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Abstract template

Precision Medicine in CTEPH: Spectral Clustering Phenotyping predicts relative haemodynamic benefit of Balloon Pulmonary Angioplasty

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- Balloon pulmonary angioplasty (BPA) has revolutionized the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH)
- Selecting patients who will derive the most significant hemodynamic benefit remains a clinical challenge.
- Current selection criteria often rely on subjective assessment or static hemodynamic thresholds.
- Aim: to use an unsupervised machine learning approach to identify objective baseline clinical phenotypes and determine their relative response to BPA in a large single-center cohort.



- We retrospectively analysed a cohort of 161 patients with CTEPH treated with BPA, adding up to a total of 776 BPA sessions.
- To minimize human bias in phenotype identification, a Spectral Clustering algorithm (using nearest neighbours' affinity, predefined to k=3 clusters) was applied using six baseline cardiopulmonary variables:
 - Pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), cardiac index (CI), 6-minute walk distance (6MWD), NT-proBNP, and WHO functional class (FC).
 - Demographic data such as age and sex were excluded from the clustering process to focus on physiological patterns. The primary outcome was defined as the relative percentage reduction in PVR from baseline to post-procedural follow-up. Additionally, a supervised Random Forest classifier was trained to extract the *Feature Importance* (predictive weight) of baseline variables in achieving a 30 % PVR reduction.



- The algorithm identified 3 distinct baseline clinical profiles with significantly different response trajectories:
 - Profile 1 (Mild impairment) consisted of patients with moderate hemodynamics and preserved functional capacity (FC II), who showed the lowest relative improvement (mean PVR reduction of $29.1\% \pm 28.6$).
 - Profile 2 (Moderate impairment) included patients with similar baseline PVR but higher functional impairment (FC III), achieving a superior PVR reduction ($35.5\% \pm 22.8$)
 - Profile 3 (Severe impairment) identified patients with the most extreme hemodynamic compromise (mean PVR 13.1 ± 4.0 WU, NT-proBNP 2819.2 ± 1499.2 pg/mL). Notably, this high-risk group acted as "super-responders," achieving a massive mean PVR drop of $57.8\% \pm 17.2$ ($p < 0.001$) and the highest rate of clinical target achievement.

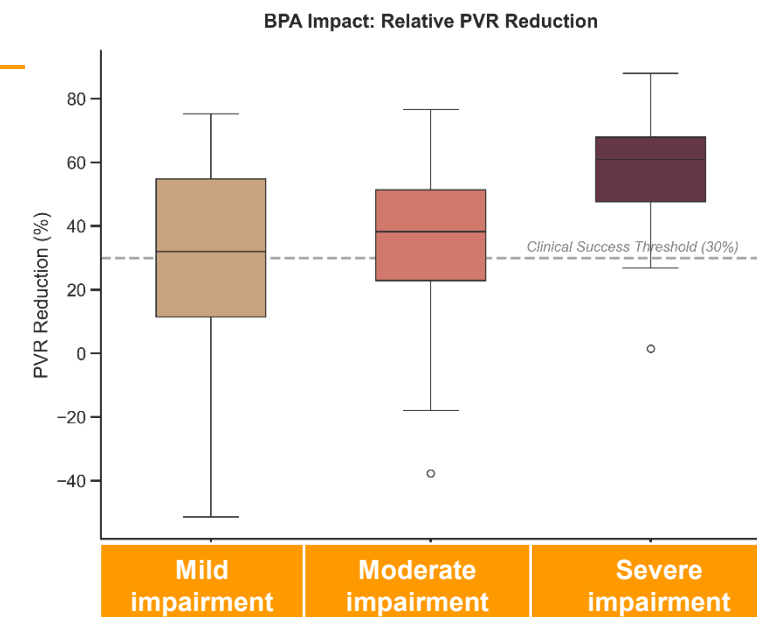
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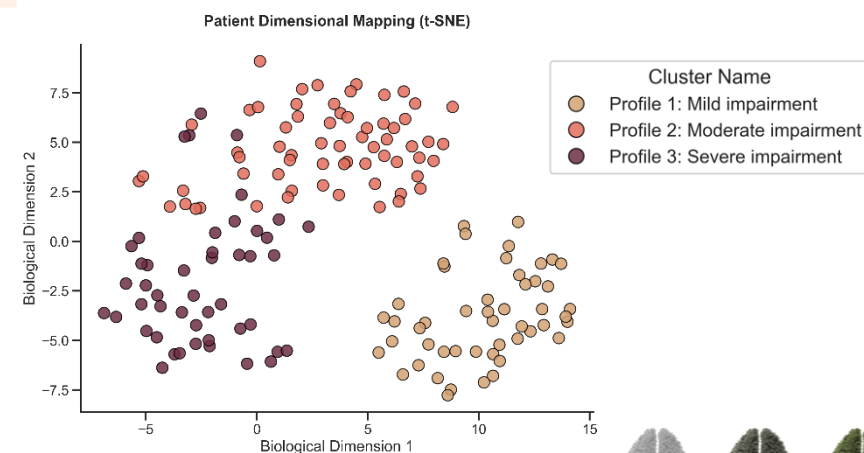
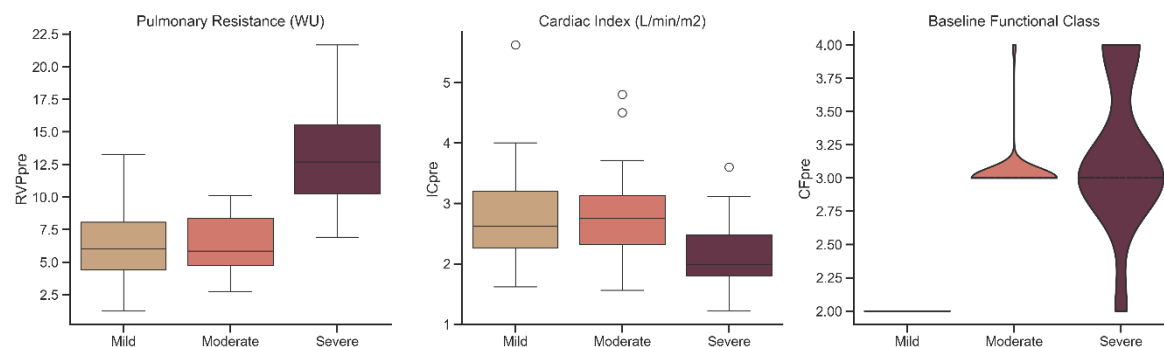


Clinical phenotypes and PVR response post-BPA

For all values in this table MEAN ± STD	Complete cohort (N=161)	Mild impairment (N=50)	Moderate impairment (N=64)	Severe impairment (N=47)	P-value
Age	59.2 ± 14.6	58.7 ± 14.1	62.1 ± 15.4	58.6 ± 14.8	0.319
Baseline PVR (WU)	8.2 ± 4.2	6.2 ± 2.5	6.2 ± 2.0	13.1 ± 4.0	< 0.001
Baseline mPAP (mmHg)	45.2 ± 11.2	41.2 ± 8	40.5 ± 8.7	56.0 ± 9.9	< 0.001
Baseline CI (Cardiac index)	2.6 ± 0.7	2.7 ± 0.7	2.7 ± 0.6	2.1 ± 0.5	< 0.001
Baseline 6MWT (min)	363.6 ± 113.4	408.9 ± 114	375.1 ± 75.4	304.1 ± 130.9	< 0.001
Baseline NT-pro BNP	1190 ± 1408.5	544 ± 712.4	504.5 ± 485.7	2819.2 ± 1499.2	< 0.001
Baseline functional class	2.7 ± 0.6	2.0 ± 0.0	3.0 ± 0.2	3.2 ± 0.6	< 0.001
Vasodilator therapy pre-BPA	1.6 ± 1.6	0.8 ± 1.1	1.3 ± 1.4	2.7 ± 1.6	< 0.001
BPA Complications number	1.2 ± 1.1	0.8 ± 0.9	1.0 ± 1.0	1.7 ± 1.2	< 0.001
% PVR reduction	40.7 ± 25.9%	29.1% ± 28.6%	35.5% ± 22.8%	57.8% ± 17.2%	< 0.001



Hemodynamic and Functional Characterization of Profiles



- Our findings reveal a significant clinical paradox in BPA treatment, often referred to as the "floor effect."
- Patients with mild or moderate PVR and preserved Functional Class (FC) have a moderate hemodynamic improvement with BPA therapy, leading to a more modest relative benefit.
- In contrast, patients with catastrophic baseline haemodynamics (who are frequently considered at higher procedural risk) possess the greatest margin for vascular recruitment. Even within patients with similar baseline PVR, a worse FC usually means a better response to BPA program.
- **This suggests that high hemodynamic severity should be viewed as a predictor of high therapeutic potential rather than a reason for exclusion from BPA programs.**



Conclusion

- Unsupervised machine learning successfully stratifies CTEPH patients into phenotypes that predict their hemodynamic response to BPA.
- Identifying these profiles allows for better management of patient expectations and reinforces the role of BPA in treating patients with severe hemodynamic compromise, who stand to gain the most significant relative benefit from the procedure.
- AI-driven phenotyping assists heart teams in providing realistic, individualized outcome predictions for CTEPH patients prior to intervention, which can help prioritize resources and optimize the sequential approach in complex CTEPH management.

