

Published in final edited form as:

Circ Heart Fail. 2013 May 1; 6(3): 584–593. doi:10.1161/CIRCHEARTFAILURE.112.000096.

Left Ventricular Dysfunction with Pulmonary Hypertension:

Part 2: Prognosis, Noninvasive Evaluation, Treatment, and Future Research

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Pulmonary hypertension (PH) secondary to left-sided heart disease (Group 2 PH) is a frequent complication of heart failure (HF) that worsens exercise capacity, risk for hospitalization, and survival independent of left ventricular ejection fraction (LVEF) or stage of HF. Increased pulmonary artery pressure (PAP) in HF patients often represents a combination of increased left-sided filling pressures (“passive” component) and elevated pulmonary vascular resistance (PVR) due to functional and structural abnormalities of the pulmonary vascular bed (“reactive” component). The latter may be reversible with standard HF treatment in the earlier stages when remodeling of the pulmonary vasculature has not set in and abnormalities in pulmonary arterial tone are the major driver for elevated PVR. However, chronic exposure to elevated pulmonary capillary wedge pressure (PCWP) may lead to permanent changes in the pulmonary arterial bed (irreversible or “fixed” PH).¹ Considering that a number of drug classes have successfully modified the natural history of pulmonary arterial hypertension (Group 1 PH) and demonstrated that intervention is possible even after pulmonary vascular remodeling has occurred,² Group 2 PH is a natural target for screening and potential intervention in patients with HF.

In the second part of this two-part review, we discuss the prognostic impact of PH in HF, the contemporary diagnostic and evaluation approaches, the current evidence from clinical studies in Group 2 PH, the challenges of appropriate patient selection in clinical trials, and potential ways to overcome these challenges in trial designs.

Prognostic Significance of Pulmonary Hypertension in Heart Failure

Echocardiographic Studies

Studies using either right heart catheterization (RHC) or echocardiography for determination of PAP have consistently shown that PH considerably worsens prognosis in HF. Abramson *et al.* first reported that tricuspid regurgitation jet velocity >2.5 m/s was associated with 3.4 times higher mortality in 108 patients with dilated cardiomyopathy followed for up to 28 months³; hospitalization rate for HF was also three times higher in these patients.³ In more recent studies, estimated right ventricular systolic pressure (RVSP) has been used to evaluate the presence of PH. Although variable RVSP cut-off points have been used to define PH in these studies,^{4–9} higher RVSP has been consistently associated with higher mortality and hospitalization rates. Of note, in a study of cardiac resynchronization therapy

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Disclosures

None.

(CRT) recipients, higher RVSP at baseline was associated with worse survival, but patients with reductions in RVSP on follow up had better outcomes.⁴ The importance of elevated PAP post-CRT has been also reported by other groups.^{10, 11}

Invasive Studies

Studies with RHC in chronic HF have mostly included patients with severe systolic dysfunction and advanced HF.^{12–14} Among 377 patients referred for transplant evaluation, 51.3% of those with mean PAP (mPAP) >20mmHg died or were transplanted urgently compared to 13.5% of those with mPAP ≤20mmHg.¹² In that study, right ventricular dysfunction further increased risk in patients with PH.¹² In a landmark study on 1134 patients with newly diagnosed cardiomyopathy, mortality sharply increased when PVR exceeded 3 Wood units (WU).¹³ In a study with serial RHC data, baseline PH predicted mortality and decompensation of HF, and worsening mPAP over time further increased risk.¹⁴ In a large series of HF patients without any specific LVEF inclusion criteria, mortality was two-fold higher in patients with PH vs. those without.¹⁵ When PH (mPAP ≥25mmHg) was further classified into passive (PVR ≤2.5 WU) vs. reactive (PVR >2.5 WU), reactive PH was associated with more pronounced risk.¹⁵ Regardless of method of PH determination (echocardiography or RHC), right ventricular dysfunction worsens outcomes further.^{12, 16}

In contrast to studies in chronic HF, results from RHC data in acute HF are conflicting.^{17, 18.} Using data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, Khush *et al.* reported that reactive PH (mPAP ≥25mmHg, PCWP >15mmHg, and PVR ≥3 WU), present in 47% of patients at enrollment, was not associated with worse 6-month outcomes.¹⁷ In contrast, in the Vasodilation in the Management of Acute Congestive (VMAC) Heart Failure trial,¹⁸ a reactive PH profile (using the same definition as in ESCAPE) was associated with higher 6-month mortality (48.3%) compared to passive PH (21.8%) or no PH (8.6%) (Figure 1). However, in VMAC, the PH profile was determined using the post-treatment values, potentially reflecting a profile closer to steady state conditions. Of note, in that study, post-treatment values of hemodynamic parameters classified 50% of patients to a different PH category compared to pre-treatment values,¹⁸ highlighting the challenges of PH profile determination in HF patients during the decompensated phase.

Table 1 summarizes the studies on prognostic significance of Group 2 PH.

Insights from Continuous Ambulatory Hemodynamic Monitoring

In patients with HF, even mild increases in chronic ambulatory PAP, monitored through wireless implantable devices, are associated with higher rates of hospitalization for HF regardless of LVEF.^{19–21} In the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) Study, the likelihood of an HF event increased progressively with higher estimated diastolic PAP (an estimate of LV filling pressure).²⁰ The estimated average diastolic PAP over 6 months among patients who presented with acute HF was 31±8 mmHg vs. 26±6 mmHg among those without events. However, the corresponding estimated RVSP was 55±15 and 45±13 mmHg, respectively, potentially indicating the presence of a reactive pulmonary vascular component among patients with events.²⁰ In the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial, a 1-mmHg lower daily average mPAP in the device-guided treatment group compared to the control group over 6 months was accompanied by fewer hospitalizations for HF (32% vs. 44%).²¹

The Role of Echocardiography

Right heart catheterization is the gold standard for the definitive diagnosis of PH. However, RHC is an invasive procedure and therefore would be better reserved for patients with advanced (Stage D) HF, where decisions on advanced therapies are contingent upon the absence of fixed PH. From a clinical trial design perspective, RHC is appropriate for the detailed characterization of hemodynamic response in phase I/IIa trials with novel vasoactive agents. However, noninvasive alternatives for PH screening and evaluation of response to investigational agents are needed for Stage C HF patients in larger, phase IIb/III clinical trials. Echocardiography is being increasingly used for these purposes. Newer echocardiographic parameters have become available to supplement the traditional RVSP estimates, including estimates of left ventricular (LV) filling pressures and PVR to better phenotype these patients.

Feasibility of RVSP Determination

A comprehensive echocardiographic evaluation of the HF patient should include estimation of RVSP based on the tricuspid regurgitation jet velocity. Potentially, an estimate of right atrial pressure using the inferior vena cava diameter and its respiratory fluctuation can be added to the transtricuspid gradient to better approximate RVSP. In the absence of pulmonary stenosis, RVSP is an adequate approximation to systolic PAP (sPAP). The reported feasibility of RVSP determination in chronic HF patients is highly dependent on the setting. In prospective cohorts focusing on right-sided hemodynamics, feasibility ranges from 80%–90% in community HF^{6, 9, 22} to almost 100% in advanced HF.^{23, 24} Feasibility is much lower when RVSP determination is not mandated by protocol or is retrospectively assessed.^{5, 7, 8, 25} Recently, Nagueh *et al.* reported that RVSP determination is feasible in 80% of patients in the acute HF setting.²⁶

Validity of Right Ventricular Systolic Pressure for Assessment of Pulmonary Hypertension

Several studies have investigated the validity of echocardiographic RVSP estimates in patients with HF using RHC values as the gold standard. As expected, most data come from patients with advanced systolic HF. In 70 patients with systolic HF, a concordance correlation coefficient of 0.88 between RHC and RVSP values was reported, with ± 20 mmHg 95% limits of agreement and no bias.²⁷ Narrower limits of agreement (< 10 mmHg) and clinically relevant correlation between RHC and RVSP ($r = 0.82$ – 0.97) have been consistently reported in Stage D HF populations.^{23, 24, 28, 29} Nagueh *et al.* have reported that echocardiographic RVSP determinations correlate well ($r = 0.83$) with invasive estimates in acute HF, with ± 15 mmHg limits of agreement.²⁶ Importantly, echocardiography identified patients with invasive sPAP > 35 mmHg with 94% sensitivity and 90% sensitivity.²⁶ A recent analysis from the ESCAPE trial suggested that the accuracy of echocardiographic RVSP estimates in systolic HF might be compromised by right ventricular systolic dysfunction.³⁰ However, it is important to note that echocardiography in ESCAPE was not protocol driven and the time differential between RHC and echocardiographic determinations was widely variable.

Although the need for noninvasive alternatives to invasive estimation of PH is higher in the community setting, most validation data for echocardiographic RVSP estimates come from referral populations, whereas data on community HF are lacking. However, the clinical validity of RVSP estimates in the community setting is supported by strong prognostic information.^{6, 9, 22} Therefore, it may be acceptable to select Stage C HF patients for clinical trials on Group 2 PH on the basis of echocardiographic evidence of PH, considering the projected risk associated with elevated echocardiographic RVSP.

Assessment of Pulmonary Vascular Resistance with Echocardiography

Direct transportation of the RHC formula (difference between mPAP and PCWP divided by the cardiac output) for echocardiographic estimation of PVR has been proposed,^{31,32} but application in practice has been limited, mainly because of the uncertainty introduced by PCWP and cardiac output estimation. Similarly, approaches based on Doppler-derived intervals have been proposed³³ but adoption has been limited. Abbas *et al.* have introduced an estimate of PVR based on the ratio of tricuspid regurgitation jet velocity (TRV) to right ventricular outflow tract time-velocity integral (TVI) (Figure 2), with good correlation to invasive estimates ($r=0.93$) and ± 0.8 WU 95% limits of agreement.³⁴ A TRV/TVI ratio of 0.175 had 77% sensitivity and 81% specificity to determine PVR >2 WU. This approach and variations thereof have been validated in liver transplant candidates,³⁵ in patients with pulmonary arterial hypertension,^{36, 37,38} in a mixed non-HF PH population³⁹, and in congenital heart disease.⁴⁰ Encouraging results have also been obtained in pediatric⁴¹ and postoperative⁴² populations. A common theme among these studies is that the TRV/TVI ratio has a high sensitivity and negative predictive value to detect elevated PVR (>1.5 – 2.0 WU), but actual correlation with invasive PVR worsens as PVR increases. Thus, noninvasive PVR estimates are best reserved as a screening tool to exclude high PVR. More recently, Dahiya *et al.* reported that correction of noninvasive PVR for LV filling pressures using the E/e' ratio improved correlation with invasive PVR in a large non-HF PH population.³⁸ In this study, corrected noninvasive PVR was a reliable surrogate of invasive PVR over 12 months of follow up after initiation of pulmonary vasoactive treatment.³⁸ It is important to note, however, that noninvasive methods for PVR assessment have not been validated in HF populations.

Treatment of Pulmonary Hypertension in Heart Failure

The epidemiological data suggest that PH could be a natural therapeutic target in patients with HF. However, no adequately powered trials of PH-specific treatment have demonstrated to date that decreasing PAP or PVR improves morbidity and mortality in HF patients. Despite promising results in acute hemodynamic studies,^{43–54} the experience with prostacyclin analogues and endothelin antagonists in outcome-driven trials in chronic and acute HF has been invariably neutral or negative to date.^{55–64} These results are in contrast to the favorable effects of these pulmonary vasoactive agents in populations with Group 1 PH.⁶⁵ However, trials with prostacyclin analogues and endothelin antagonists in HF did not target patients with evidence of concomitant PH, but rather enrolled relatively unselected HF populations on the premise that a more comprehensive neurohormonal blockade would improve outcomes for all HF patients.⁶⁶ Only recently the focus has shifted to HF patients with concomitant PH, investigating predominantly the effects of phosphodiesterase type 5 (PDE5) inhibitors^{67–70} (Table 2). Besides demonstrating favorable effects on physiologic endpoints in patients with systolic HF and PH,^{67, 69} long-term sildenafil treatment improved hemodynamics in a single-center trial of patients with preserved ejection fraction (HFpEF) and PH.⁶⁹ It is important to note however, that the degree of right ventricular dysfunction and right heart congestion in this study was higher than that seen in typical HFpEF populations.⁷¹

Following the paradigm of other pulmonary vasoactive agents, the long-term effects of PDE5 inhibitors were initially tested in unselected HF populations,^{72–74} on the basis of early encouraging experience from short-term use in patients with HF and erectile dysfunction^{75–77} and the favorable effects of these agents on endothelial function.^{78–80} However, despite promising effects on exercise capacity^{69, 70, 72, 73, 81} and pulmonary hemodynamics,^{69, 70, 72, 73, 82} these phase II trials with PDE5 inhibitors were not powered to detect effects on clinical outcomes, both for unselected and selected HF populations. In fact, no outcome-driven trials have been conducted with PDE5 inhibitors in HF to date. The NIH-

funded (1U01HL105562-01A1) Phosphodiesterase Type 5 Inhibition with Tadalafil Changes Outcomes in Heart Failure (PITCH-HF) trial will be the first clinical trial to (1) investigate the effect of pulmonary vasoactive treatment on mortality and hospitalizations in patients with HF and PH and (2) the effects of PDE5 inhibition on clinical outcomes in HF.

Thus, while appropriately powered trials are underway, agents that enhance the cyclic guanosine monophosphate (cGMP) signaling appear to hold promise in patients with HF and PH, as they may not share the profile seen with more pulmonary arterial selective drug classes such as prostacyclin analogues or endothelin receptor antagonists. The pulmonary selectivity of the latter, which omit parallel unloading of the LV while pulmonary venous flow is enhanced, could potentially underlie the failure of these agents in HF. High PVR may be a protective adaptation to LV failure,⁸³ as selective pulmonary arterial vasodilation might worsen left heart congestion and trigger pulmonary edema. In contrast, agents that also unload the LV, such as nitroprusside, safely improve PAP and PVR without acute increase in left atrial pressures.⁸⁴ Therefore, therapeutic interventions with “balanced” pulmonary arterial and systemic vasodilator effects could be more promising. Drugs with such desirable hemodynamic profiles include cGMP-enhancing agents such as nitrates,⁸⁵ though this class is limited by tolerance and resultant oxidative stress induction^{86–88}; PDE5 inhibitors⁸⁹; and soluble guanylate cyclase (sGC) stimulators and activators hold promise in this respect.⁹⁰

Pulmonary Hypertension in Heart Transplant Candidates

Fixed PH increases mortality both early and late after heart transplantation (HT), because the right ventricle may fail when a normal donor heart faces significantly elevated PVR in the post-HT period.⁶⁶ Mortality increases continuously with increasing PVR and no threshold confidently precludes right ventricular failure, supporting the view that PVR should be considered a relative rather than an absolute contraindication to HT.^{91–93} However, a resting PVR >5 WU indicates that the patient may not be a good candidate for HT or, alternatively, that they should be offered heterotopic HT or heart-lung transplantation.⁹⁴ On the other hand, if PVR can be reduced to <2.5 WU without hypotension, post-HT outcomes are comparable to patients without PH.^{95, 96} In a series of 410 HT recipients, reversible PH did not affect negatively short- or long-term (5-year) survival⁹⁷; however, residual post-HT PH was associated with decreased long-term survival. In another series of 217 patients who received HT, 10-year survival among the 40 patients with reversible PH was comparable to those without PH (61% vs. 63%).⁹⁸

Left ventricular assist device (LVAD) implantation improves pulmonary hemodynamics in patients not responding to vasodilatory treatment, suggesting that LVAD may be a strategy for HT candidates with fixed PH.⁹⁹ In several studies, PVR was significantly reduced and patients became eligible for HT with good post-HT outcomes.^{100–105} Both pulsatile¹⁰⁴ and continuous-flow¹⁰³ LVADs improve pulmonary hemodynamics and candidacy for HT. Long-term survival post-HT in these patients was similar to that of HT recipients without PH who either received¹⁰⁵ or did not receive LVAD.¹⁰² However, there are no data directly comparing patients with PH who received vs. those who did not receive LVAD.¹⁰⁶ Improvement in hemodynamics has been reported early after LVAD implantation even in severe PH, and this improvement lasts with longer support.¹⁰⁴ A recent study reported that the timeframe in which significant reductions in mean PAP, PCWP, and PVR of patients with fixed PH occur is within 6 months after LVAD placement with no additional benefit after that period, giving thus reasonable time for HT candidacy decisions.¹⁰⁷

Favorable outcomes were observed after HT in a small series of patients with initially unresponsive PH who regained “reversibility” of PH following a 12-week treatment with

oral sildenafil in a small prospective uncontrolled trial.¹⁰⁸ In a small retrospective study, HT candidates with severe PH on sildenafil who continued to receive sildenafil after HT had significant reduction in PVR/TPG, successful HT, and comparable post-transplant survival with those without PH.¹⁰⁹ In another retrospective study of patients with severe Group 2 PH, pre- and post-HT survival was better in those receiving sildenafil.¹¹⁰ These preliminary findings suggest that pulmonary vasoactive treatment could precondition previously disqualified HT candidates for safe transplantation.

Pulmonary Pressures from Implanted Devices as a Therapeutic Target

Recent trials with implanted devices for hemodynamic monitoring demonstrated that goal-directed therapies based upon real-time diastolic PAP assessments, as a surrogate of left-sided filling pressures, might reduce HF hospitalizations.^{20, 21} In the COMPASS-HF study,²⁰ the risk for HF events was 1.10 per 6 months when daily median estimated diastolic PAP was ≥ 25 mmHg at baseline and remained chronically ≥ 25 mmHg vs. 0.47 when pressures declined to <25 mmHg for more than half of the days. Patients with low baseline daily median estimated diastolic PAP (<25 mm Hg) who increased only after initiation of the ambulatory monitoring to ≥ 25 mm Hg for the majority of their days, had a high HF event rate during 6 months of 1.10, compared with a rate of only 0.23 in those who remained low at <25 mm Hg.²⁰

However, the 21% reduction in HF events by the implanted device remained nonsignificant.¹¹¹ Although the CHAMPION trial was not restricted to HF patients with PH,²¹ maintenance of less elevated filling pressures could also represent an appealing target for PAP-active drugs such as the cGMP-enhancing PDE5 inhibitors or sGC stimulators.

Ongoing Clinical Trials

Currently, a number of clinical trials in various planning and conduct stages are investigating the effects of PDE5 inhibitors and sGC activators in HF patients with or without PH. The recently completed, NIH-funded Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure (RELAX) trial is a double-blind, placebo controlled phase III trial testing the hypothesis that the PDE5 inhibitor sildenafil will improve exercise capacity after 24 weeks of therapy in patients with HFpEF.¹¹² This trial will also assess the effects of sildenafil on a host of pathophysiological parameters postulated to impact clinical status and exercise performance in HFpEF. Results are awaited in Spring 2013. The Study to Test the Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Systolic Dysfunction (LEPHT) trial is a phase IIb, double-blind placebo-controlled trial enrolling patients with LVEF $\geq 40\%$ and mPAP ≥ 25 mmHg at rest.¹¹³ Patients on optimized HF therapy received placebo or the sGC activator riociguat for 16 weeks with mPAP as the primary efficacy endpoint; secondary endpoints include LVEF, exercise capacity, quality of life, and other hemodynamic and echocardiographic measurements. Follow-up was completed in August 2012 and results were announced during the 2012 American Heart Association Scientific Sessions. Riociguat was well tolerated but no significant reduction in mPAP was observed with any of the three doses tested. However, (1) cardiac index increased without changes in heart rate or systemic blood pressure, (2) systemic and pulmonary vascular resistance decreased in parallel, and (3) quality of life improved in patients receiving 2 mg tid riociguat.¹¹⁴ As previously discussed, the phase III PITCH-HF will be the first clinical trial to investigate the effect of PDE5 inhibition on hard outcomes in patients with HF. In order to accomplish this goal, 2102 patients with HF and reduced LVEF ($<40\%$), NYHA class II-IV symptoms, and either mPAP ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise, or RVSP ≥ 40 mmHg at rest, will be assigned to receive either the PDE5

inhibitor tadalafil or placebo for an average of 2.5 years. The trial is currently in the planning stages.

Future Steps and Study Designs

There are two distinct uses of elevated PAP as a therapeutic target in HF. Acute fluctuations in PAP secondary to increased LV filling pressures and elevated PCWP are a signal of impending acute HF.¹⁹ Noninvasive monitoring of these fluctuations can potentially serve as a treatment goal to fine-tune HF therapy and eventually improve outcomes.²¹ Chronic PAP elevation despite optimal therapy, on the other hand, is more likely to signify a permanent remodeling component in the pulmonary vasculature and a plausible target for long-term treatment in patients with HF. Oral agents with combined pulmonary and systemic vasodilatory activity appear to be promising to this end and their therapeutic role is being evaluated in ongoing clinical trials.^{93, 113} However, two related challenges need to be addressed in the planning stage of such trials: (1) how to identify patients with the most promising benefit vs. risk profile; and (2) which surrogate markers to use, either as selection criteria to optimize the benefit-risk ratio or as phase II endpoints.

To address specificity in patient selection, careful characterization of responder profiles would be required as part of dose-finding phase II studies. Due to the complexity of the various hemodynamic profiles in HF with PH, this would require in-depth mechanistic phase II trials, including RHC, echocardiography, and cardiopulmonary exercise testing. These profiles could then identify the appropriate population for long-term, outcome-driven trials to establish clinical benefit. Subsequently, simplified phase III designs would be desirable to ensure feasibility and better representation of the HF population at large.

The issue of surrogate markers and endpoints poses a challenge for HF clinical trials in general¹¹⁵ and in HF with PH in specific. Hemodynamic (e.g. echocardiographic RVSP) and circulating (e.g. B-type natriuretic peptide) markers in HF are characterized by short-term dynamic changes under the influence of multiple confounders. Current evidence suggests that functional surrogates (improvement in B-type natriuretic peptide or exercise capacity) do not always match the results of outcome-driven trials.¹¹⁶ On the other hand, although improvement in structural characteristics of the failing heart appears to match long-term outcomes better,¹¹⁷ it is difficult to implement this approach in the case of HF with PH. Effects on LV function may not be apparent in the traditional remodeling time frame (6 to 12 months) because the target is primarily the pulmonary circulation; and the right ventricle, the primary chamber of interest in PH, is notoriously difficult to quantify echocardiographically outside the research arena. Hence, the optimal surrogates in this population remain an open question. In this direction, ancillary studies with novel biomarkers (e.g. markers of cGMP pathway activity) as part of the ongoing phase III trials might help bridge this gap.

Conclusion

Group 2 PH portends worse prognosis and is a plausible therapeutic target in HF. Evaluation of right-sided hemodynamics with RHC is the gold standard for stage D patients and for initial detailed characterization of responses to novel agents in phase I/IIa trials. Echocardiography is a reasonable alternative for screening, enrollment, and response monitoring among the large stage C population for phase IIb/III trials. The initial experience with selective pulmonary vasodilating agents in unselected HF populations has been disappointing. However, shifting the focus to cGMP-enhancing agents, which provide a more balanced vasodilation, and selecting patients on the basis of elevated PAP, has yielded promising results in phase II studies. Phase III clinical trials currently underway will answer

the fundamental question: does reduction of PVR and/or PAP on a long-term basis improve outcomes in HF with PH?

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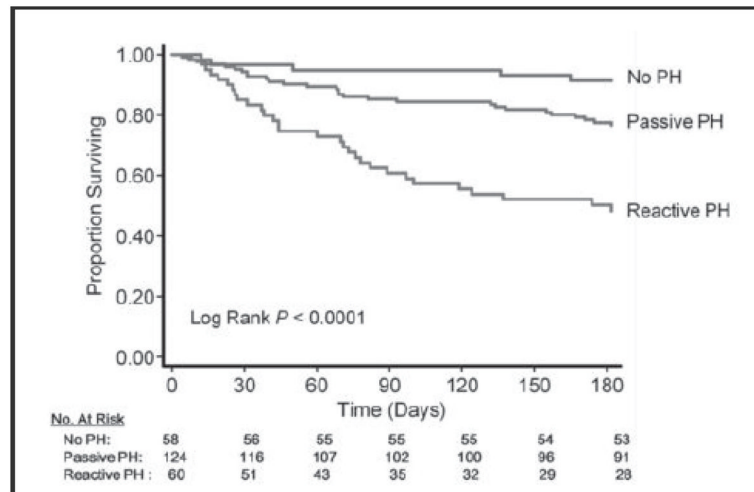


Figure 1. Six-month survival among patients hospitalized with acute heart failure according to their post-treatment pulmonary hypertension profile. Reproduced with permission from Aronson et al., *Circ Heart Fail.* 2011;4:644–650.

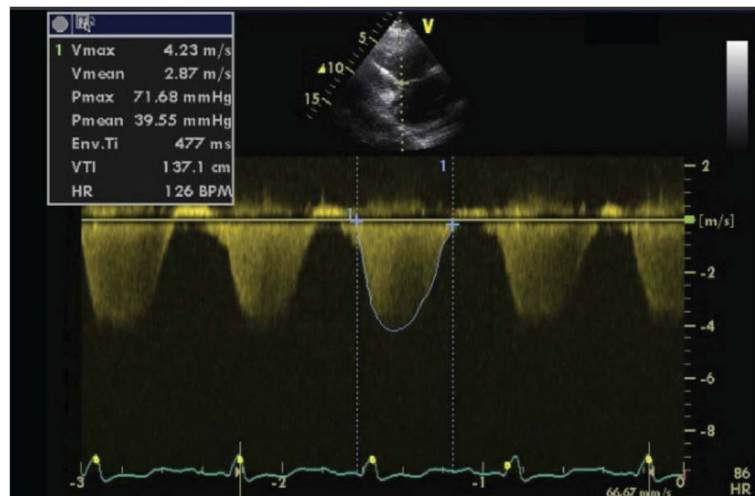


Figure 2.

Echocardiographic estimation of pulmonary vascular resistance using the tricuspid regurgitation jet velocity (TRV) and the corresponding time-velocity integral (TVI). In this patient, despite a gradient of 72mmHg through the tricuspid valve, the estimated pulmonary vascular resistance (PVR) would be $PVR = TRV(m/s)/TVI(cm) \times 10 + 0.16 = (4.23/137.1) \times 10 + 0.16 = 0.47$ Wood Units, suggesting the absence of a significant reactive component.

Table 1
Prognostic Significance of Pulmonary Hypertension in Patients with Heart Failure

Study	N	Population	Method	Follow up	Threshold	Outcome	Effect
Heart Failure with Reduced Ejection Fraction							
Abramson 1992 ³	108	Dilated CMP; mean LVEF 17.2%	Echo	28 months (maximum)	Tricuspid regurgitation jet velocity >2.5m/s	Mortality HF admission Combined	57% vs. 17%; RR 3.4 75% vs. 26%; RR 2.9 89% vs. 32%; RR 2.8
Ghio 2001 ¹²	377	Tx evaluation; LVEF 21.8±6.7%	RHC	17±9 months	Continuous mPAP	Mortality or urgent Tx	aHR 1.10 per 5 mmHg (95% CI 1.00 to 1.21)
Cappola 2002 ¹³	1134	New-onset CMP; LVEF: N/A	RHC	4.4 years (average)	PVR >3.0 WU (vs. PVR <2.5 WU)	Mortality	aHR 1.86 to 2.04 (depending on PVR level)
Grigioni 2006 ¹⁴	196	NYHA class III-IV; LVEF 27%±9%	RHC	24±20 months	mPAP >25 mmHg	Mortality plus acute HF	Adjusted RR 2.30 (95% CI 1.42 to 3.73)
Shahaly 2008 ⁴	270	CRT recipients; LVEF 22.6%±9.7%	Echo	19.4±9.0 months	RVSP 45 mmHg (vs. RVSP <30 mmHg)	Mortality HF admission	34% vs. 12%; aHR 2.62 (95% CI 1.07 to 6.41) 40% vs. 9%; aHR 6.35 (95% CI 2.55 to 15.8)
Szwejkowski 2012 ⁸	1612	LVSD, loop diuretics, and measured RVSP	Echo	2.8±2.5 years	RVSP >52mmHg (vs. <33 mmHg)	Mortality	60.7% vs. 47.4%; aHR 1.50 (95% CI 1.19 to 1.90)
Heart Failure with Preserved Ejection Fraction							
Lam 2009 ⁶	244	In- and out-patients; LVEF 50%	Echo	2.4±1.2 years	Continuous RVSP	Mortality	aHR 1.20 per 10 mmHg
Heart Failure with Reduced or Preserved Ejection Fraction							
Damy 2010 ⁷	413	270 with LVEF 45% 143 with LVEF >45% and measurable TR	Echo	66 (56-74) months*	Q4 vs. Q1-Q3 RVSP	Mortality	NT-proBNP-adjusted HR 1.46 (95% CI: 1.07 to 1.98)
Tatebe 2012 ¹⁵	676	HF patients NYHA II-IV referred for RHC	RHC	2.6 years (median)	mPAP 25mmHg PVR 2.5 WU PVR >2.5 WU	Mortality	29.1% (PH) vs. 15.3% (no PH) 24.0% (passive PH) 37.9% (reactive PH)
Bursi 2012 ⁹	1049	Community in- and out-patients with HF	Echo	2.7±1.9 years	Tertiles RVSP (<41, 41-54, >54 mmHg)	Mortality	T2 vs. T1: aHR 1.45 (95% CI 1.13 to 1.85) T3 vs. T1: aHR 2.07 (95% CI 1.62 to 2.64)
Acute Heart Failure							
Kjaergaard et al. 2007 ⁵	388	Admitted for HF; LVEF 33 (23-50)%	Echo	2.8 years	Continuous RVSP	Mortality	HR per 5mmHg 1.09 (95% CI 1.04 to 1.14)
Khush et al. 2009 ¹⁷	171	Clinical trial; SBP 125 mmHg; LVEF 30%	RHC	6 months	mPAP 25mmHg; PVR 3 WU (Pre-treatment values)	Mortality Readmission	No difference No difference

Study	N	Population	Method	Follow up	Threshold	Outcome	Effect
Aronson <i>et al.</i> 2011 ¹⁸	242	Clinical trial; LVEF 25% ±13%	RHC	6 months	mPAP >25 mmHg PVR > 3 WU ("passive") PVR >3 WU ("reactive") (Post-treatment values)	Mortality	Reactive PH: 48.3%; Passive PH: 21.8%; No PH: 8.6% Passive vs. No PH: aHR 1.7 (95% CI: 0.6 to 4.5) Reactive vs. No PH: aHR: 4.8 (95% CI: 2.1–17.5)

aHR: adjusted hazard ratio; CMP: cardiomyopathy; CRT: cardiac resynchronization therapy; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PCWP; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RR: risk ratio; RVSP: right ventricular systolic pressure; SBP: systolic blood pressure; TR: tricuspid regurgitation; Tx: transplantation; WU: Wood units

* Follow-up for the entire cohort of 2100 patients (measured and unmeasured RVSP).

Table 2
Long-term, Placebo-Controlled Studies in Patients with Heart Failure and Pulmonary Hypertension

Study	Drug	Duration	Population	N	Results
Lewis et al. 2007 ⁶⁷	Sildenafil (25 to 75 mg t.i.d.)	12 weeks	NYHA class II-IV, LVEF <40%, mPAP >25 mmHg	34	Sildenafil increased peak VO ₂ and cardiac output and reduced PVR with exercise; no effect on PCWP, blood pressure, or heart rate; improved 6-MWT distance and reduced HF admissions; higher incidence of headache
Kaluski et al. 2008 ⁶⁸	Bosentan (8-125 mg b.i.d.)	20 weeks	NYHA class IIIB-IV, LVEF <35%, RVSP 40 mmHg (echo), supine SBP 100 mmHg	94	No difference from baseline to week 20 in RVSP (0.1±11.5 mm Hg, p = 0.97) or other echocardiographic parameter; more SAEs in the bosentan arm
Guazzi et al. 2011 ⁶⁹	Sildenafil (50 mg t.i.d.)	1 year	LVEF 50%, RVSP 40 mmHg (echo)	44	Sildenafil reduced mean PAP by 42.0±13.0%, improved right ventricular function, and reduced right atrial pressure by 54.0±7.2% and PCWP by 15.7±3.1%
Guazzi et al. 2012 ⁷⁰	Sildenafil (50 mg t.i.d.)	1 year	LVEF <45%, mean PAP 25-35mmHg	32	Sildenafil increased peak VO ₂ and exercise ventilation efficiency, and decreased PCWP, mean PAP, and pulmonary vascular resistance

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; RVSP: right ventricular systolic pressure; SAE: serious adverse event; SBP: systolic blood pressure