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Risk stratification refinements with inclusion of hemodynamic variables at follow-up in patients with pulmonary arterial hypertension

Announcer:

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Dr. McLaughlin

Hello. I'm Dr. Vallerie McLaughlin from the University of Michigan, and welcome to this Journal Club: Risk Stratification Refinements with Inclusion of Haemodynamic Variables at Follow-Up in Patients with Pulmonary Arterial Hypertension.

So we all know that hemodynamics are predictive in PAH, but they're not really systematically recommended to assess risk at follow-up. If you look at the current ESC/ERS guidelines, they really leave it to the discretion of the managing physician to repeat hemodynamics, and they really lean on functional class, hall walk and biomarkers for risk assessment. So this study aimed to assess the added value of hemodynamics in prevalent patients to predict the risk of death or lung transplantation when used according to the 4 strata risk assessment, using the ERS/ESC model.

So if we think about hemodynamics, there have been many studies that looked at hemodynamics, starting back with the NIH Registry in 1991. Before there was any therapy available, the hemodynamic predictors of risk were right atrial pressure, mean pulmonary artery pressure, and cardiac index. But when looked at in many other studies, the hemodynamics effect to predict prognosis have really been inconsistent. And in fact, some studies have even suggested that a higher mean pulmonary artery pressure is better; it might correlate with function of the right ventricle.

So this is a study from the French group, and they looked at the patients with PAH in the French registry who were newly diagnosed from January of 2009 to December of 2020. The classical hemodynamic definition of mean pulmonary pressure greater than 25, or equal to 25, wedge less than or equal to 15, and PVR [pulmonary vascular resistance] greater than 3, was what determined whether or not the patient had PAH. They looked at those who had at least 1 follow-up right heart catheterization. They excluded some patients, including those with PVOD [pulmonary veno-occlusive disease], unrepaired congenital heart disease, portal hypertension, those with a positive vasodilator response, because that's obviously a different group, and those with missing data, to calculate the 4 strata, so functional class, hall walk, or biomarkers. And the measurements on follow-up right heart catheterization included mean pulmonary pressure, wedge pressure, cardiac output by thermodilution, and mixed venous oxygen saturation (SvO₂).

The primary outcome for this analysis was a very hard outcome. All-cause mortality or lung transplantation, so very, very hard outcomes. They used Cox proportional hazard regression for the statistical analysis, and a refined tool was created based on the noninvasive variables and the hemodynamics. So this is a newly created tool that was compared with the 4 strata method using time-dependent receiver operating curve statistics.

So this is a little bit about the patients that were included in the study. The largest groups were those with idiopathic PAH and connective tissue disease-related PAH. The 6-minute hall walk at baseline at the time of diagnosis was 301 meters, quite a wide

standard deviation, but a pretty sick population. 68% of them were functional class 3 or 4. The most common therapy within the first 3 months was monotherapy in half of the patients. Now remember, they took patients that were enrolled starting in 2009, so that probably is why there's a large proportion of patients with monotherapy followed by dual combination therapy, so almost 40%, and, of course, the sickest of the sick get up-front triple-combination therapy. So that was the mix of the therapies that were decided upon at baseline. And at 3 years of follow-up, 30% had died and 3% underwent lung transplantation. So the 1-, 2-, 3-, and 5-year survival was 97%, 89%, 79%, and 63% respectively. So pretty typical of our current era of PAH treatment.

The median time until that first follow-up was about 5 months. So this is kind of the protocol that is used often in France; at 4 to 5 months they do that first right heart catheterization. And at first follow-up, there were significant improvements in functional class, hall walk, biomarkers, and hemodynamics. In fact, 61% of the patients had achieved functional class 1 or 2 status at the time of the first follow-up. The 6-minute hall walk had improved by about 37 meters, from 301 to 338, and the PVR decreased from 9 to 6 wood units, so about a 33% reduction in PVR in that group as a whole.

The risk stratification using the 4-risk strata method at the time of that first follow-up, so 31% were low risk, 39% intermediate-low, 24% intermediate-high, and 6% were high risk. So you can see the bulk of the patients, more than 60% of the patients, fell into the intermediate-risk group and there's a pretty good distribution there between intermediate-low and intermediate-high. So the low-risk patients and the high-risk patients, it's really interesting the hemodynamics didn't impact the outcomes, and so the results really focused on those patients with intermediate risk, so almost 800 patients. And in these patients, the predictors that were associated with transplant-free survival included the right atrial pressure, the mean pulmonary pressure, cardiac output and index, PVR, stroke volume index (SVi), and mixed venous oxygen saturation. And when they did time-dependent receiver operating curve analysis, they used that to identify the optimal thresholds for these different hemodynamics, maximizing the sensitivity and specificity. So the thresholds were 8 for right atrial pressure, 47 for mean pulmonary artery pressure, 2.56 for cardiac index, 5.7 for PVR, 37 for our stroke volume index, and 65% for SvO₂. So actually pretty consistent with some other reports that we've seen in the literature.

And then, when they adjusted for all of the noninvasive 4 strata scores and used all of those predictive hemodynamics, cardiac output, PVR, at follow-up were associated with the risk of death and lung transplantation. And SVi and SvO₂ were the best variables to predict transplant-free survival in patients with low-intermediate or high-intermediate risk. And so, interestingly, that SVi cutoff of 37 is exactly what's in the 2022 ESC/ERS guidelines.

So to summarize, over 1,200 patients had that right heart cath within the first year. Amongst the patients who were low risk or high risk, using the 4 strata, the hemodynamics did not add anything to those prognoses. But among the intermediate-risk patients, either intermediate-low or intermediate-high, stroke volume index and mixed venous O₂ really did add further prognostic information. And so this led to the development of a refined strata model using SVi greater than 37 and SvO₂ greater than 65%. And that was better than the 4 strata method.

So refining that, you can see this table here that takes you through that risk. So on the left you see the noninvasive 4 strata approach. So on the top, low risk doesn't add anything to the transplant-free survival, and these patients have a very good prognosis. High risk, it doesn't add anything, and these patients have a very poor prognosis. But if you look at the intermediate-low risk, if those patients have at least one or the other, potentially both, but at least one or the other, an SVi greater than 37 and an SVO₂ greater than 65%, their 1-year survival was much better, 97% versus 94%, and 3-year survival 81% versus 69%, than the intermediate-low-risk patients who did not have one of those criteria. And similarly for the intermediate-high-risk patients, if they had one of those good prognostic criteria, their 1- and 3-year survival was better than if they did not. So we go from 4 strata to 6 strata by applying these hemodynamic criteria to the patients at intermediate-low and intermediate-high risk.

And here you see the survival curves of those different groups. So low on the top, intermediate-low with good hemodynamics, the second one. Now I think it's really important to point out that that intermediate-low with good hemodynamics, their 1-year survival is pretty close to low, but their 3-year survival is not as good as low. So that's still not as good as we would like. Then comes intermediate-low with poor hemodynamics. Intermediate-high with good hemodynamics is better than intermediate-high with bad hemodynamics, but they're still not very good.

So to conclude, patients who are at low or high risk by the 4 strata method, in those patients, the hemodynamics do not further improve risk stratification. Among patients with intermediate risk, either intermediate-low or intermediate-high, stroke volume index and SvO₂ were the best hemodynamic predictors of transplant-free survival. And then the prognostic performance of the 6 strata approach, so using the 4 strata approach to start out with, and then for those at intermediate risk, applying the hemodynamics, so now you have 6 strata. That approach was better than the 4 strata approach.

So I think this paper is really interesting. I think that we had a great leap when we had the 4 strata method available, separating that

intermediate-risk group to intermediate-low and intermediate-high, because that intermediate-risk group is really big. But now this even further refines that and gives us more information in patients who are at intermediate-low or intermediate-high by the 4 strata technique, adding these hemodynamic variables.

So thank you for joining me for this Journal Club today.

Announcer:

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