Work Loop Power Analysis

Mechanical work in myocardial slices

This document explains the theory behind and physiological relevance of IonWizard's Work Loop Power Analysis.

Introduction

Pressure-Volume Loop

Pressure-volume (PV) loops provide a detailed representation of the heart's functions during each beat. One loop represents a complete cardiac cycle and shows how pressure and volume within the ventricle change as the heart fills with blood, contracts, ejects blood, and relaxes. The loop is divided into four main phases, as shown in Figure 1:

I). Ventricular Filling, the mitral and tricuspid valves are open, the ventricles are relaxed and fill with blood.

II). Isovolumic contraction (IVC), the pressure builds while all valves are closed.

III). Ventricular ejection, the aortic and pulmonary valves open, and blood is pumped out of the heart.

IV). In **Isovolumic relaxation (IVR)**, all valves close and the heart relaxes before the next filling phase begins.

PV loops allow visualization of the complete mechanical properties during cardiac function, capturing both active contraction and passive relaxation. Two key concepts in interpreting PV loops are preload, the initial filling or stretch of the ventricle before contraction (phase I), and afterload, the pressure the ventricle must overcome to eject blood (phase III). Changes in these conditions shift the shape and position of the PV loop, which is commonly used to assess cardiac performance.

Introduction – Pressure-Volume Loop (cont.)

PV loops are used in clinical care where in-depth cardiac mechanics are necessary to guide treatment or evaluate therapeutic interventions. They are typically obtained during invasive procedures such as cardiac catheter-ization and are valuable during cardiac surgery and the management of advanced heart failure.

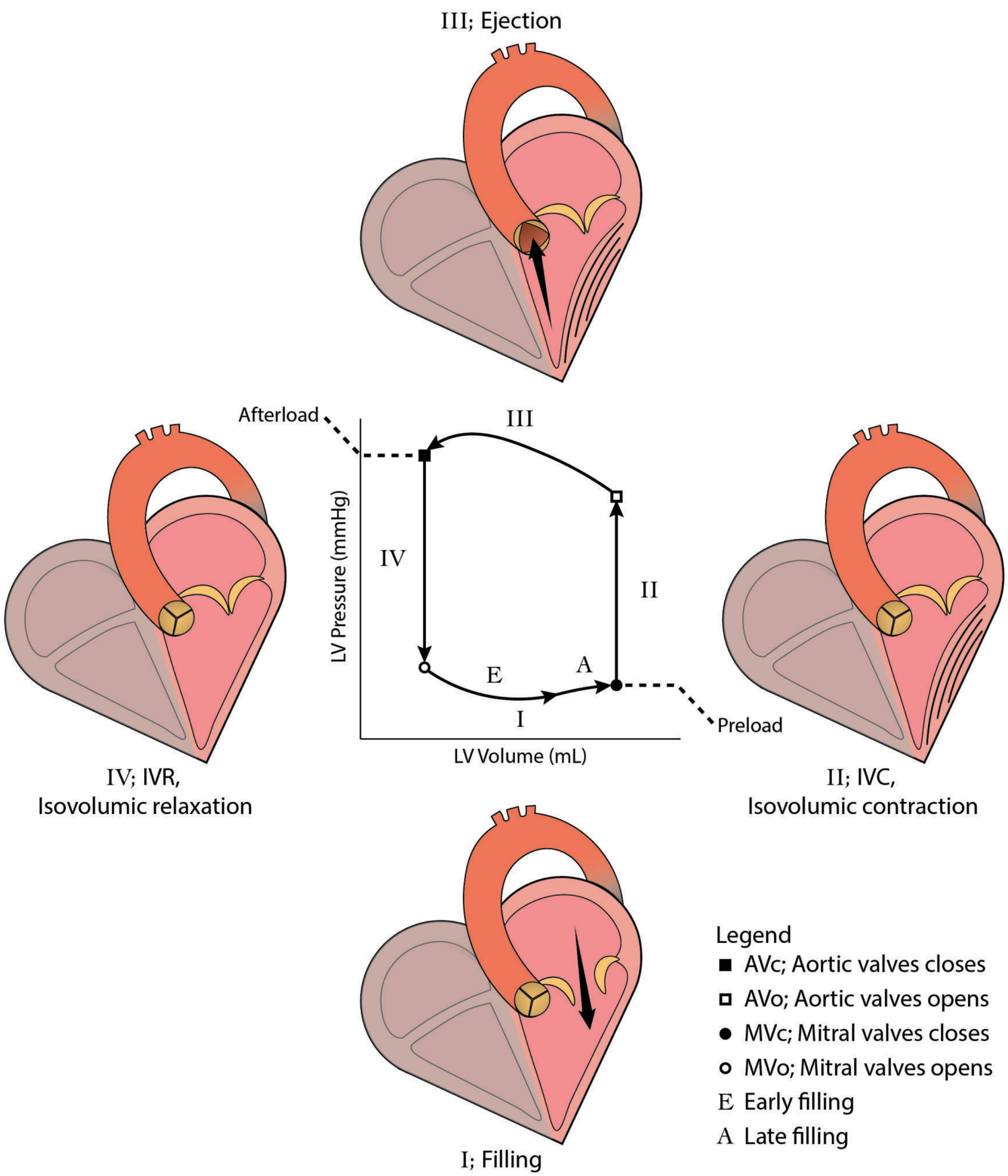


Fig 1. Schematic Pressure-Volume Loop. The loop illustrates the 4 phases of the cardiac cycle, including ventricular filling (I), isovolumic contraction (II), ventricular ejection (III), and isovolumic relaxation (IV), with valve states indicated by distinct symbols. Preload is represented by the ventricular volume at the end of filling (I), and afterload corresponds to the pressure the heart must overcome during ejection (III).

Introduction (cont.)

Force-Length Loops

In cardiac research, detailed insight into mechanical performance is crucial for developing targeted therapies and understanding how the heart adapts to pathological conditions. To achieve this, PV loops, used in whole-heart or in vivo settings, have been adapted in isolated cardiomyocytes and cardiac tissues, such as papillary muscles or cardiac slices, also referred to as living myocardial slices (LMS).

In these models, pressure and volume are replaced with their mechanical analogs: force and length (Figure 2). This adaptation allows investigators to mimic the full cardiac cycle ex vivo using controlled electrical stimulation and mechanical loading. The result is a force-length loop that captures key features of cardiac mechanics in a (patho)physiologically relevant way. The force-length loop offers a more direct and interpretable link to clinical function, making it easier to translate experimental findings into patient-relevant parameters.

I). During **Filling**, the voice-coil motor lengthens the slice, stretching the relaxed tissue mimicking blood filling the ventricle and increasing passive tension.

II). In **Isovolumic contraction (IVC)**, the motor holds the slice at a fixed length, while electrical stimulation triggers active contraction.

III). In **Ejection**, the motor shortens the slice while it remains actively contracting, mimicking the work-producing phase of systole.

IV). In **Isovolumic relaxation (IVR)**, the motor holds the slice at constant length as the tissue relaxes after contraction.

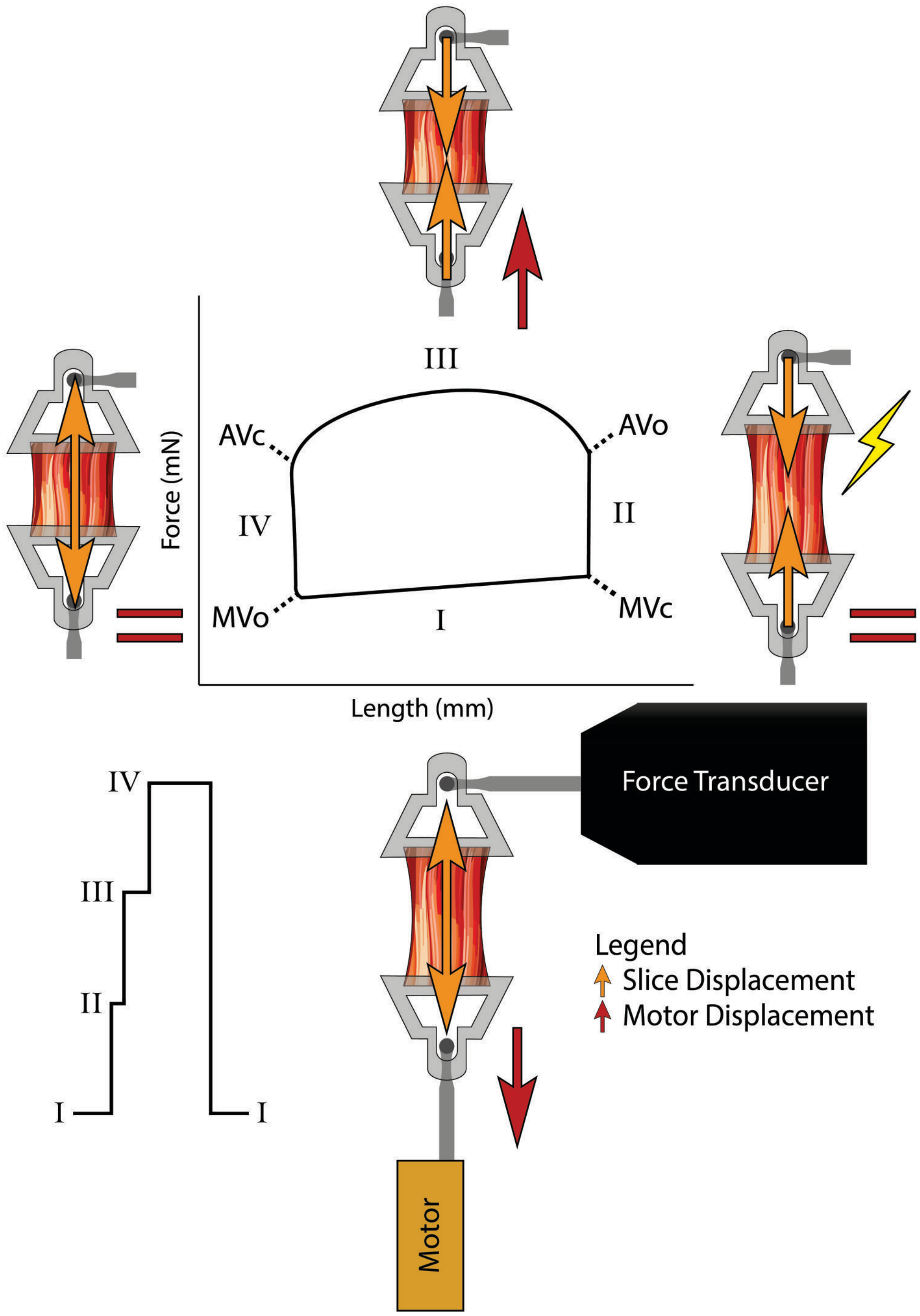
IonWizard's Work Loop Power Analysis allows investigators to extract parameters from the force-length loop that describe the mechanical properties of tissue. In this application note, we describe how these outputs are derived and how they relate to (patho)physiological heart function.

Force–length loops are particularly well-suited for in-depth mechanical characterization of myocardial tissue, and their interpretation often relies on three commonly used biomechanical terms:

Introduction – Force-Length Loop (cont.)

- ·Stiffness is resistance to stretch; higher stiffness means the tissue deforms less for a given load.
- Compliance is the ability of the tissue to stretch in response to load, the inverse of stiffness.
- Elastance is a dynamic measure of stiffness, often described as the slope of the end-systolic or end-diastolic relationship.

Fig 2. Schematic Force-Length Loop in the Cardiac Slice System. In isolated cardiac cells and ex vivo tissue, force corresponds to pressure, while length corresponds to volume. This PV-loop reconstruction illustrates the four phases: filling (I), isovolumic contraction (IVC, II), ejection (III), and isovolumic relaxation (IVR, IV). These phases are defined by valve transition points and are visualized in the IonWizard software as "States", as shown in the state diagram in the lower left of the figure.



Analysis Outputs

1. State

The Work Loop Power Analysis performs calculations organized into 7 groups. The first group, titled "State", focuses on the kinetics of the work loop, capturing the timing and duration of each phase.

Figure 2 illustrates a typical force-length loop and the four corresponding states. During data collection in IonWizard, the software detects states I through IV, each representing a distinct mechanical phase of the cardiac cycle. Transitions between these states occur when specific valves open or close. To simplify, we focus on opening and closing the aortic and mitral valves (AVo, AVc, MVo, and MVc).

The outputs in the "State" grouping describe the time it takes to reach a transition or the duration of a phase. The following analysis screenshot shows the first few groups of PV parameters (Figure 3), highlighted in red are the state parameters. The units for the state parameters are in seconds.

Note that although state I is filling, time zero is the stimulation event triggering contraction occurring at the beginning of state 2.

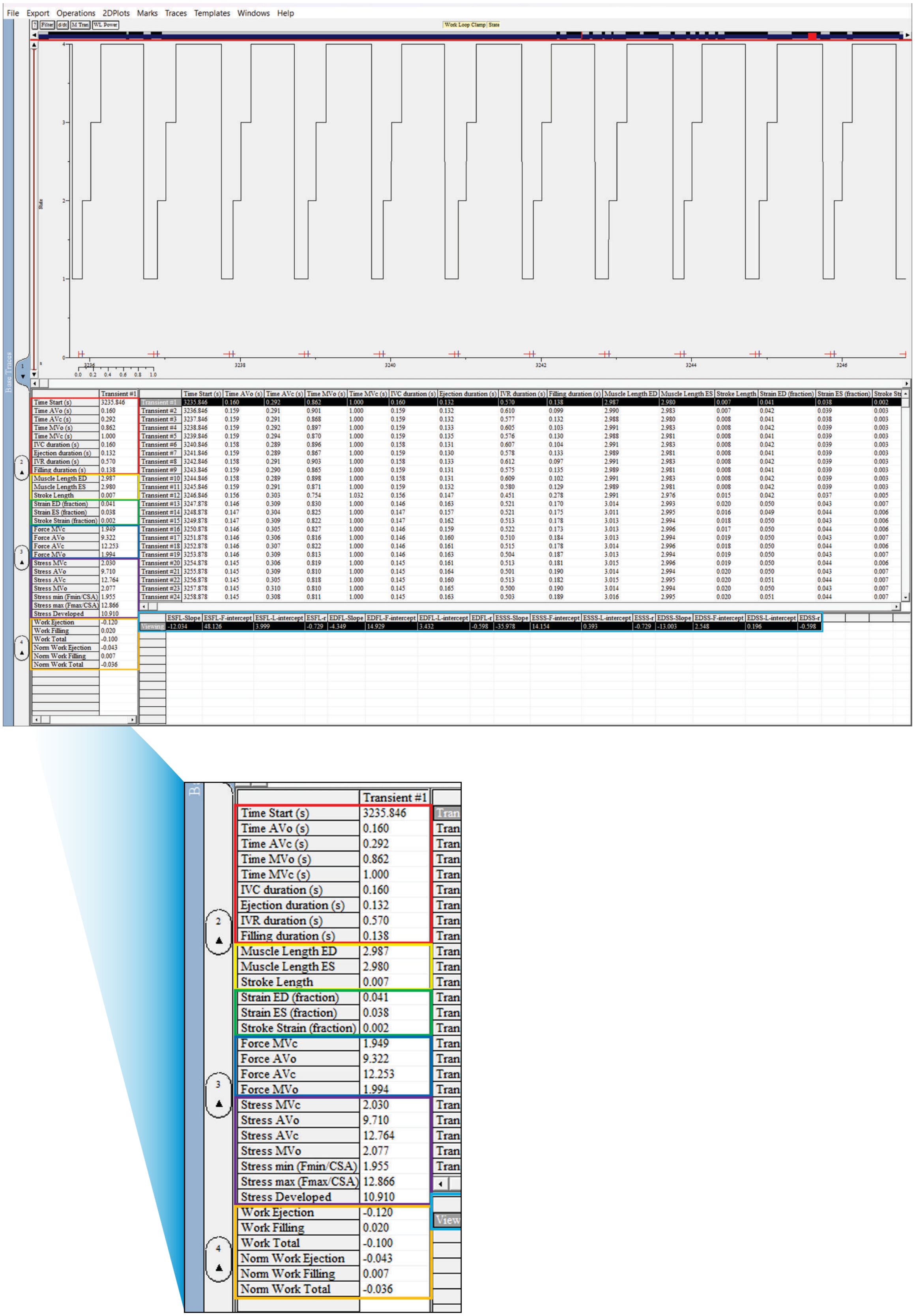
These timing-based parameters reflect the fundamental characteristics of the force-length loop and may serve as early indicators of changes in cardiac performance, such as delayed contraction or impaired relaxation.

Table 1. State Parameters. Timing and duration of work loop phases.

Parameter	Measure of
Time Start (s)	Time since the start of the experiment when the analysis begins
Time AVo (s)	Time when the aortic valve opens; marks the end of IVC
Time AVc (s)	Time when the aortic valve closes; marks the end of ejection
Time MVo (s)	Time when the mitral valve opens; start of filling
Time MVc (s)	Time when the mitral valve closes; the end of the full cycle
IVC duration (s)	Duration of isovolumic contraction (Time AVo – Time of Stimulus)
Ejection duration (s)	Duration of the ejection phase (Time AVc – Time AVo)
IVR duration (s)	Duration of isovolumic relaxation (Time MVo – Time AVc)
Filling duration (s)	Duration of the filling phase (Time MVc – Time MVo)

Analysis Outputs – State (cont.)

Fig 3. Screenshot of the Work loop Analysis in IonWizard. The top panel displays repeated states representing cardiac tissue work loops. The table below highlights calculated parameters grouped by category: State (red), Length (yellow), Strain (green), Force (blue), Stress (purple), Work (orange), and End-Systolic and End-Diastolic Relationships (light blue). All but End-Systolic and End-Diastolic Relationships are shown again in the zoomed inset below the main IonWizard screenshot.



Analysis Outputs (cont.)

2. Length

The second group of parameters describes values associated with tissue length, specifically the end-diastolic and end-systolic muscle lengths (Muscle Length ED and ES), along with the stroke length, which is the difference between the two (Figure 3, highlighted in yellow).

These parameters reflect the overall mechanical performance of the cardiac tissue. A larger stroke length typically corresponds to greater contractile shortening, indicating stronger mechanical function. In contrast, the ED and ES lengths offer insights into the tissue's ability to relax and contract effectively during each cycle. An increased ED length suggests better relaxation, while a decrease may indicate impaired relaxation or increased stiffness. Conversely, a lower ES length indicates stronger contraction, whereas a higher ES length points to reduced contractility.

Table 2. Length Parameters.

Parameter	Measure of
Muscle Length ED	Muscle length at the end of filling; reflects diastolic relaxation
Muscle Length ES	Muscle length at the end of contraction; reflects systolic shortening
Stroke Length	Difference between ED and ES length; reflects the ability of tissue to shorten and return

3. Strain

The third group of parameters describes strain, a measure of tissue deformation. Strain is calculated as the change in tissue length relative to the initial resting length and is presented as a unitless fraction. The outputs include strain at end-diastole (ED), end-systole (ES), and total stroke strain (Figure 3, highlighted in green). Strain ED reflects the muscle stretch prior to contraction; this reflects a combination of tissue stiffness and preload. Strain ES indicates the degree of shortening, which serves as a marker of contractile function. Total stroke strain is a measure of how effectively cardiac muscle contracts and relaxes. These measures provide a normalized contraction performance independent of muscle length, enabling direct comparison across different tissue preparations.

Analysis Outputs – Strain (cont.)

Table 3. Strain Parameters.

Parameter	Measure of
Strain ED (fraction)	Stretch before contraction; reflects compliance
Strain ES (fraction)	Degree of tissue shortening; reflects the contractile function
Stroke Strain (fraction)	Total strain amplitude; reflects overall tissue shortening across the cycle

4. Force

The fourth group of outputs includes the measured force at specific state transitions in the cardiac cycle (Figure 3, highlighted in blue). Force is reported as an absolute value and reflects contractility and tension. Because it is not normalized for tissue size, it is most useful for comparing the same preparation, such as before and after treatment. Force at MVc indicates passive tension at the end of diastolic filling, providing an indicator of passive stiffness. Force at AVo represents peak contractile strength at the start of ejection. Force at AVc reflects residual tension after ejection, related to the dynamics of relaxation. It could indicate a rapid or delayed relaxation. Force at MVo marks the baseline force after IVR, just before filling begins, indicating either impaired or efficient relaxation. Together, these values characterize both passive mechanical properties and active contractility of the tissue across the cardiac cycle.

Table 4. Force Parameters.

Parameter	Measure of
Force MVc	Passive stiffness at the end of filling; reflects the preset preload
Force AVo	Peak contractile force at the start of ejection; reflects the preset afterload
Force AVc	Residual force after ejection; related to relaxation dynamics
Force MVo	Baseline force at the end of relaxation; indicates relaxation efficiency

4. Stress

The fifth group describes tissue stress, calculated as the force divided by the cross-sectional area (muscle width x muscle thickness). Stress is reported at each state transition (MVc, AVo, AVc, and MVo), as well as the minimum, maximum, and total stress developed during the work loop (Figure 3, highlighted in purple).

Analysis Outputs – Stress (cont.)

> **Note:** To obtain meaningful force measurements, be sure to enter the dimensions of the cardiac slice during setup. These values are user-defined and are essential for accurate normalization and interpretation of results.

Unlike force, stress provides a normalized measure of tissue mechanics, allowing for direct comparison between slices. Stress at MVc represents the passive stiffness of the tissue at the end of the filling. Stress at AVo indicates peak contractile strength at the start of ejection. Stress at AVc reflects the residual tension after ejection and is related to the dynamics of relaxation. A lower stress at AVc may indicate rapid relaxation, while a higher stress at AVc may suggest delayed or impaired relaxation. Stress at MVo represents the baseline stress after relaxation, prior to filling, indicating either impaired or efficient relaxation. Minimum and maximum stress values reflect the full dynamic range of tension during the cycle, while developed stress (maximum – minimum) indicates the total contractile output over one loop.

Table 5. Stress Parameters.

Parameter	Measure of
Stress MVc	Normalized passive stiffness at the end of filling
Stress AVo	Normalized peak contractile stress at the start of ejection
Stress AVc	Normalized residual stress after ejection; related to relaxation efficiency
Stress MVo	Normalized baseline stress after relaxation; before filling
Stress min (Fmin/CSA)	Normalized minimum stress during the loop; usually at the end of relaxation
Stress max (Fmax/CSA)	Normalized maximum stress during the loop; usually at peak contraction
Stress Developed	Normalized total developed stress (Max – Min); reflects overall contractile performance

6. Work

The sixth group of output parameters describes mechanical work, calculated as the area enclosed by the force-length loop, as shown in Figure 3 (orange). The area represents the stroke work, the mechanical energy produced by the cardiac slice during one full contraction cycle and serves as an indicator of cardiac efficiency.

Analysis Outputs – Work (cont.)

Work is defined as the product of force and stroke length, while normalized work is corrected for cross-sectional area, allowing for comparisons across tissues of different sizes. Both work and normalized work are further divided into ejection (work during contraction), filling (work during relaxation), and total.

In general, a greater work loop area corresponds to stronger contraction and more efficient mechanical function. When combined with other parameters (e.g., stress and strain), work provides a meaningful measure of cardiac energy utilization and efficiency, especially in the context of disease modeling or treatment response.

Table 6. Work Parameters.

Parameter	Measure of
Work Ejection	Mechanical work during contraction
Work Filling	Mechanical work during relaxation
Work Total	Net work over one full contraction–relaxation cycle (generally negative, as ejection work > filling work)
Norm Work Ejection	Work Ejection normalized to the cross-sectional area
Norm Work Filling	Work Filling normalized to the cross-sectional area
Norm Work Total	Work Total normalized to the cross-sectional area

Note: Work is calculated based on muscle length and force. Muscle shortening during contraction results in negative work values, while muscle lengthening during relaxation produces positive work values.

7. End-Systolic and End-Diastolic Relationships

While the previous six output groups describe the cardiac tissue properties within a single contraction cycle, the end-systolic force-length (ESFLR) and end-systolic stress-strain (ESSSR) relationships are useful measures of how the tissue behaves across multiple cycles with varying loading conditions (Figures 3 and 4, light blue).

	ESFL-Slope	ESFL-F-intercept	ESFL-L-intercept	ESFL-r	EDFL-Slope	EDFL-F-intercept	EDFL-L-intercept	EDFL-r
Viewing	-12.034	48.126	3.999	-0.729	-4.349	14.929	3.432	-0.598

	ESSS-Slope	ESSS-F-intercept	ESSS-L-intercept	ESSS-r	EDSS-Slope	EDSS-F-intercept	EDSS-L-intercept	EDSS-r
Viewing	-35.978	14.154	0.393	-0.729	-13.003	2.548	0.196	-0.598

Fig 4. End-Systolic and End-Diastolic Relationships. IonWizard analysis outputs are shown in light blue.

Analysis Outputs – End-Systolic and End-Diastolic Relationships (cont.)

These relationships are generated by analyzing multiple work loops under different mechanical loads, simulating the response of cardiac tissue in conditions such as exercise or pressure/volume overload. They reflect the intrinsic mechanical behavior of the myocardium and provide load-independent assessments of both contractile strength (systolic) and passive stiffness (diastolic).

The force-length (FL) relationship describes how absolute force changes with muscle length and is most useful when comparing conditions within the same sample (*i.e.,* before and after intervention). The stress-strain (SS) relationship is the normalized equivalent, adjusting for the cross-sectional area to enable comparison between different tissue slices or groups. End-systolic and end-dialostolic force-length relationships correspond to the slopes of points tangential to work loops under differing mechanical loads (Figure 5).

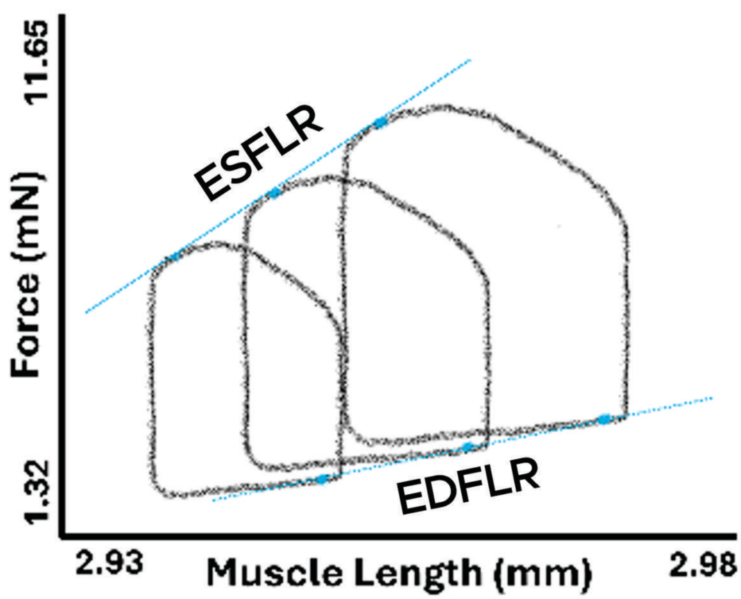


Figure 5. End-Systolic and End-Diastolic Relationship Slopes. The slopes of points tangential to work loops under differing mechanical loads reveals the ES/EDFLR.

While the slope of these relationships is the primary functional readout, the intercepts can also provide useful context, particularly when slopes are similar, by revealing baseline shifts in force or resting length, which may indicate tissue remodeling or changes in passive mechanical properties.

Analysis Outputs – End-Systolic and End-Diastolic Relationships (cont.)

A steeper slope in force-length and stress-strain relationships indicates higher stiffness or elastance, and therefore lower compliance. Clinically, changes in diastolic compliance are often associated with pathology:

- A steeper slope (lower compliance) may signal tissue stiffening, as seen in hypertrophic cardiomyopathy.
- A shallower slope (higher compliance) may reflect reduced contractile function or structural weakening, as occurs in dilated cardiomyopathy.

Table 7. End-Systolic and End-Diastolic Relationship Parameters.

Abbreviation	Relationship	Measure of	Use as
ESFL	End-Systolic Force Length	Force vs length at end of contraction	Load-independent measure of contractile strength
EDFL	End-Diastolic Force-Length	Force vs length at end of filling	Stiffness or compliance
ESSS	End-Systolic Stress-Strain	Stress vs strain at end of contraction	Normalized load-independent measure of contractile strength
EDSS	End-Diastolic Stress-Strain	Stress vs strain at end of filling	Normalized stiffness or compliance

Table 8. Parameters Derived from Force–Length Relationships.

Parameter	Meaning	Interpretation
Slope	Slope of linear fit	Primary readout; indicates stiffness (diastole) or contractile strength (systole) depending on the phase analyzed
F-intercept (Force)	Force when length =0	Secondary; indicates contractile reserve or change in force generation
L-Intercept (Length)	Length when force=0	Secondary; reflects baseline length and possible shifts in tissue compliance
R (Correlation Coefficient)	Goodness of fit for linear regression	Values closer to 1 are more indicative of the reliability of the correlation

Clinical Translation

In the cardiac slice system, preload and afterload are defined by the user. As a result, changes in measured parameters reflect the intrinsic mechanical behavior of the tissue under controlled loading conditions. The table below summarizes how key pathological traits correspond to output metrics from the IonWizard Work Loop Analysis. This overview is not exhaustive but serves as a guide to interpreting mechanical data in a disease-relevant context. For a more complete understanding of myocardial function, we recommend evaluating multiple parameters across different mechanical domains.

Table 8. Representative Cardiac Conditions and Distinct Mechanical Readouts.

Pathological trait	Associated conditions	Parameters of interest
Increased passive stiffness	Hypertrophic and restrictive cardiomyopathy, HFpEF, fibrosis	↑ Force/Stress MVc, ↑ EDFL/EDSS Slope, ↓ Strain ED
Impaired relaxation	Diastolic dysfunction, HFpEF, calcium handling defects, late ischemia	↑ Force/Stress MVo, ↑ Force/Stress AVc, ↑ IVR Duration
Reduced contractility	HFrEF, dilated cardiomyopathy	↓ Force/Stress AVo, ↓ Stroke Length, ↓ Stress Developed, ↓ Work, ↓ ESFL/ESSS Slope
Increased afterload	Pressure overload (e.g., aortic stenosis, concentric hypertrophy), exercise	↑ Force/Stress AVo, ↑ Work Ejection, ↑ ESFL /ESSS Slope
Chamber dilation	Chronic aortic and mitral regurgitation, eccentric hypertrophy, dilated cardiomyopathy	↑ Muscle Length ED, ↑ Stroke Length, ↓ Work Ejection, ↑ Strain ED

HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction.

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