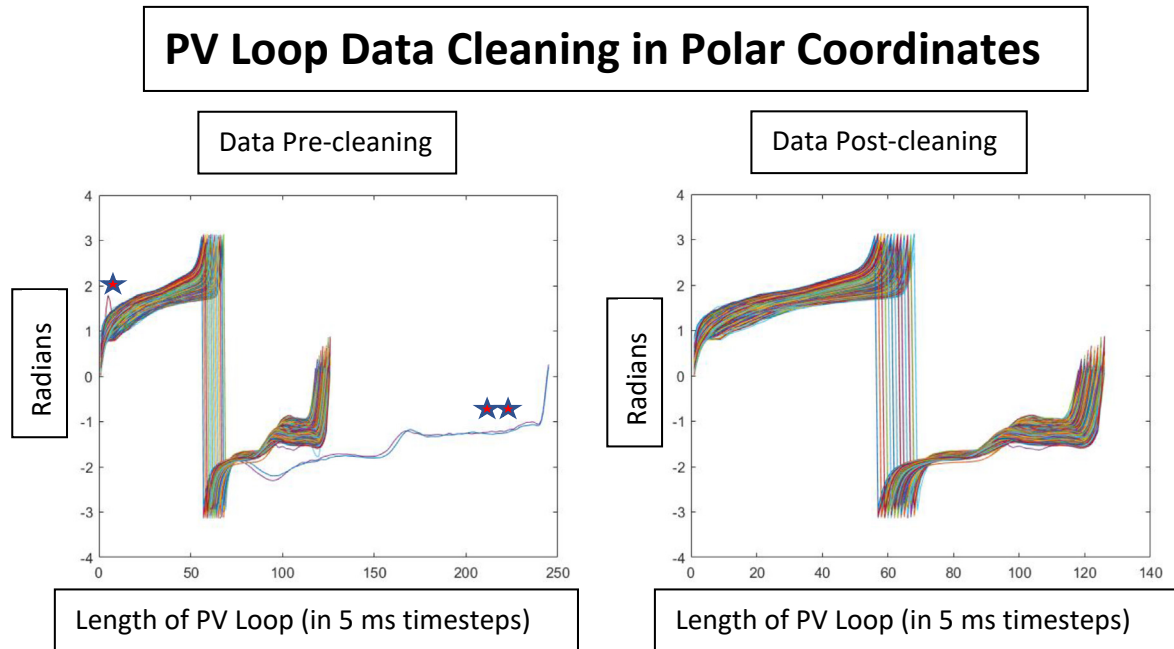
Two primary points must be determined: the point at the upper left and lower right of the PV loops. These points define the end-systolic and end-diastolic relationships. It is easy to “eye-ball” where these should lie on the graph but more challenging to determine programmatically. Lankhaar et al²⁵ suggested an algorithm for “automatic corner point detection” in their review of models of the PV relationship (see their Appendix and Fig 9). They described iterating over the points on the PV curve that are above the middle and to the left of the middle of the loop ([Supplementary Fig 3, A](#); *black points* within the *blue box*). Once these points have been enumerated, one can algorithmically loop over them and determine which is the greatest distance from the center of the loop, which Lankhaar et al identified as the optimal point. Using this method, one can determine a relatively good approximation of this upper left most point. This method, however, has limited precision in the determination of the actual corner point ([Supplementary Fig 3, B](#)), because the distance is computed in PV Euclidean

space and larger pressure changes occur in mm Hg than do volume changes in mL (ie, the y-axis is “longer” than the x-axis in the given units; thus, measuring the distance will favor points higher on the loop than those more to the left). An example in which this point is close, but slightly misidentified using the method of Lankhaar et al is shown in [Supplementary Fig 3, B](#)). We, therefore, adapted this algorithm ([Supplementary Fig 3, B](#)). For each point in the right upper quadrant of the loop, we do not use the maximum distance but instead compute the tangent of each point and find the unique point within this area for which the tangent projected to the x-axis is closest to the x intercept. This chosen left upper quadrant point represents the true corner point. The right lower quadrant point is then computed to be the furthest distance from the optimal left upper quadrant point, as in the method reported by Lankhaar et al. Once determined, the curves representing the end-systolic PV relationship and end-diastolic PV relationship can be created, and the hemodynamic parameters can be computed. The end-systolic PV relationship is fit between V_0 , the minimum of the PV loop, and the right lower corner point using a first order exponential. Stroke work is computed using the MATLAB function `polyarea`, which computes the area inside the polygon described by the loop.

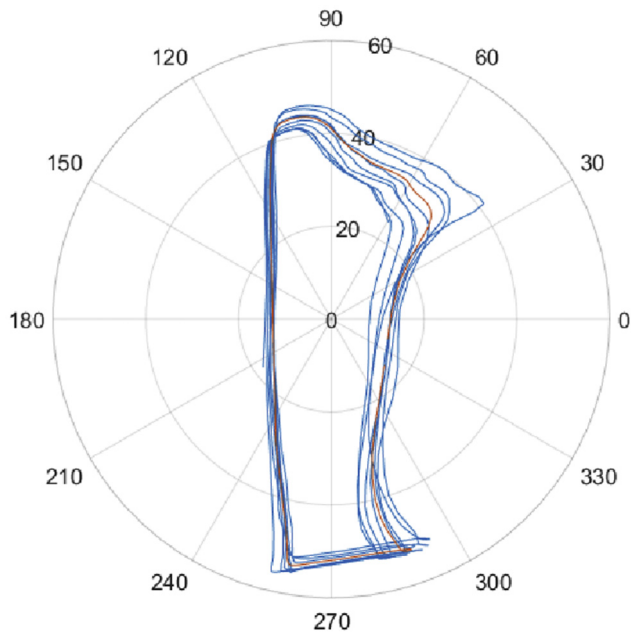
APPENDIX 4.

Example of pressure-volume data and MATLAB code used to analyze it

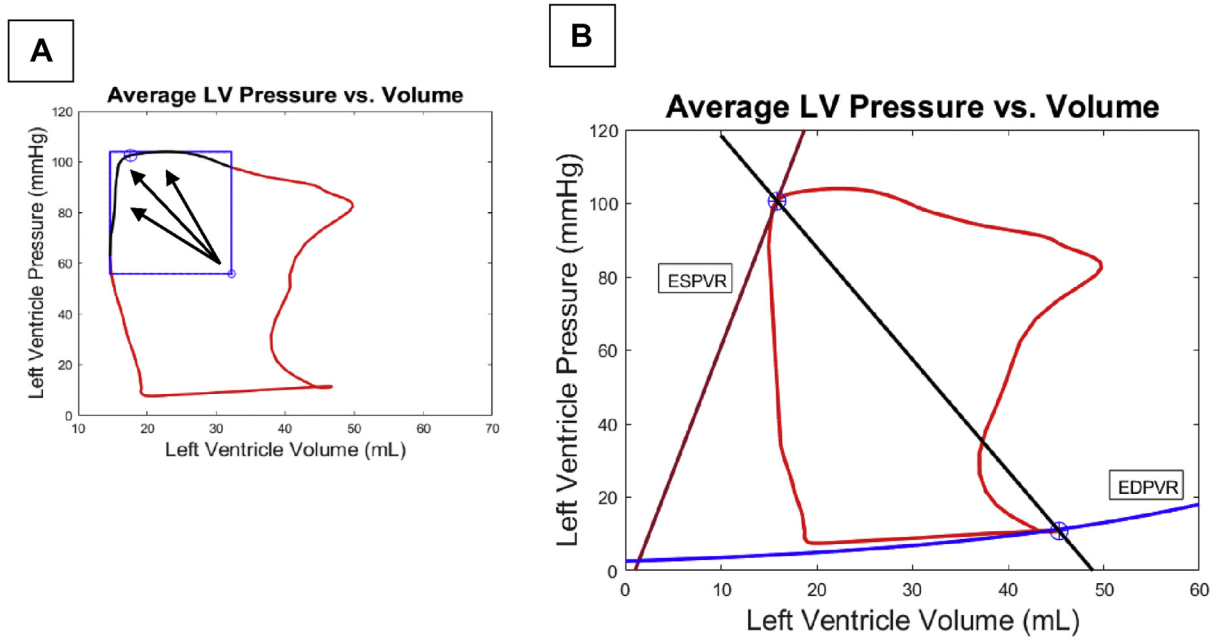
The data and an example analysis of one swine that was hemorrhaged during the study period as a part of another research trial are provided. The data were repurposed for our report to provide an example of how to approach these data. The raw pressure-volume loop data ([Supplementary File 1: 2445_PVloop5mili.xlsx](#); raw pressure-volume data taken in 5-ms time steps; within `code.zip` with the MATLAB code), example code to implement data cleaning and analysis ([Supplementary File 2: code.zip](#); an example of MATLAB code to implement data cleaning and analysis), and [Supplementary Videos 1 and 2](#) showing the raw and cleaned data are provided. These have been uploaded and are publicly available (available at: https://figshare.com/projects/PV_Loop_Data_Analysis/122878).



Supplementary Fig 1. Pre- and post-clean pressure-volume (PV) loop data: theta vs time. Each *colored line* represents one loop, converted to polar coordinates. Each loop starts at theta = 0 radians and progresses around the loop back to theta = 0 radians to begin a new loop. Rules were constructed around what the theta progression should fit. Clearly, some loops shown (**Left**) did not fit the expected progression and were removed (**Right**).



Supplementary Fig 2. Raw pressure-volume (PV) loops (*blue*) with an interpolated PV loop (*red*) representing the average physiology across numerous cardiac cycles, plotted in polar coordinates. These data are also shown in Fig 2 as Cartesian coordinates.



Supplementary Fig 3. Determination of left upper and right lower corner points algorithmically. **A**, An example pressure-volume (PV) loop (red line) with points in the left upper segment (blue box) of the PV loop identified (black line). Arrows represent distances from the center point to the points along the line. The blue target represents the point on the line that is the greatest Euclidean distance from the center point, which is not precisely in the true corner. **B**, Curves representing end-systolic PV relationship (ESPVR) and end-diastolic PV relationship (EDPVR) drawn through the computed corner point with corner point detection via tangent computation.