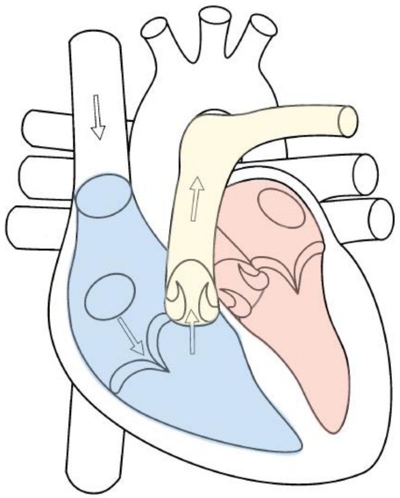


A machine learning approach to predict emergent right ventricular pressure-volume loop phenotypes in pulmonary hypertension

Team Lavender

Members: Nikita Sivakumar, Cindy Zhang, Connie Chang-Chien, Pan Gu, Yikun Li, Yi Yang

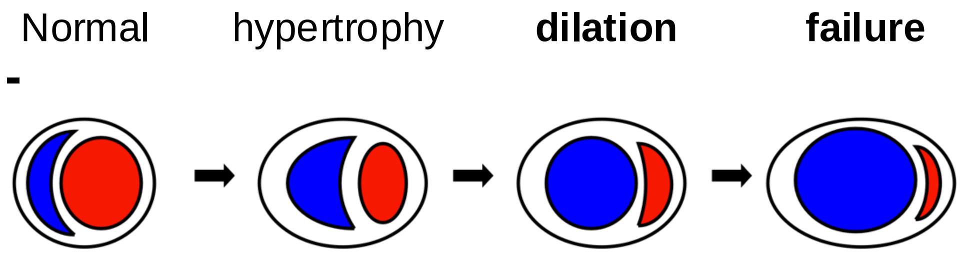
Clinical PI: Catherine Simpson

Engineering PIs: Joseph Greenstein, Casey Taylor

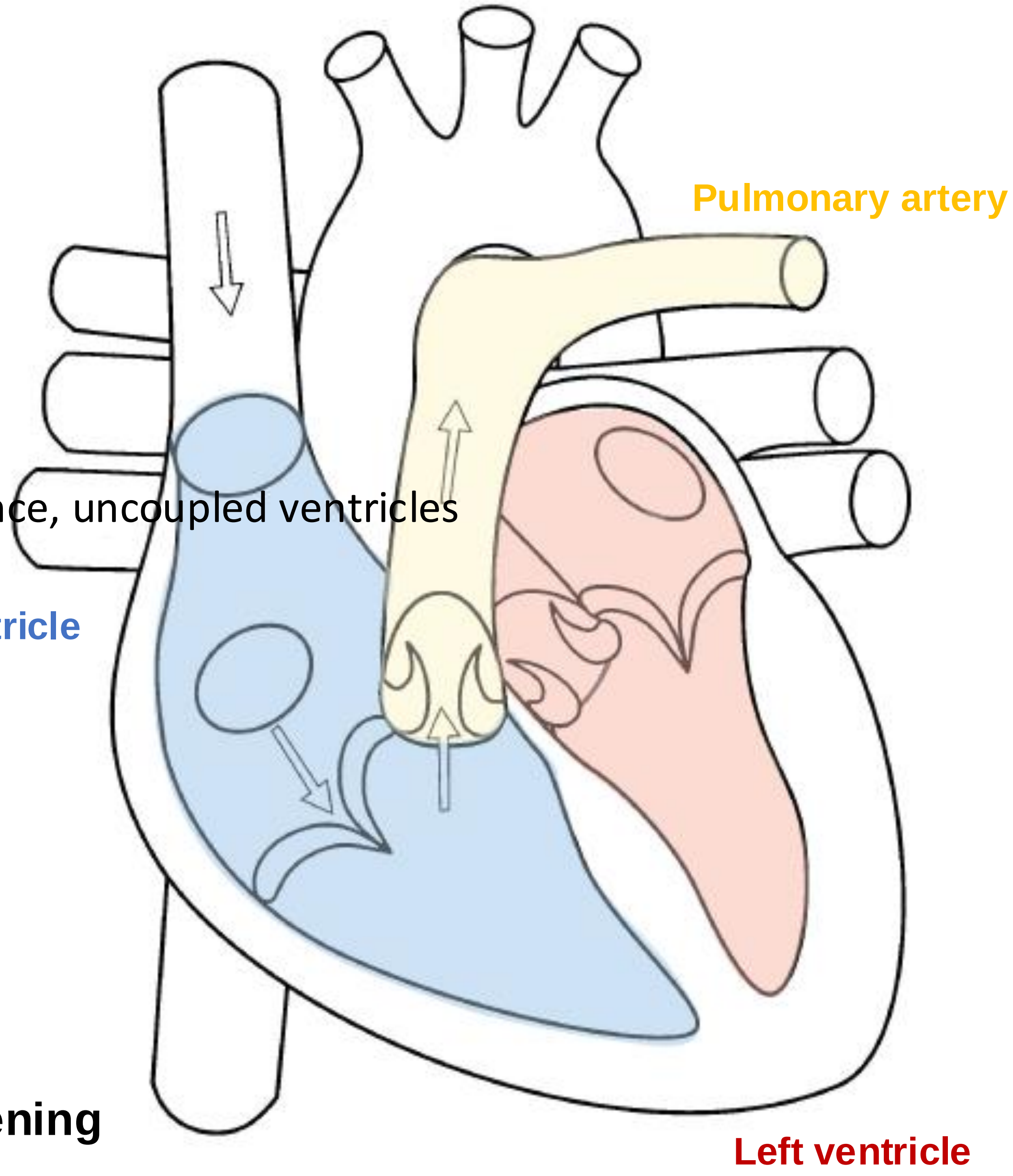
Pulmonary hypertension

PH defined hemodynamically by a mean pulmonary arterial pressure (mPAP) of > 20 mmHg at rest

Increased afterload leading to hypertrophy
Induces remodeling of the right ventricle
- Adaptive: concentric hypertrophy, microcirculation preservation,
- Maladaptive: eccentric hypertrophy, oxygen demand/supply imbalance, uncoupled ventricles

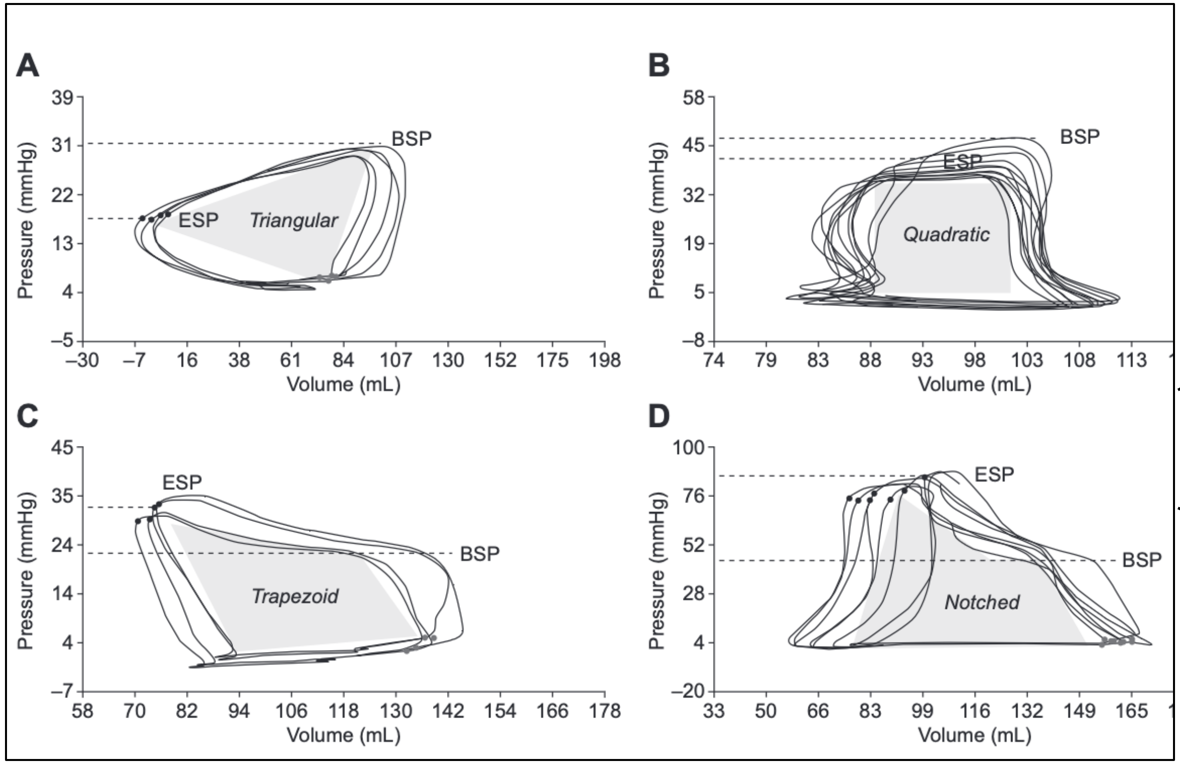


Credit: Catherine Simpson



Maladaptive RV-PA coupling remodeling drives clinical worsening
High prognostic value, better characterization is needed

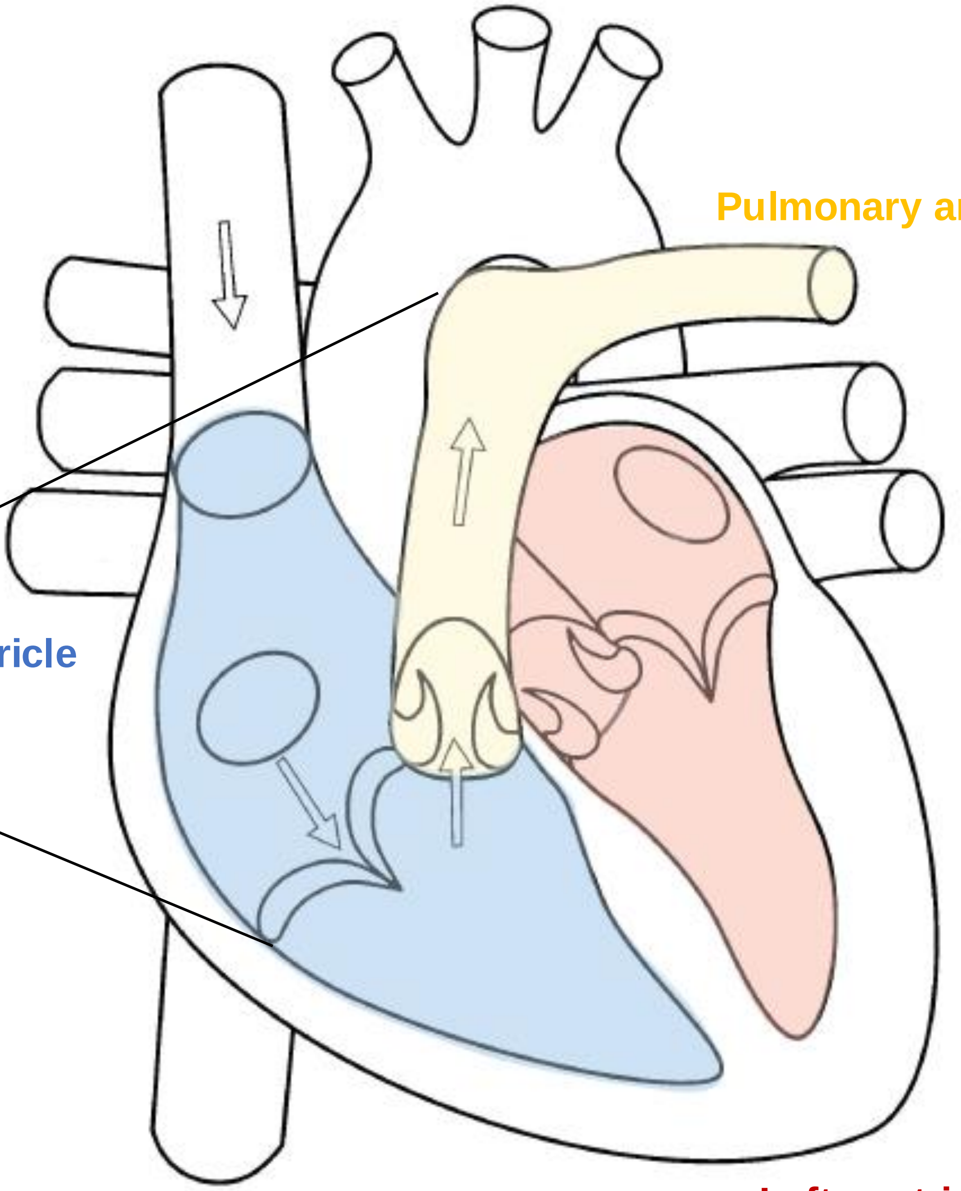
Measuring RV function



Richter, Manuel J., et al. "Right ventricular pressure-volume loop shape and systolic pressure change in pulmonary hypertension." American Journal of Physiology-Lung Cellular and Molecular Physiology 320.5 (2021): L715-L725.

Pulmonary artery

Right ventricle



Left ventricle

Multi-beat pressure-volume loops are the gold standard for assessing RV-PA coupling, can measure ratio of elastances

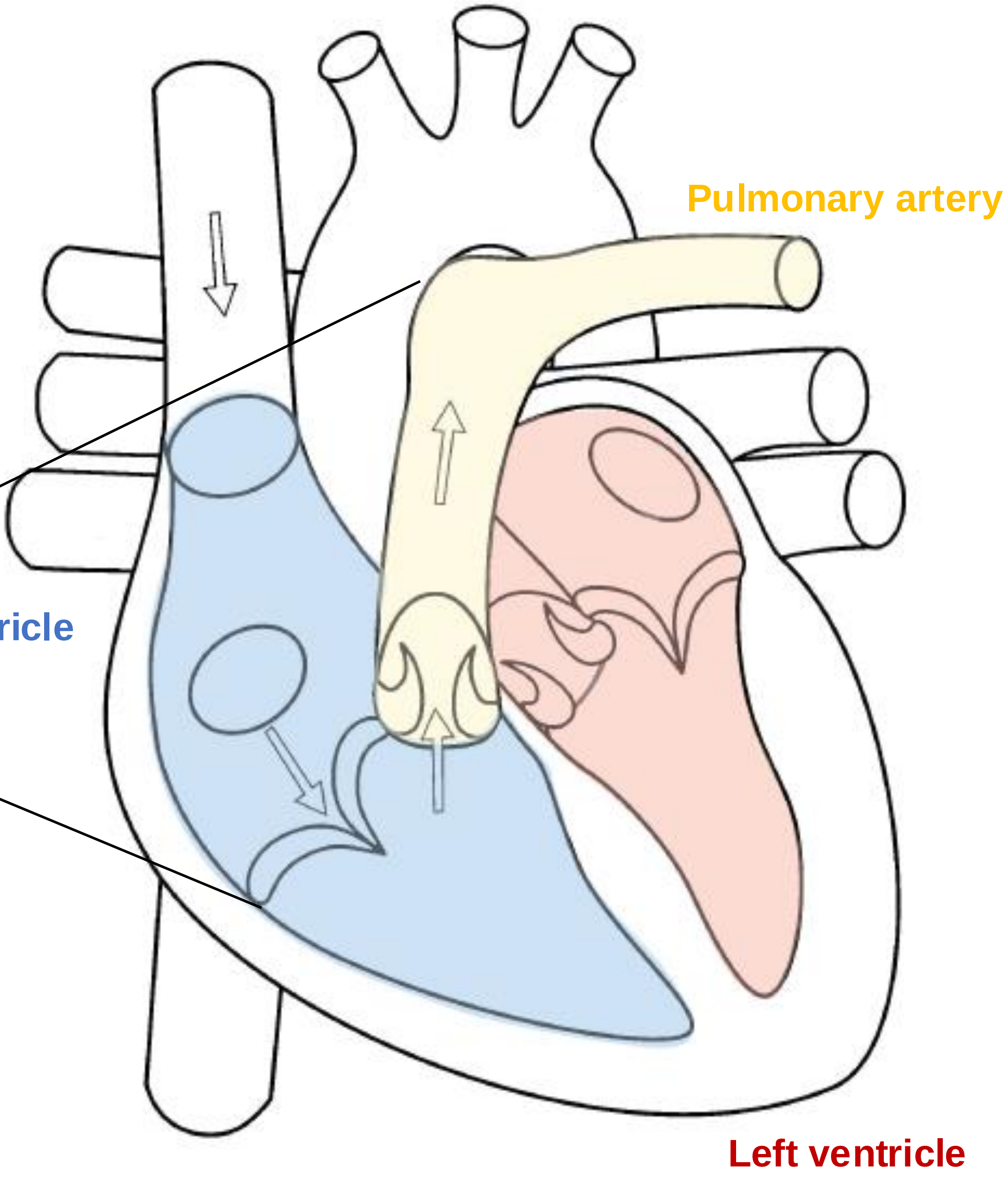
Measuring RV function

Right heart catheterization (RHC)

Magnetic resonance imaging (MRI)

Echocardiogram (ECHO)

Metabolomics



Conventional clinical measurements for RV function assessment. But do not include pressure-volume capabilities

Pulmonary hypertension clinical classifications

Five clinical classifications based on etiology stratify patients for treatment

Pulmonary vasodilators

Diuretics

Oxygen, Inhalers

Surgery

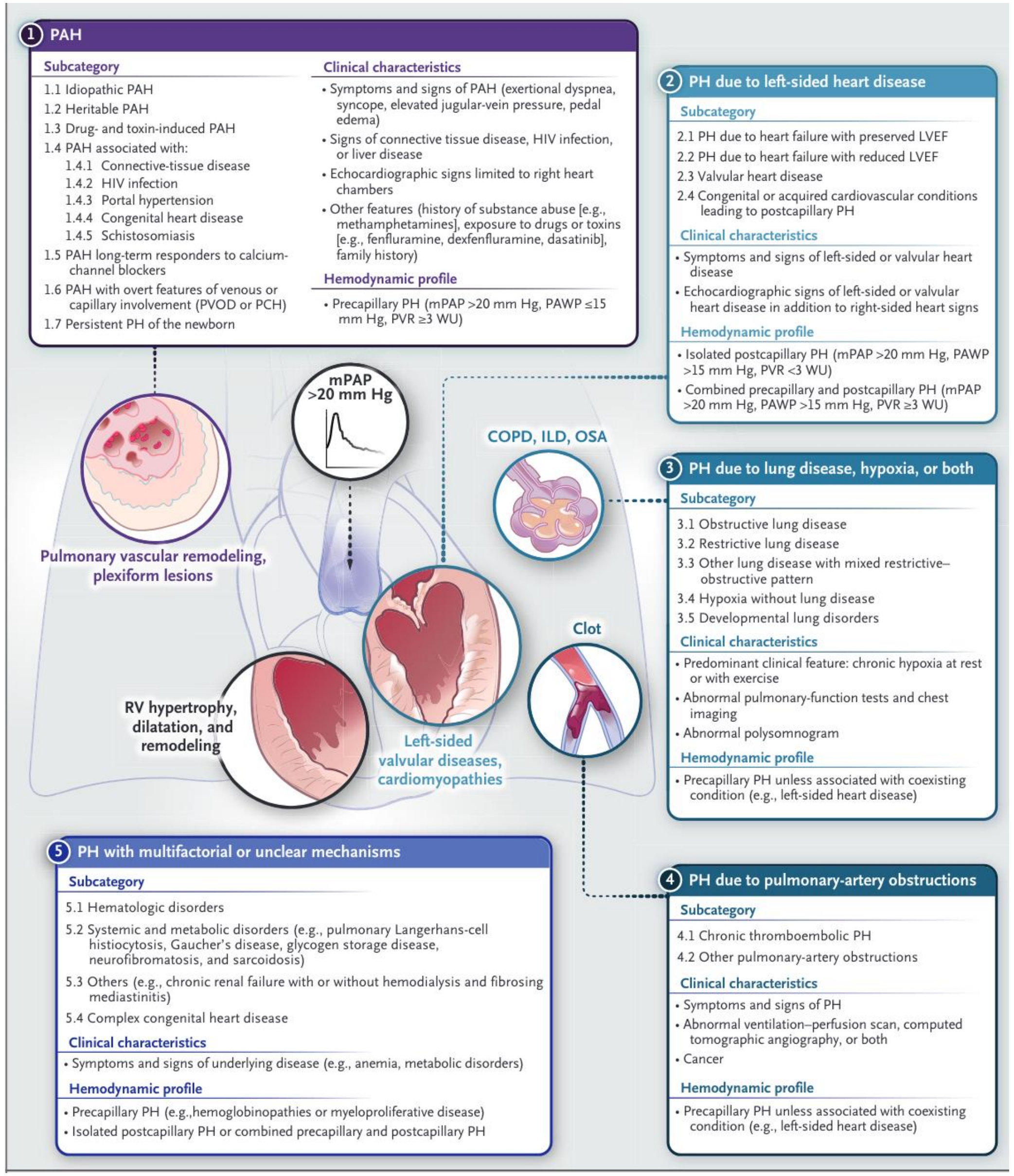
TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH (table 3)
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers (table 4)
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions (table 6)
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms (table 7)
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

Simonneau, et al. *European Respiratory Journal* 53.1 (2019).

We hypothesize that underlying etiology does not capture differences in RV state



Hassoun, Paul M. "Pulmonary arterial hypertension." New England Journal of Medicine 385.25 (2021): 2361-2376.

Significance & Innovation

1% of the global population is diagnosed with PH

10% of population above 65 years of age have PH

PH is a heterogeneous disease with a multitude of causal and contributing factors

The tale of the right ventricle and pulmonary hypertension

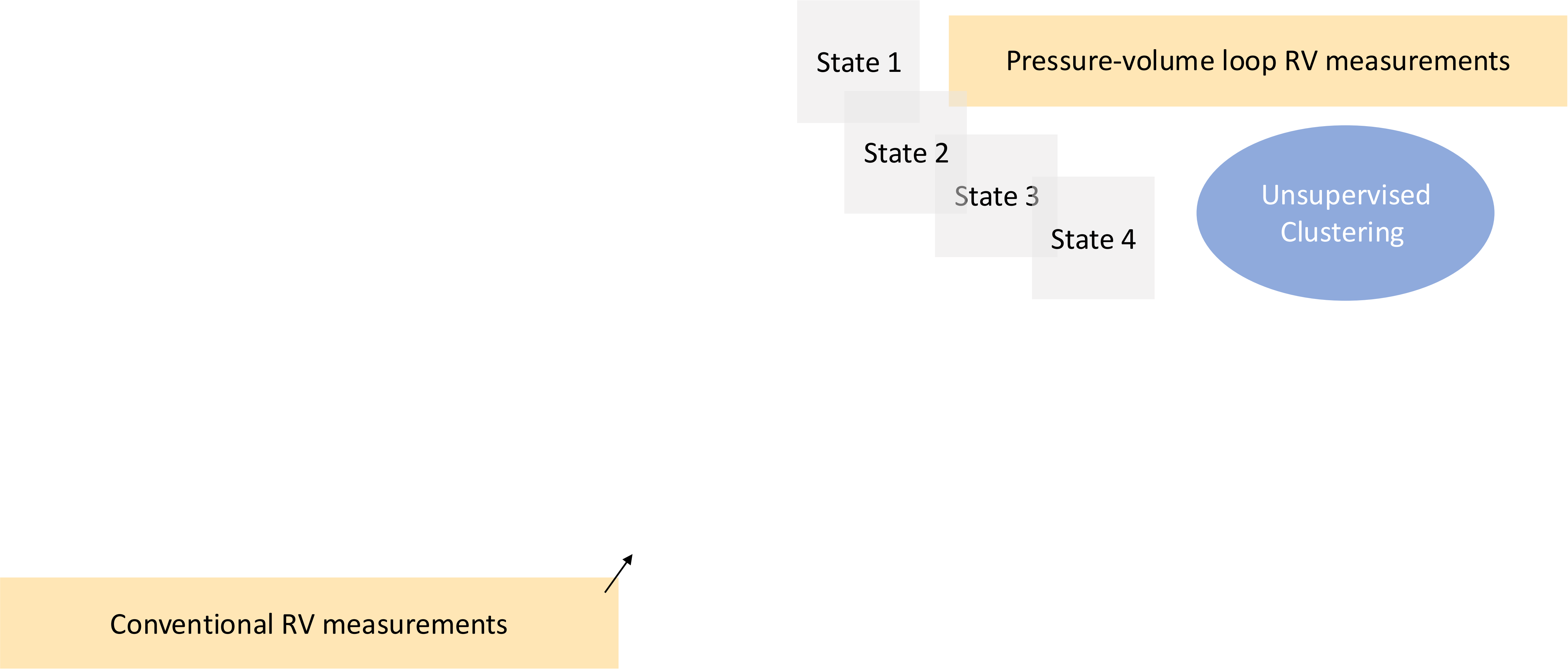
Can we map accessible right ventricle measurements to a dataset of advanced pressure-volume loop measurements of the right ventricle in a way that yields meaningful predictive insights about PH prognosis?

Pressure-volume loop RV measurements

Conventional RV measurements

The tale of the right ventricle and pulmonary hypertension

Can we map a dataset of "conventional" right ventricle measurements to a dataset of advanced pressure-volume loop measurements of the right ventricle in a way that yields meaningful predictive insights about PH prognosis?



The tale of the right ventricle and pulmonary hypertension

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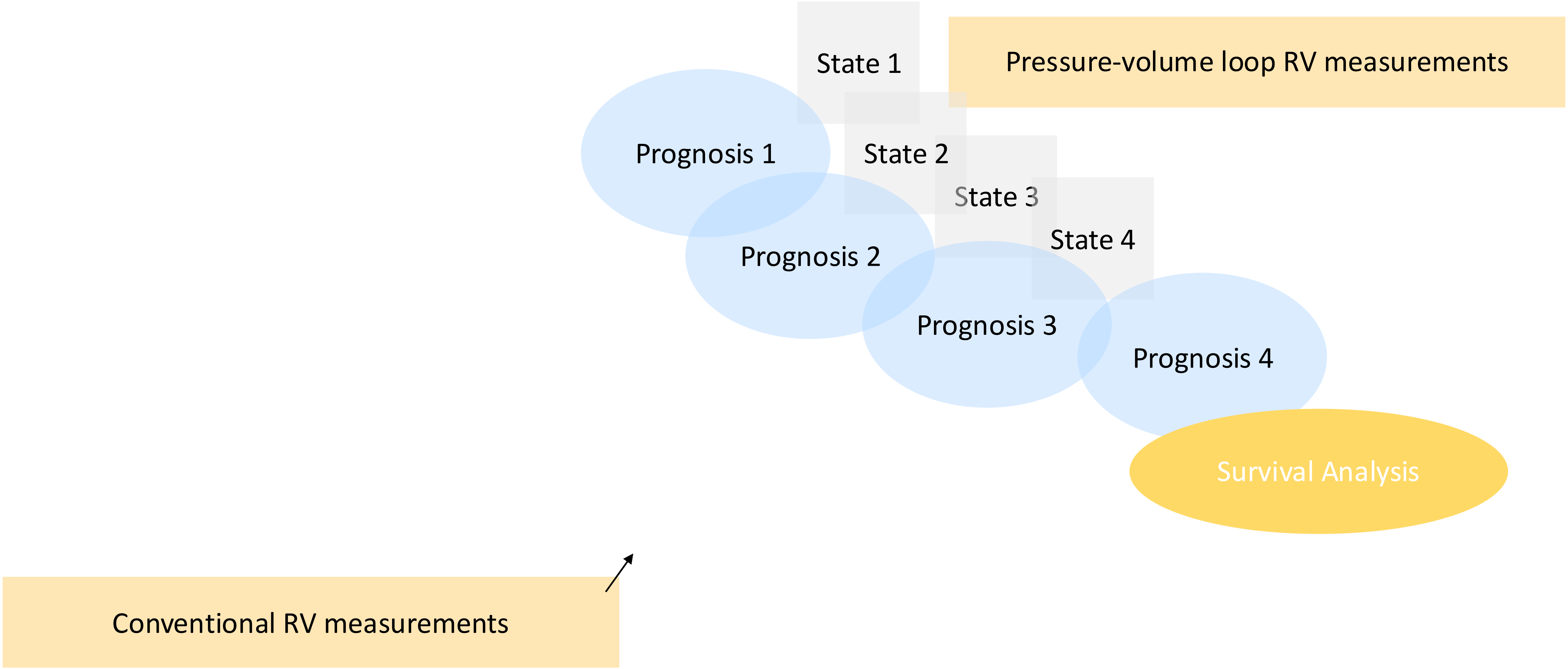
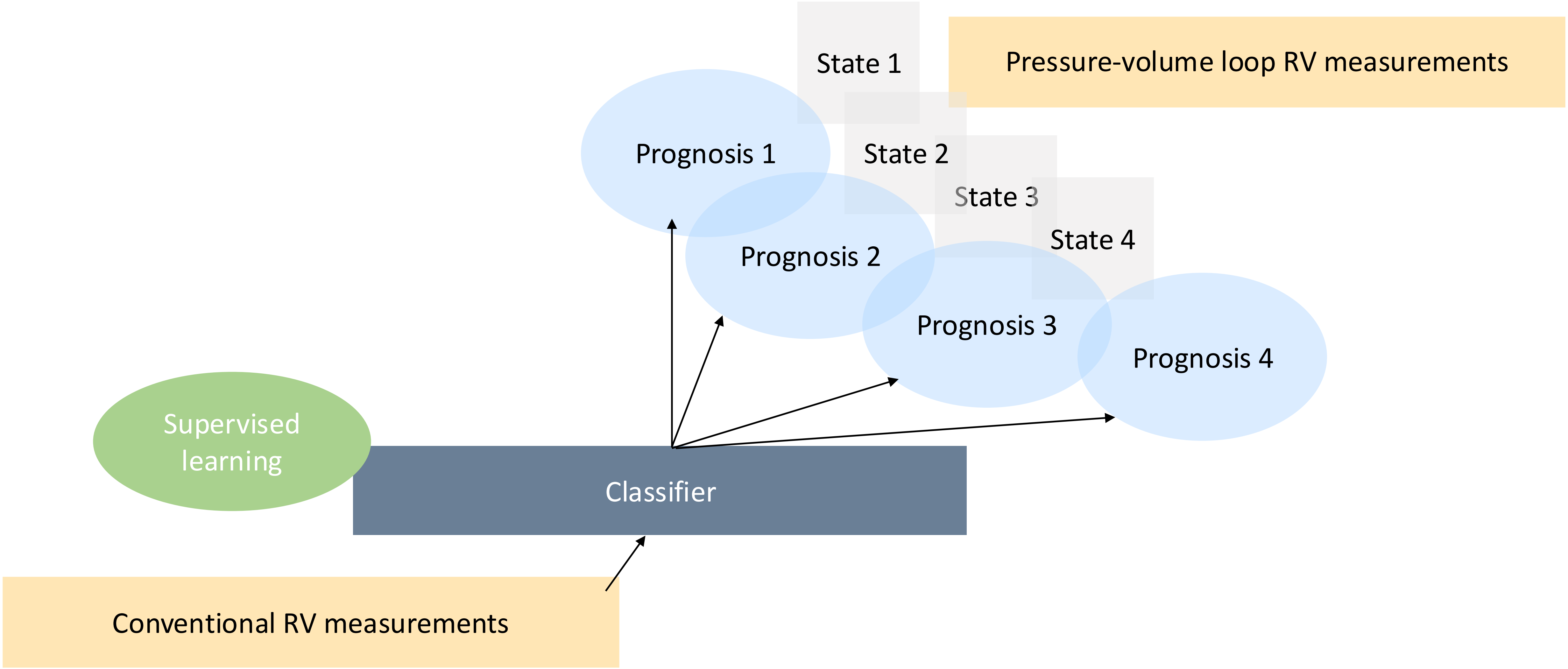


The tale of the right ventricle and pulmonary hypertension

Can we map a dataset of "conventional" right ventricle measurements to a dataset of advanced pressure-volume loop measurements of the right ventricle in a way that yields meaningful predictive insights about PH prognosis?

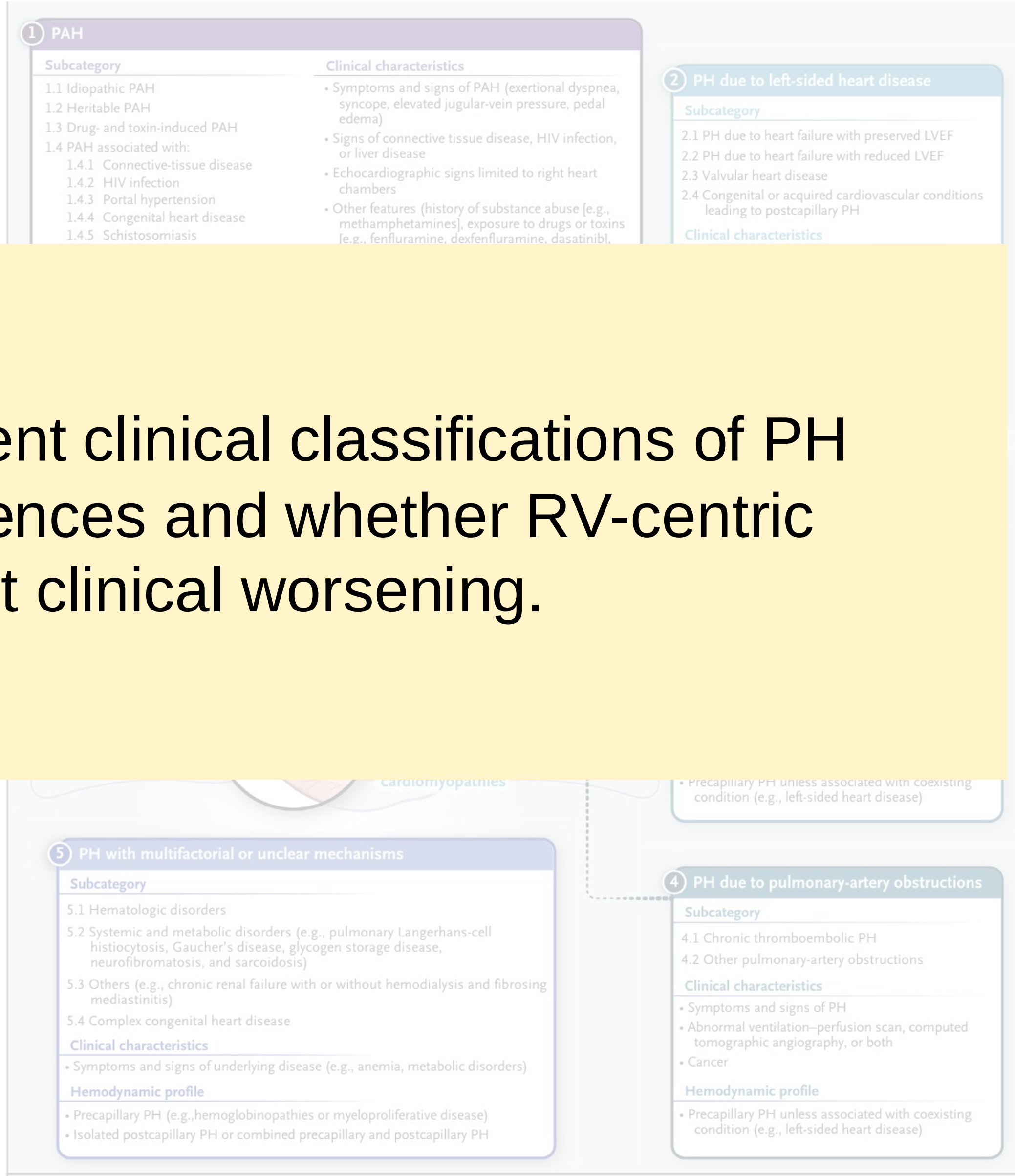


Pulmonary hypertension clinical classifications

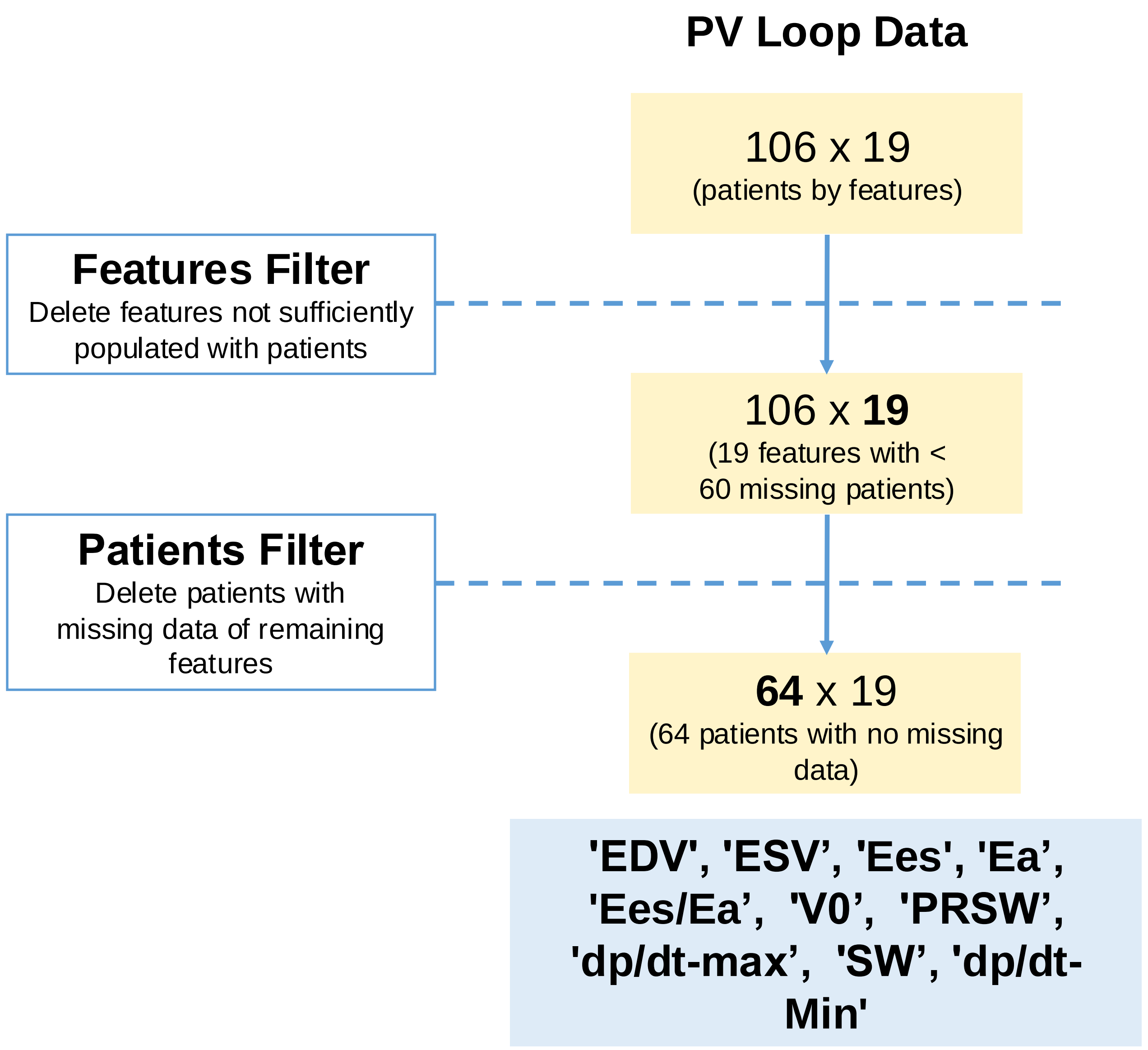
Five clinical classifications based on etiology stratify patients for treatment

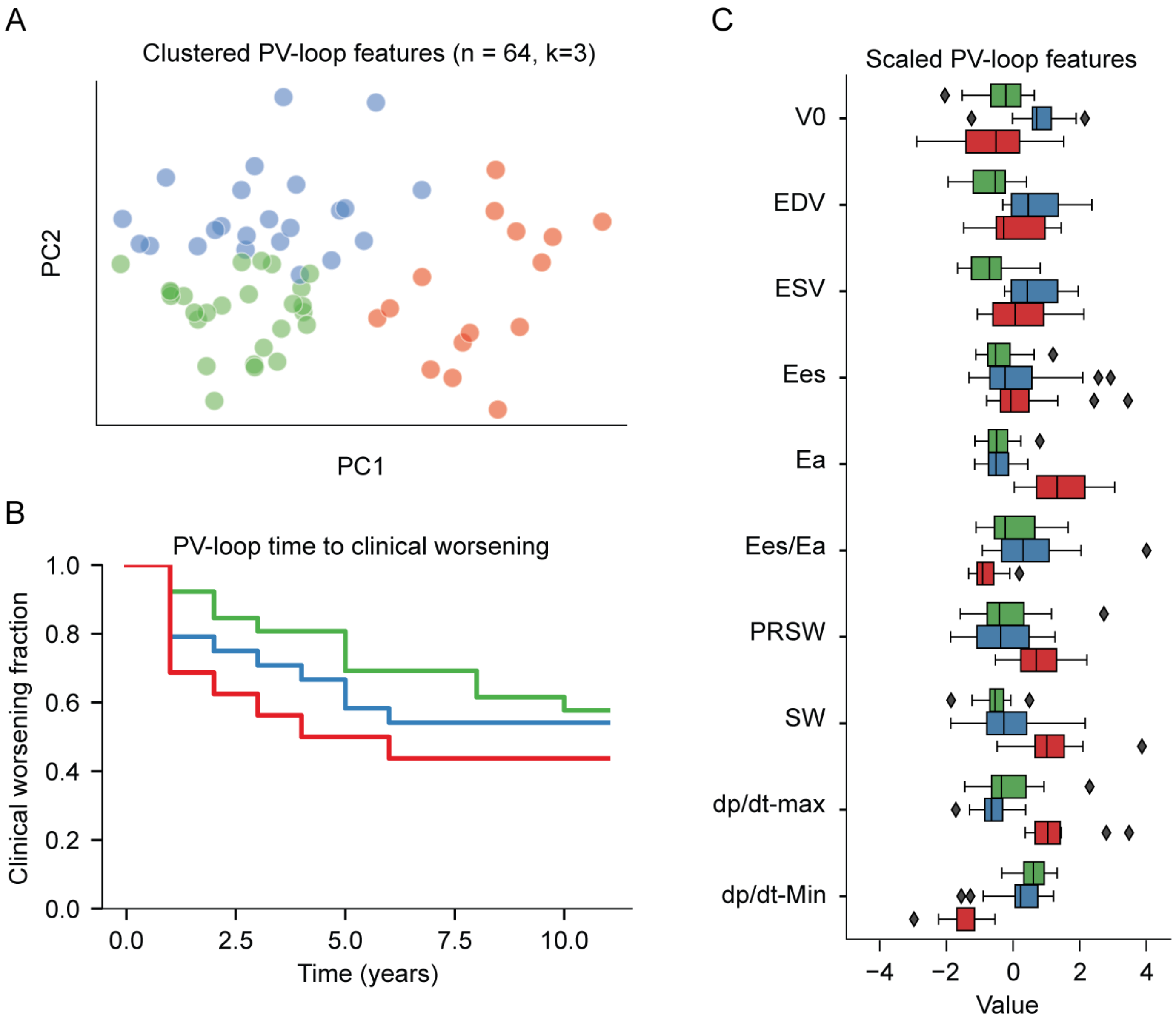
Aim 1. Demonstrate the extent to which current clinical classifications of PH distinguish underlying pathobiological differences and whether RV-centric measurements could better predict clinical worsening.

The underlying etiology may not capture differences in RV state



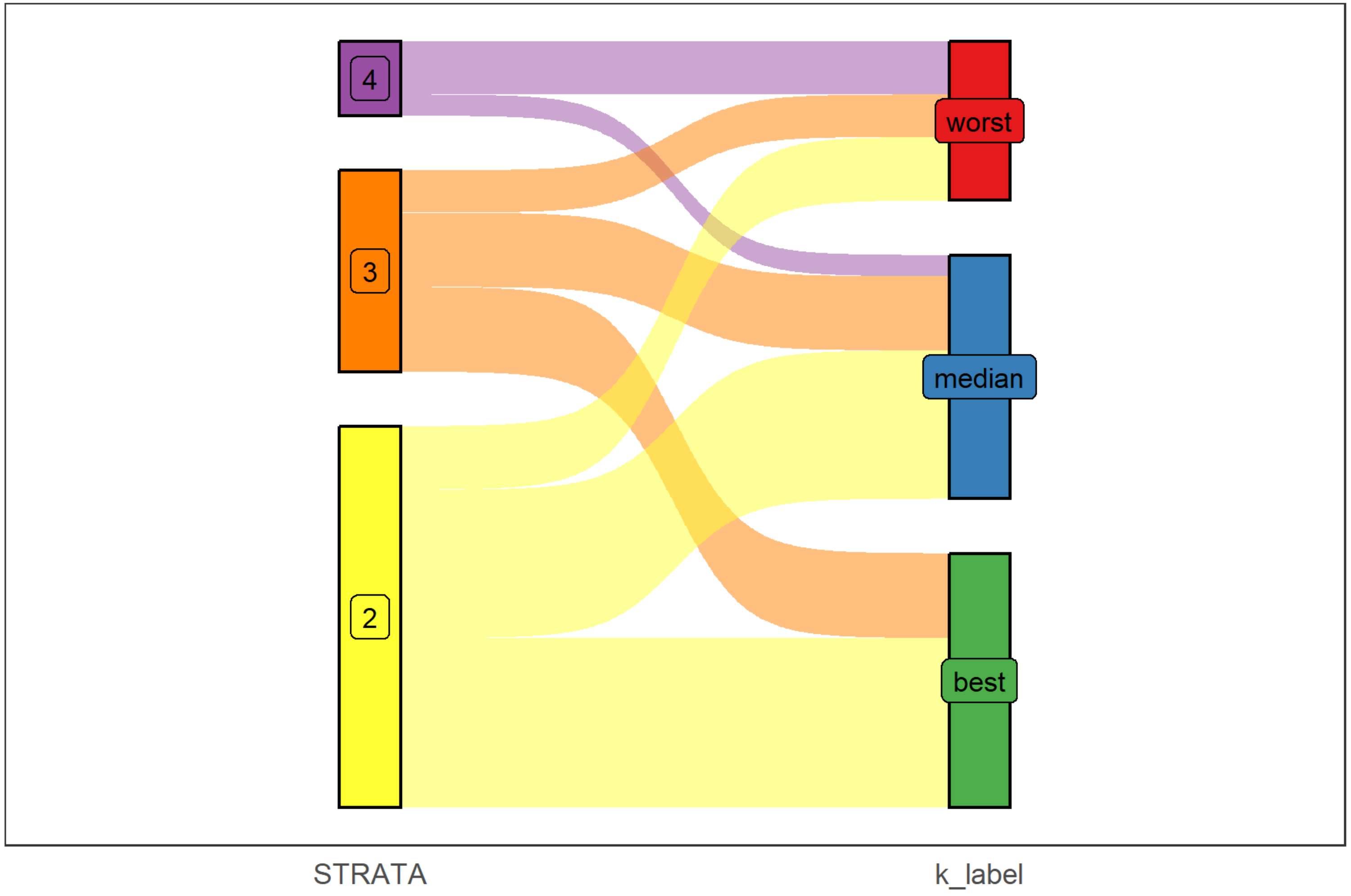
Hassoun, Paul M. "Pulmonary arterial hypertension." New England Journal of Medicine 385.25 (2021): 2361-2376.


PV Loop Data
106 x 19
(patients by features)
Features Filter
Delete features not sufficiently populated with patients
106 x 19
(19 features with < 60 missing patients)
Patients Filter
Delete patients with missing data of remaining features
64 x 19
(64 patients with no missing data)
'EDV', 'ESV', 'Ees', 'Ea', 'Ees/Ea', 'V0', 'PRSW', 'dp/dt-max', 'SW', 'dp/dt-Min'



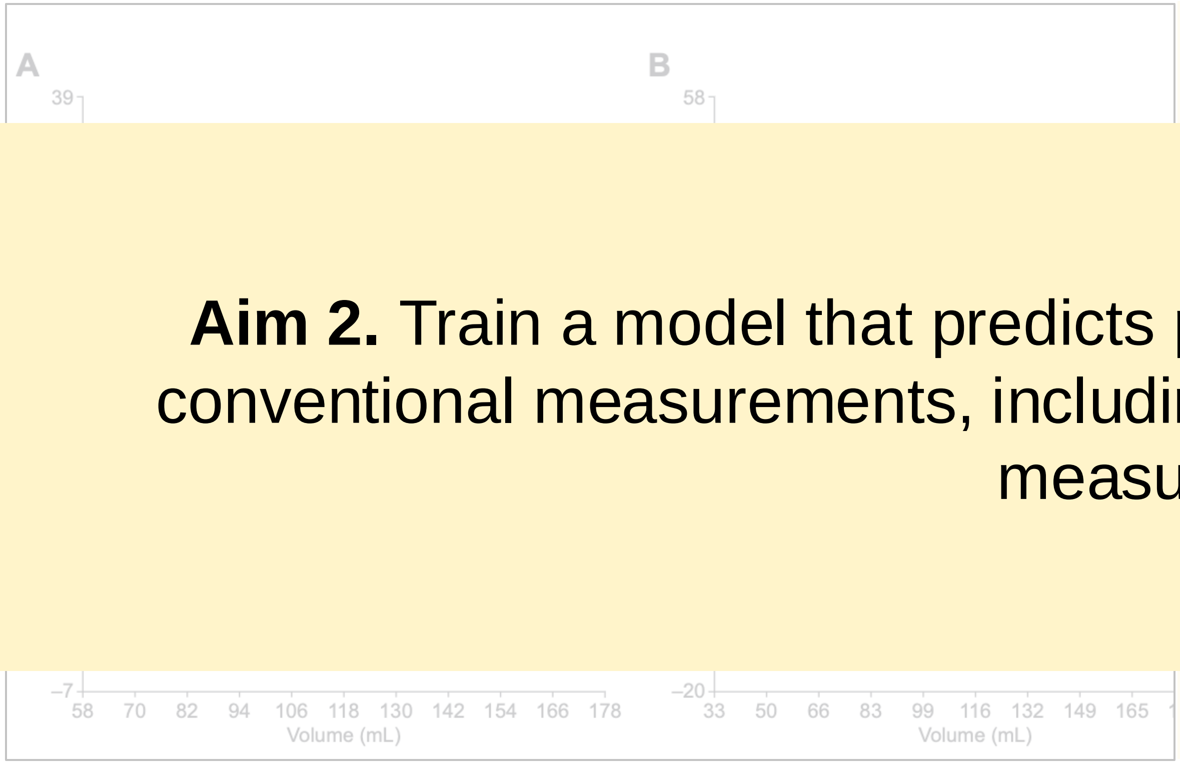
The clusters produced by unsupervised clustering have significantly different survival rates

	best	median	worst
EDV	119.73 +/- 23.0	173.0 +/- 33.0	149.3 +/- 36.0
ESV	53.75 +/- 18.0	95.86 +/- 24.0	84.69 +/- 34.0
Ees	0.59 +/- 0.0	0.8 +/- 0.0	0.86 +/- 0.0
Ea	0.54 +/- 0.0	0.53 +/- 0.0	1.41 +/- 0.0
Ees/Ea	1.24 +/- 1.0	1.6 +/- 1.0	0.65 +/- 0.0
V0	-9.72 +/- 29.0	35.5 +/- 28.0	-24.46 +/- 52.0
PRSW	20.21 +/- 7.0	19.16 +/- 8.0	28.18 +/- 7.0
dp/dt-max	425.15 +/- 112.0	370.78 +/- 67.0	615.51 +/- 118.0
SW	1790.65 +/- 579.0	2276.27 +/- 1122.0	4019.41 +/- 1296.0
dp/dt-Min	-347.97 +/- 84.0	-413.16 +/- 142.0	-733.49 +/- 121.0



Existing clinical paradigms do not distinguish underlying pathobiological differences

Clinical need



Richter, Manuel J., et al. "Right ventricular pressure-volume loop shape and systolic pressure change in pulmonary hypertension." American Journal of Physiology-Lung Cellular and Molecular Physiology 320.5 (2021): L715-L725.

Right heart catheterization (RHC)

Aim 2. Train a model that predicts pressure-volume loop shape based on conventional measurements, including right heart catheter, MRI, and ECHO measurements.

Metabolomics

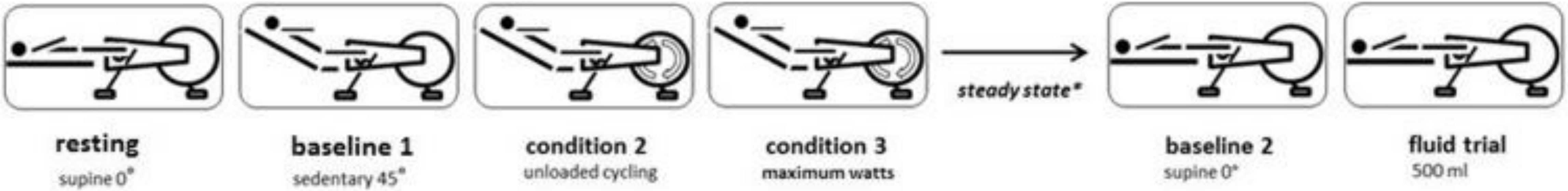
We hypothesize that conventionally measured RV variables map to distinct PV-loops and this relationships could support a new paradigm for clinical classification of PH.

RHC measurements at rest and with exercise

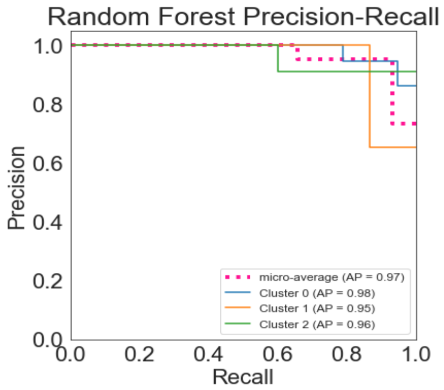
Exercise RHC

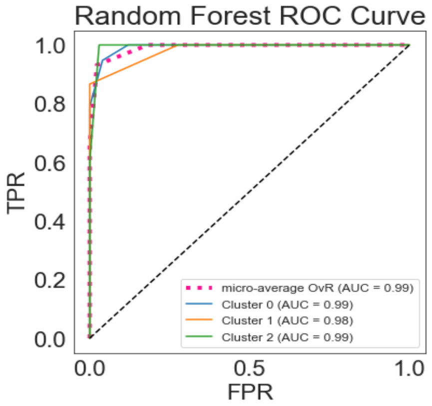
Rest RHC

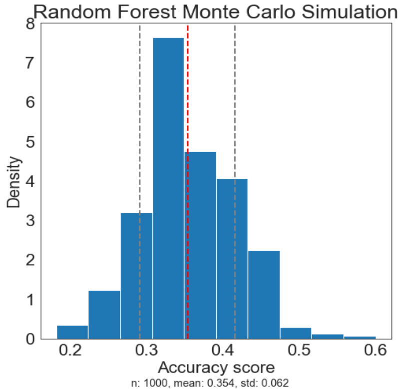
Fluid Challenge

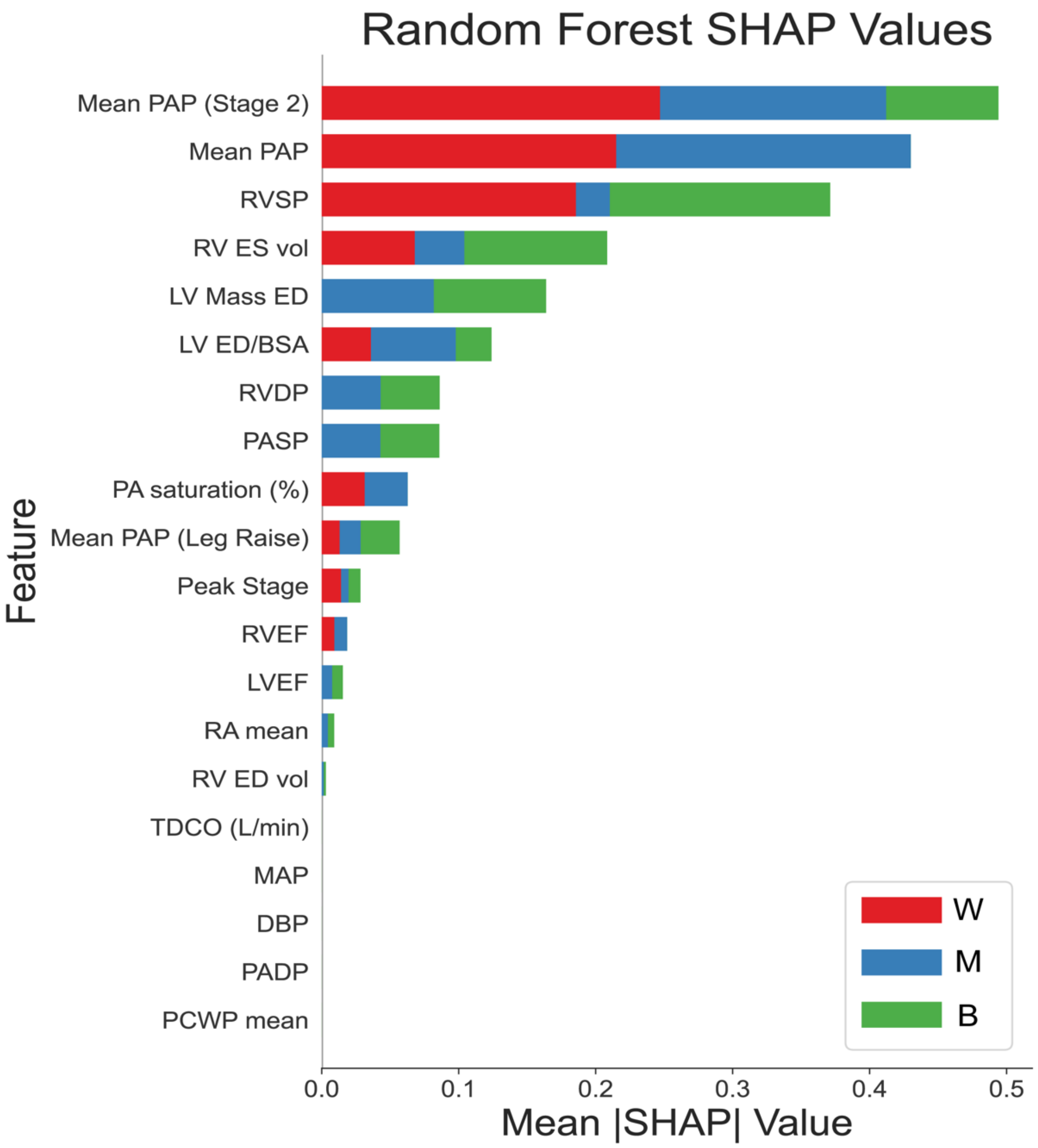


* Measurement after sufficient recovery time (at least 10 minutes); Alignment of oxygen uptake and vital Signs



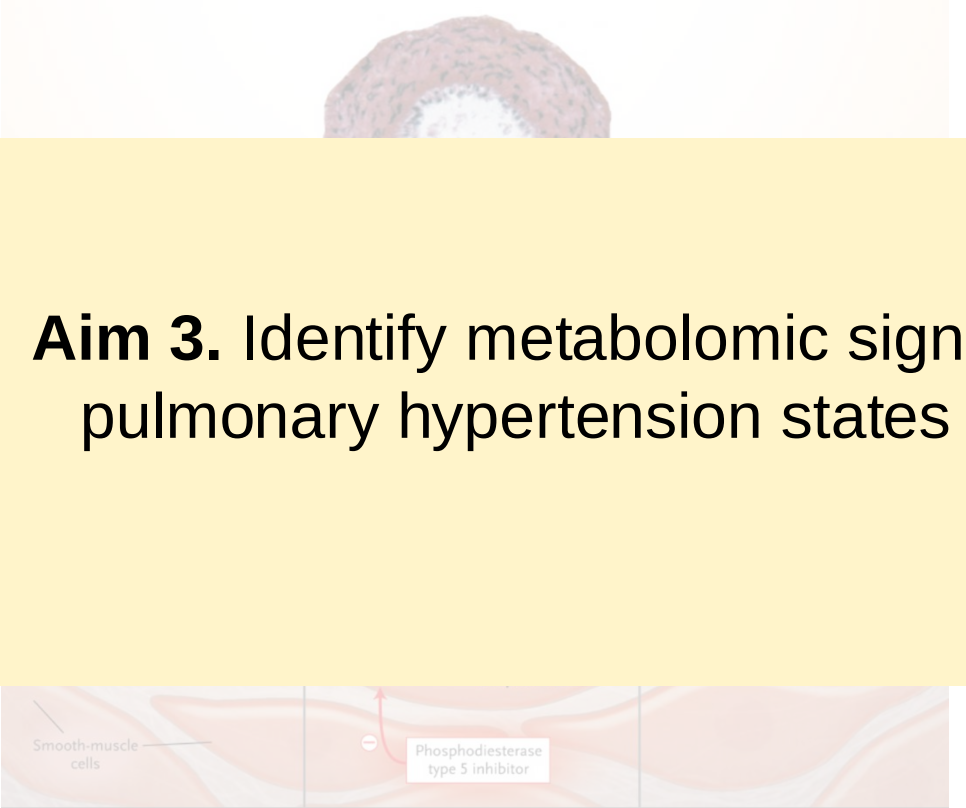


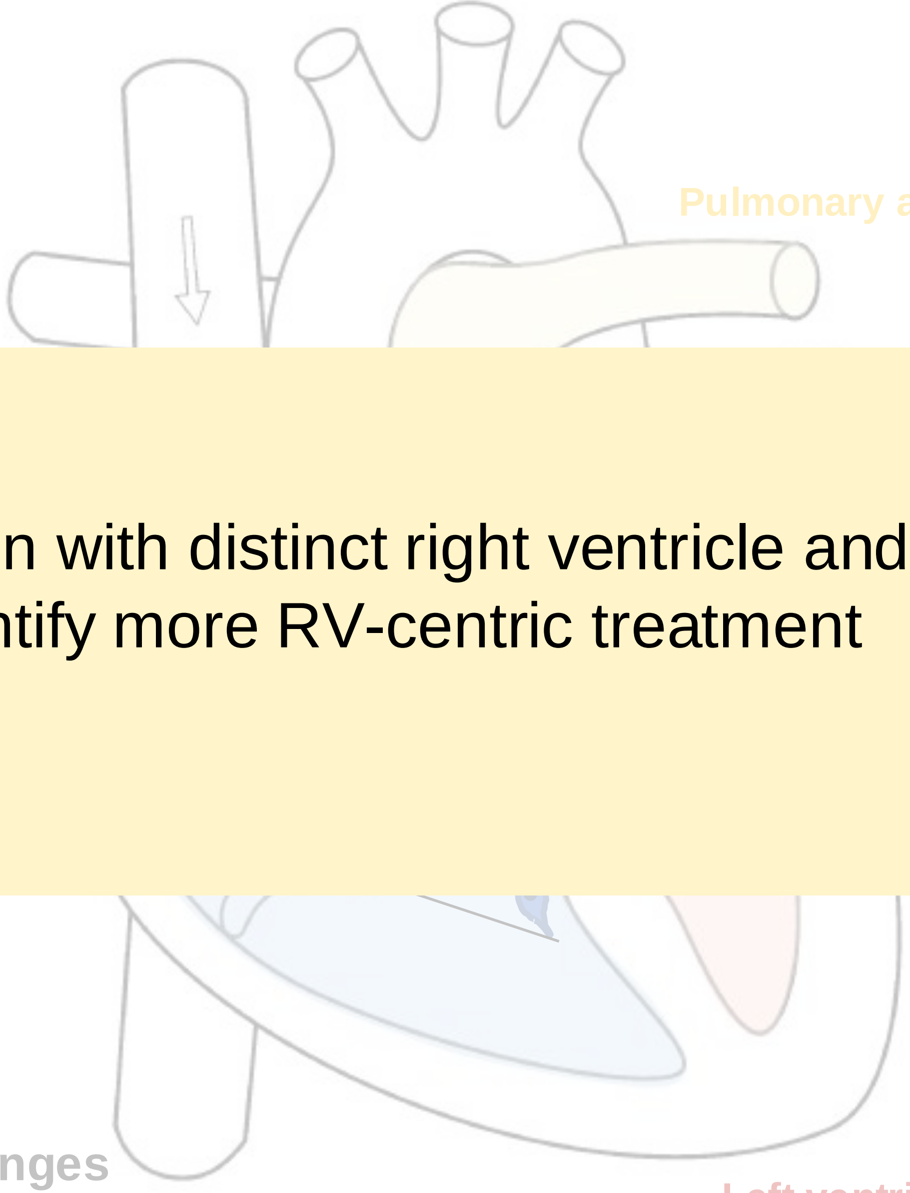




Top predictive features have significant COX Hazard ratios as well

Hypertrophy is intrinsically multiscale

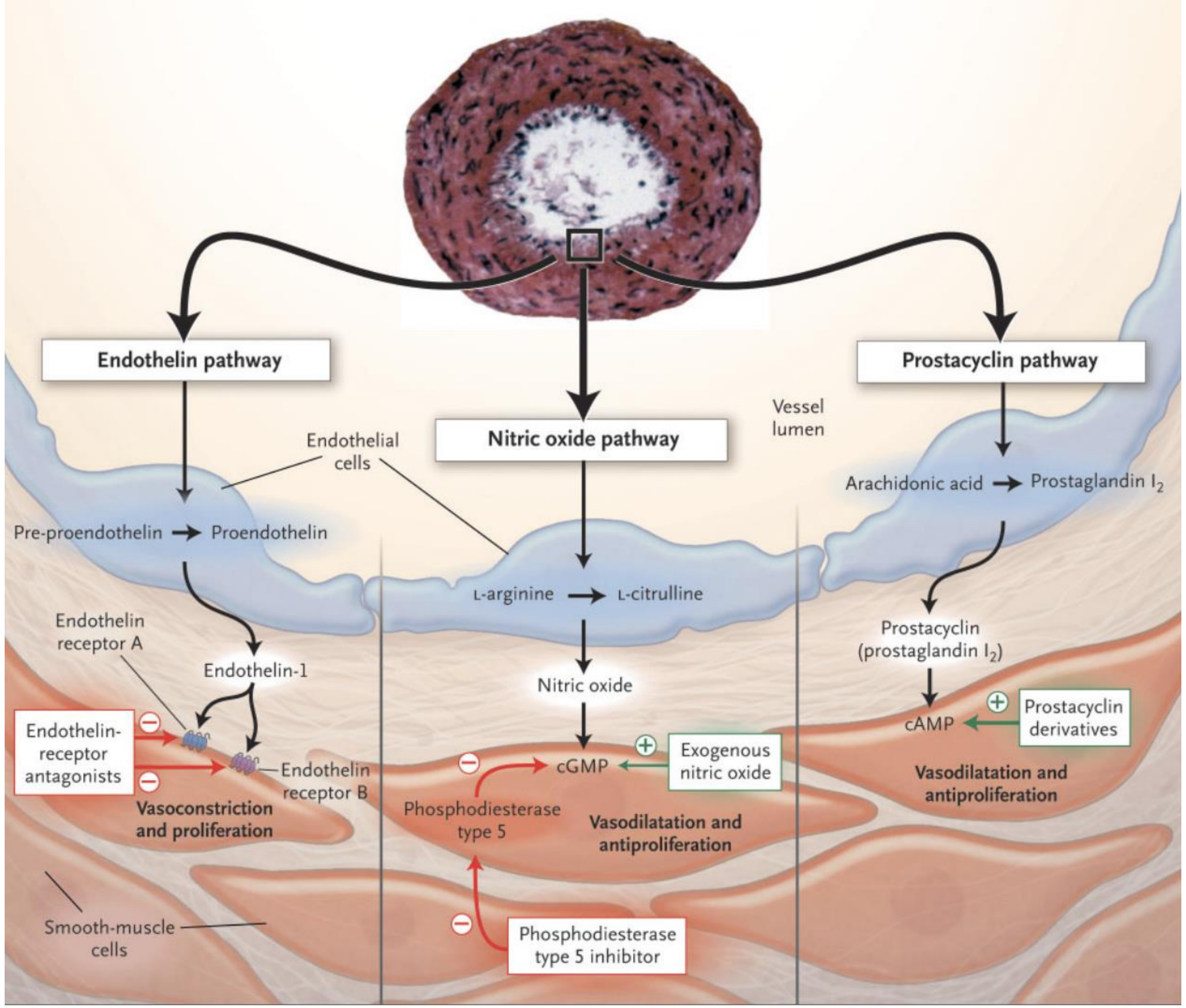




Aim 3. Identify metabolomic signatures that align with distinct right ventricle and pulmonary hypertension states in order to identify more RV-centric treatment strategies.

We hypothesize that distinct RV states are associated with changes in the metabolome that could be critical treatment targets.

Aim 2. Identify metabolomic signatures that align with distinct right ventricle (RV) and/or PH states.

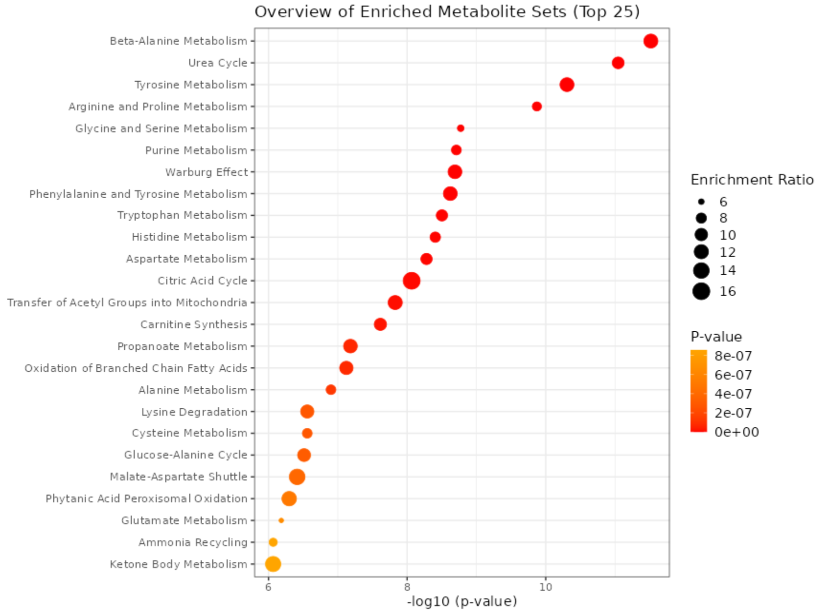


Glycolysis-related

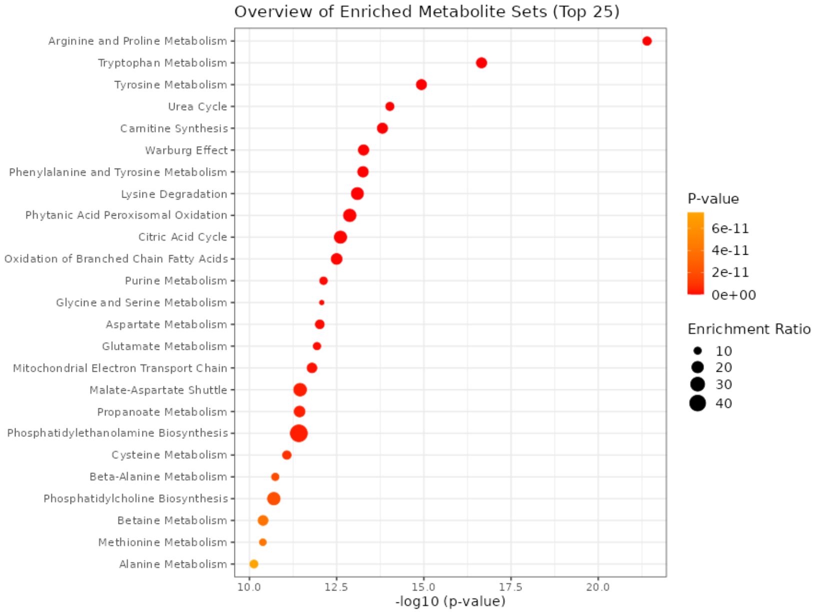
Fatty Acid Oxidation-related

TCA Cycle-related

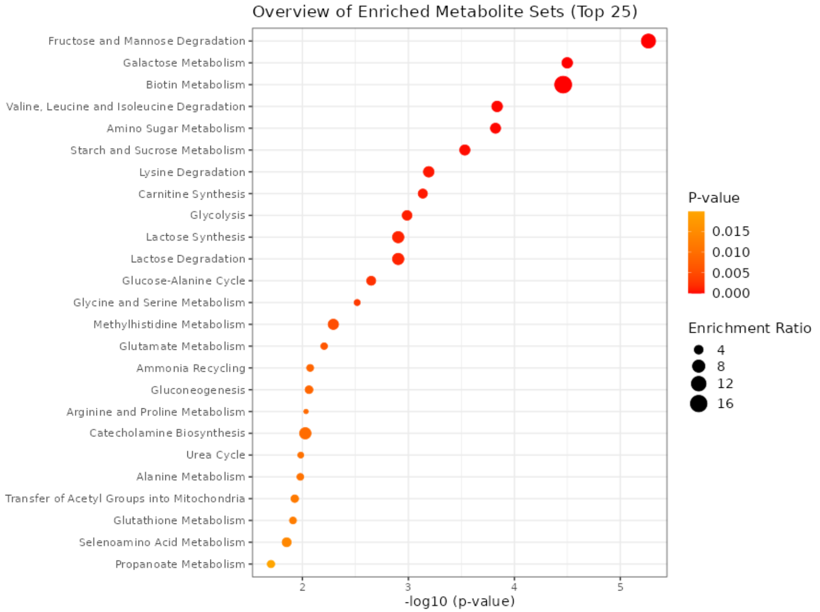
Best (0) v. Worst (1)

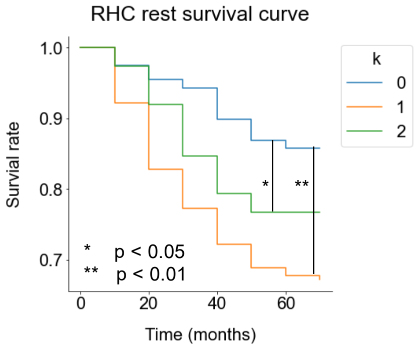


Best (0) v. Medium (2)



Worst (0) v. Medium (2)





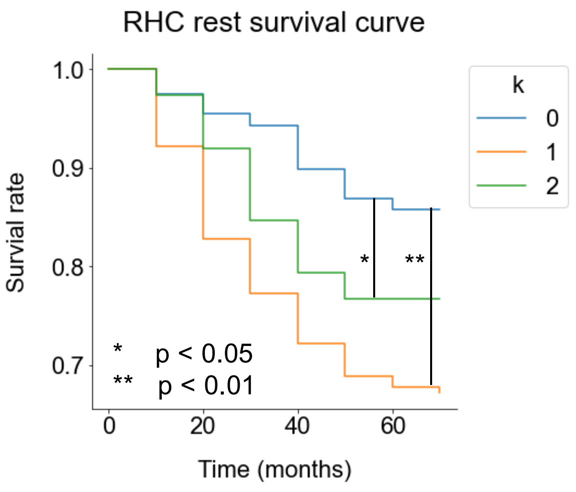
1. **Beta-alanine metabolism**
2. **Urea cycle**
3. **Tyrosine metabolism**

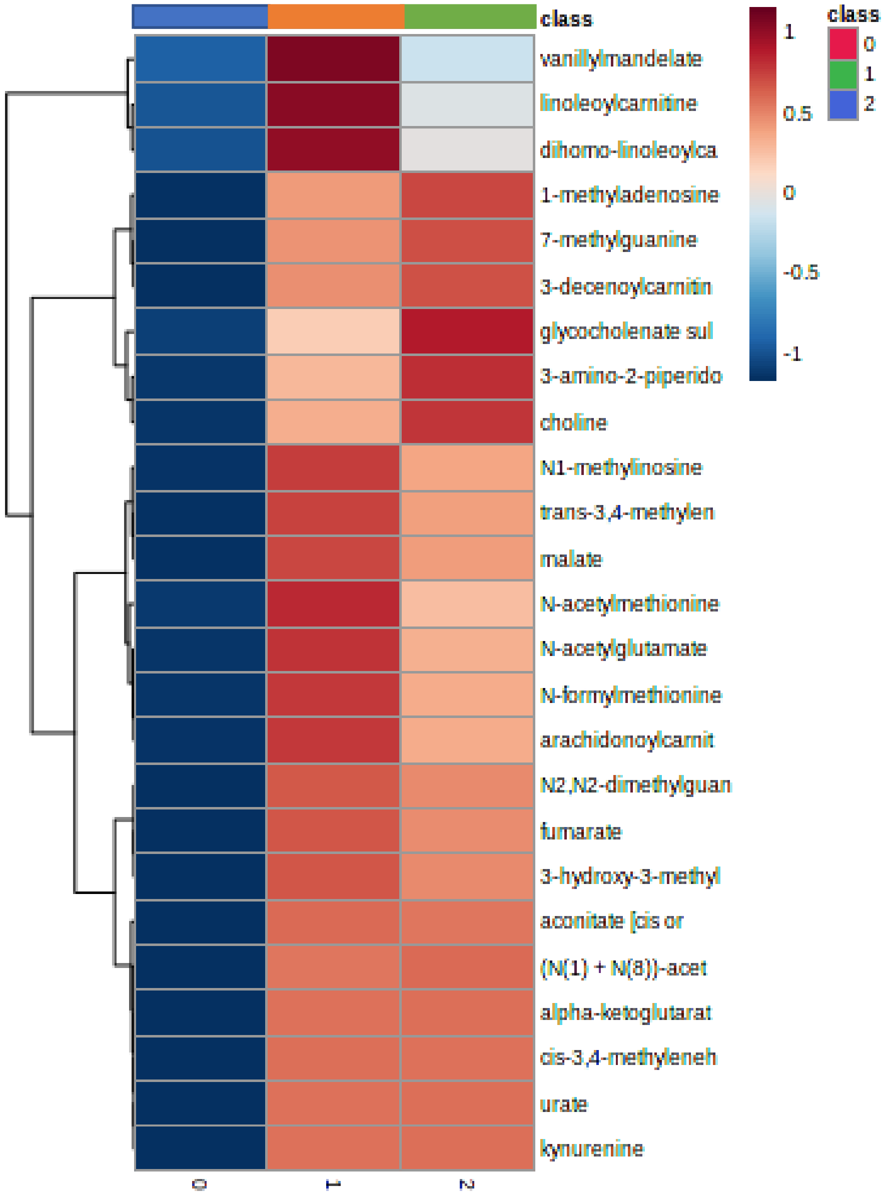
1. Arginine and proline metabolism
2. **Tryptophan metabolism**
3. **Urea cycle**

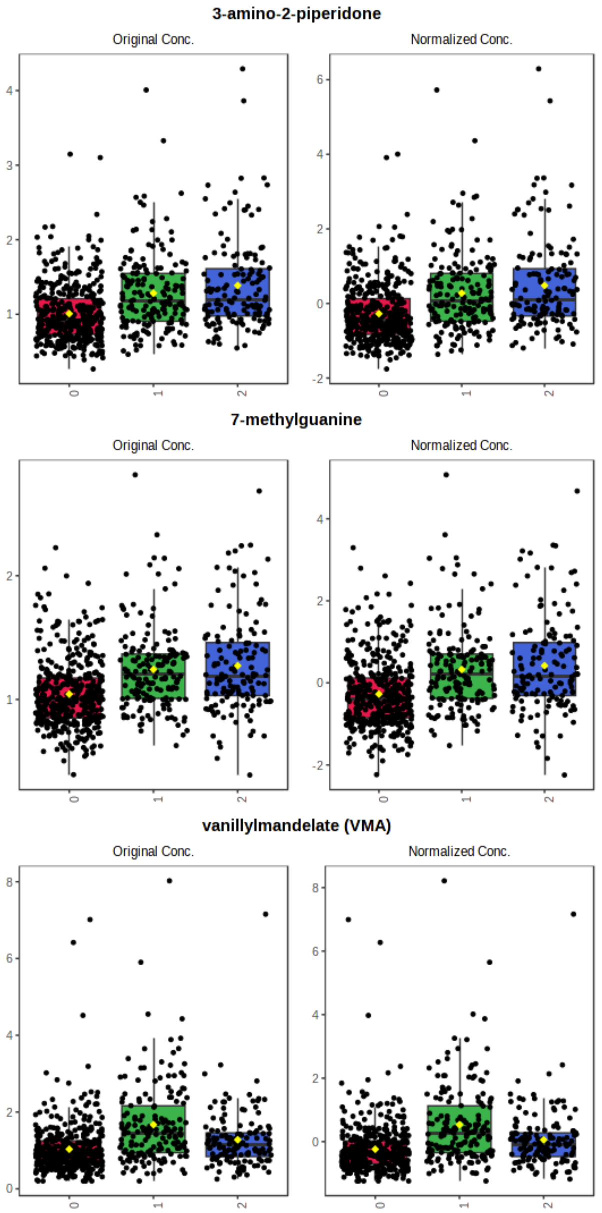
1. Fructose and mannose degradation
2. Galactose metabolism
3. Biotin metabolism

Bolded pathways have known PH implications

Aim 3: RHC rest significantly different metabolites







Top 3 Metabolites

- 3-amino-2-piperidone
- 7-methylguanine
- Vanillylmandelate (VMA)

Clusters with worse survival have elevated metabolite levels.

Compiled Key Metabolites and Pathways

Metabolome Dataset	Top 3 Associated Metabolites	Top Associated Pathways
RHC Rest	1. vanillylmandelate (VMA) (Tyrosine metabolism) 2. N-formylmethionine (Methionine, Cysteine, SAM and Taurine Metabolism) 3. N-acetylmethionine (Methionine, Cysteine, SAM and Taurine Metabolism)	1. Phosphatidylethanolamine biosynthesis 2. Citric Acid Cycle 3. Molate-Aspartate Shuttle
RHC Fluid Challenge	1. 7-methylguanine (Purine metabolism, guanine containing) 2. N-acetylmethionine 3. linoleoylcarnitine (C18:2)*	1. Phosphatidylethanolamine biosynthesis
RHC Exercise	1. aconitate [cis or trans] (TCA/Citric Acid Cycle) 2. N2,N2-dimethylguanosine (Purine metabolism, guanine containing) 3. vanillylmandelate (VMA)	1. Phosphatidylethanolamine biosynthesis 2. Glycerol Phosphate transport 3. Citric Acid Cycle
MRI	1. 2-pyrrolidinone (Glutamate metabolism) 2. 3-ureidopropionate 3. 3-amino-2-piperidone (Urea cycle, Arginine and Proline Metabolism)	1. Phosphatidylethanolamine biosynthesis 2. Citric Acid Cycle 3. Porphyrin Synthesis
ECHO	1. 3-amino-2-piperidone 2. N2,N2-dimethylguanosine 3. 7-methylguanine	1. Phosphatidylethanolamine biosynthesis 2. Phosphatidylcholine Biosynthesis

Metabolite Literature

Phosphatidylethanolamine biosynthesis as a measure of mitochondria ER unit integrity

Circulating plasma metabolomic profiles differentiate rodent models of **pulmonary hypertension** and idiopathic **pulmonary** arterial **hypertension** patients

JH Zhao, YY He, SS Guo, Y Yan, Z Wang… - … of **Hypertension**, 2019 - academic.oup.com

… , 14 **pathways** were involved while the **phosphatidylethanolamine biosynthesis pathway** ranked … In hypoxia-induced PH rat model, methionine metabolism **pathway** was identified as the …

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The role of Nogo and the mitochondria–endoplasmic reticulum unit in **pulmonary hypertension**

G Sutendra, P Dromparis, P Wright, S Bonnet… - Science translational …, 2011 - science.org

… in the **pathway** that leads from hypoxia to **hypertension** in the … of the hypoxia-to-PAH **pathway** are becoming clearer as well; … mitochondrial **synthesis** of **phosphatidylethanolamine** (PtdEtn…

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Autophagic protein LC3B confers resistance against hypoxia-induced **pulmonary hypertension**

SJ Lee, A Smith, L Guo, TP Alastalo, M Li… - American journal of …, 2011 - atsjournals.org

… of the autophagic **pathway** (16). The conversion of microtubule-associated protein-1 light chain 3B (LC3B) from LC3B-I (free form) to LC3B-II (**phosphatidylethanolamine** conjugated form…

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References

- Hassoun PM. Pulmonary Arterial Hypertension. N Engl J Med [Internet]. 2021 Dec 16 [cited 2022 Nov 3];385(25):2361–76. Available from: https://www.nejm.org/doi/10.1056/NEJMra2000348
- Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J [Internet]. 2019 Jan [cited 2022 Nov 3];53(1):1801913. Available from: http://erj.ersjournals.com/lookup/doi/10.1183/13993003.01913-2018
- Humbert, et al. N Engl J Med 2004;351:1425-36.
- Richter, Manuel J., et al. "Right ventricular pressure-volume loop shape and systolic pressure change in pulmonary hypertension." American Journal of Physiology-Lung Cellular and Molecular Physiology 320.5 (2021): L715-L725.
- Joby, A. (2021, July 19). In *What Is K-Nearest Neighbor? An ML Algorithm to Classify Data*. Retrieved from https://learn.g2.com/k-nearest-neighbor
- You, T. (2019, June 12). Understanding Random Forest. *Towards Data Science*.
- Raj, A. (2020, November 7). Perfect Recipe for Classification Using Logistic Regression. *Towards Data Science*.
- Hemnes et al. (2017, October 27). PVDOMICS: A Multi-Center Study to Improve Understanding of Pulmonary Vascular Disease Through Phenomics. *Circulation research*, *121*(10), 1136–1139. https://doi.org/10.1161/CIRCRESAHA.117.311737
- Hoeper, M. M., Humbert, M., Souza, R., Idrees, M., Kawut, S. M., Sliwa-Hahnle, K., Jing, Z.-C., & Gibbs, J. S. R. (2016, March 11). *A global view of pulmonary hypertension*. The Lancet Respiratory Medicine. Retrieved November 8, 2022, from https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(15)00543-3/fulltext
- Xu W, Janocha AJ, Erzurum SC. Metabolism in Pulmonary Hypertension. Annu Rev Physiol. 2021 Feb 10;83:551-576. doi: 10.1146/annurev-physiol-031620-123956.