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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Vasoreactivity in Pulmonary Hypertension

Announcer:
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Dr. Chin:
Welcome to CME on ReachMD. I'm Dr. Kelly Chin and today I'm reviewing vasoreactivity in pulmonary hypertension and what it means for patients.

So quick overview, topics to be covered include vasodilator testing, how to do it, how to interpret it, and who should be tested, and then following this, what treatment should be implemented, specifically focusing on calcium channel blockers, and in both idiopathic PAH as well as which forms of associated PAH these can be considered. And then, we'll wrap up with overall treatment recommendations and follow-up.

So how to do a vasodilator challenge? This is typically done following a patient's first right-heart catheterization while they're still there in the cath lab and a full set of hemodynamics have been obtained. And it is indicated in all patients with idiopathic heritable and drug- and toxin-associated pulmonary arterial hypertension. But because you often don't know right at that moment whether a patient falls into one of those categories or not, at our center we recommend vasoreactivity testing at first cath in all patients with precapillary pulmonary hypertension. Meaning if the wedge is high, we don't do it. Otherwise, we recommend going ahead with the vasodilator test.

The medications that can be used are inhaled nitric oxide at 10 to 20 parts per million, inhaled iloprost at 5 to 10 mcg, or IV epoprostenol, though the latter has fallen out of favor because it can cause hypotension. Additionally, if using inhaled nitric oxide with a simple nasal cannula or simple face mask, where you're not getting 100% of the nitric oxide that you have the machine dialed in at, we recommend increasing the nitric oxide to 40 parts per million so that you ensure that what reaches the patient is actually going to be in that range.

A positive test is a drop in pulmonary mean pressure by at least 10 mmHg, and to less than 48 mmHg absolute, along with no decline in cardiac output or cardiac index. And this suggests the potential for a long-term response to calcium channel blockers.

So where did this all come from? Well, the first big study really to look at this came from Stuart Rich in 1992. At that point, clinicians were desperately looking for a treatment for pulmonary hypertension. Nothing was approved, nothing was working, although there were hints here and there that some patients appeared to respond to vasodilators. And they were trying everything, things like hydralazine and other high blood pressure medications.

So what Stuart Rich and colleagues did was treat 64 patients with calcium channel blockers. And they very carefully measured hemodynamics at baseline, at 24 hours, and in most patients, annually after that when they were able to. And what they were able to show was that a subgroup of patients responded very well, and that these patients at 24 hours already had markedly improved hemodynamics.

So the figure on the right shows the pulmonary pressures at 24 hours and annually thereafter, and you can see the very large drops in

pressure. This same group is in the survival curve on the left, the ones with the open circles where you see around 90% survival even at 5 years. In contrast, the patients who did not have a good response at 24 hours were also long-term poor responders, and you can see that in the survival curve as the straight line that had a similar survival to those in the NIH Registry, where there were no effective treatments for these patients at that time.

Now, they used a definition of vasodilator responder that was a 20% drop in pulmonary pressures and in PVR [pulmonary vascular resistance], and that has subsequently changed in a large part based on this next study that was completed by Olivier Sitbon and his colleagues in France. They looked at 557 patients. They received vasodilator testing with either inhaled nitric oxide or IV epoprostenol. And they applied what was known as the Rich criteria there, the 20% drop in pulmonary pressures in PVR, and what they found was that 70 patients responded, which was 13%, but only half did well on this with long-term calcium channel blocker therapy.

And so on the right is the survival curve, and they came up with new criteria based on looking back at the patients who did well and the patients who did not do so well. They come up with the more rigorous criteria that we still use today, which is the 10 mm drop in pulmonary pressure to a final pressure less than 40 mmHg. They also found that the clinical response at 1 year also predicted long-term outcome. And this is also a really important factor, and I'll show this in more detail in a newer study that was completed just in the last year, is that with so many other treatments for pulmonary hypertension for patients who aren't having a good response, then we want to find this as early as possible. So the treatment escalation is an option.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Kelly Chin, and I'm reviewing vasoreactivity in pulmonary hypertension and what it means for patients.

So the final study that I want to go through was published just this last year from a number of centers in Germany. This is the largest center to date. There were almost 2,000 patients who underwent vasodilator testing and they tracked long-term response following this. 184 patients met the hemodynamic criteria for an acute response, that's the 10 mmHg drop to a pressure less than 40, so this is around 10%. And on the left, you can see the overall survival for these patients. So at 5 years, nearly 90%. So as a group, they did very well. But you could further identify longer-term outcomes by looking at how patients were doing at 6 to 12 months, and those who had a sustained clinical response over that first 6 to 12 months had excellent survival, near 100%, while those who didn't did not do as well, with survival at just a little over 70%.

Now, they looked at this group in a little more detail to see if perhaps further revision to the vasodilator criteria was indicated, and they did note that those who were long-term responders had a little more of a drop in PVR, and had a little bit of a larger increase in pulmonary arterial compliance. But they did not recommend changing the criteria because that might be too restrictive and you would fail to identify some patients who would have responded.

The other important finding from this study was the ability to predict long-term outcome based on also the clinical response to calcium channel blockers as they were treated over the first 6 months. So what we're looking at here is 6-minute walk distance and NT-ProBNP levels, and in particular, you can see the really large improvement in NT-ProBNP levels at 6 months in those with a long-term response to calcium channel blockers versus much smaller changes for those who did not respond long term. The 6-minute walk distance changes look a little less dramatic, but the scale goes all the way from 0 to 800, so this was also a fairly large improvement in 6-minute walk distance for those who were the long-term responders, versus much smaller improvements for those who were not.

So then, as far as treatment, how did things go in this study? So most patients were started on calcium channel blocker monotherapy following their positive vasodilator response, and that's the patients in light blue on this scale. But more than 20% also received a PAH medication, mostly PDE5 inhibitors and ERAs at diagnosis. And then you can see, as time goes on, the proportion receiving a calcium channel blocker with a PAH medication increases, and then in red, there's also a little over 10% of patients in whom calcium channel blockers were withdrawn, either due to lack of continued response or intolerability of the side effects.

So now, we come to recommendations to put this all together. So this applies to patients with idiopathic heritable and drug- and toxin-associated PAH. And this is a sort of mini treatment algorithm focused on the calcium channel blockers, but also on follow-up. So if we start at the top, you perform vasodilator testing, as we've discussed. For patients with a response, and only for patients with a response, calcium channel blocker monotherapy should be initiated. And then, follow-up at 3 to 4 months is recommended. This should include functional class, walk distance, and either BNP or NT-ProBNP. And in most patients, hemodynamics and right heart imaging, usually with echocardiogram, is recommended. And to be considered a long-term responder, then, at follow-up, what we would like to see is a low-risk profile for those noninvasive measures. And then on hemodynamics, it should really be near normal, a fairly high bar for these patients who usually do have a very good response to calcium channel blockers, but not always.

Following this risk assessment, if all of those criteria – good hemodynamics, low-risk criteria – then continuation of calcium channel blockers alone with repeated risk reassessment periodically is recommended. And then for patients who are not at low risk or whose

hemodynamics do not meet these criteria, then the addition of approved PAH therapies is recommended. Whether to stop calcium channel blockers at this time or not is still an area of debate. Some people will repeat vasodilator testing during the follow-up catheterization to see if there's still a response, and also, sometimes to consider increases in calcium channel blockers based on this. But there's not a well-established pathway in this regard.

As far as dosing, the PAH Guidelines recommend starting low because these are antihypertensive medications and you don't want to drop patients' blood pressure too much, but with escalation to the maximum approved doses for hypertension. And then in most cases, well beyond that to the maximum tolerated dose or until you've achieved the hemodynamic effects of near normalization of pulmonary pressures.

So on this slide I have, from the recent German study, the actual dosing that was achieved for patients on various different calcium channel blockers. And these are the mean doses of the maximal tolerated dose as well as the range of doses that were utilized. So for amlodipine, for example, which was the most commonly utilized calcium channel blocker, the average maximum tolerated dose was 15 mg, which is well above typical antihypertensive dosing, and the range of doses was from 5 to 40 mg was the highest dose recorded in this study. So typically, fairly high doses are frequently required in order to get the hemodynamic effects that we want to see.

What about other forms of pulmonary hypertension? So I mentioned earlier that this was indicated for idiopathic heritable and drug- and toxin-associated PAH. What this study looked at was, what about other associated forms of pulmonary hypertension? And unfortunately, although some subgroups do respond acutely, there weren't responders long term to calcium channel blockers. So, for example, you see in yellow the connective tissue disease group and the PVOD [pulmonary veno-occlusive disease] group both had 10% to 12% respond acutely to vasodilator testing, but almost no one responded long term. And then for the portopulmonary, HIV, and congenital heart disease groups, there was neither an acute response nor a long-term response to calcium channel blockers, and this contrasts with what was previously shown in idiopathic patients. And then, at the top of the slide, the appetite suppressant patients in this study, where a sizable portion did respond to both acute vasodilator testing and calcium channel blockers.

So then, wrapping things up, just to summarize what we've talked about. The main things to remember are the subgroups to test are idiopathic, heritable, and drug- and toxin-associated PAH. But in many cases, you may not know what subgroup of pulmonary hypertension a patient has at first right heart catheterization, and so testing and other forms of precapillary PAH is acceptable, but those subgroups should not be treated with a calcium channel blocker. The definition is the 10 mmHg drop in pulmonary pressures to a final pressure less than 40 with no decline in cardiac output or index.

When starting calcium channel blockers, start low, but the effective doses are frequently high, and monitor for systemic hypotension and peripheral edema as the main side effects to watch for. Serial follow-up with walk distance, functional class, natriuretic peptides, echo and cath is recommended. And with this, you should be able to identify patients who may require escalations in therapy to other approved PAH medications.

I hope you found this information useful. Thank you for joining me today.

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