Sarcoidosis and Pulmonary Hypertension

Dr Oksana Shlobin: Welcome to the roundtable on sarcoidosis-associated pulmonary hypertension (SAPH), moderated by myself and Dr Anjali Vaidya, Co-Director of the Pulmonary Hypertension, Right Heart Failure, and CTEPH Program at Temple University Lewis Katz School of Medicine. Our discussants are Dr Roxana Sulica, Associate Professor of Medicine and Director of the Pulmonary Hypertension Program at NYU Langone, Dr Bob Baughman, Professor of Medicine at University of Cincinnati, and Dr Stacy Mandras, Medical Director of Pulmonary Hypertension Program at AdventHealth.

Dr Anjali Vaidya: Sarcoidosis is probably one of the biggest topics within WHO group 5 PH. There are a lot of excellent publications and reviews on this topic, and many are written by all of you. We thought that rather than doing another review article on that topic, we would have a discussion with your expertise to talk about your experiences and observations in this broad area. One of the first things we thought we would touch upon is the multiple mechanisms by which patients with sarcoidosis can develop pulmonary hypertension.

I would like to start by focusing on a few main mechanisms: the parenchymal lung disease causing vascular destruction, the granulomatous involvement of the pulmonary arterial bed to resemble PAH, and the extrinsic and external compression of bulky lymphadenopathy. I want to get a sense from your experiences in terms of what you see most frequently and what you think the prevalence of PH is in your patients with pulmonary sarcoid.

Dr Roxana Sulica: I can start the conversation. The prevalence question depends on the kind of practice you have: a sarcoid practice in which you end up diagnosing patients with pulmonary hypertension versus a pulmonary hypertension practice with sarcoidosis referrals when patients are referred to you for suspicion of PH.

Currently, 100% of the patients I am seeing have pulmonary hypertension. When I was in Mount Sinai with a dedicated sarcoidosis clinic, we observed SAPH in 20% of patients. Again, if you look at patients from advanced lung programs evaluated for transplantation, pulmonary hypertension can be seen in up to 75% of that referral patient population. To summarize, SAPH is a well-recognized complication of sarcoidosis, but the prevalence depends on the clinical setting.

In terms of the mechanism, there is a myriad of reasons for patients with sarcoid to develop pulmonary hypertension. Hence, they are placed in group 5 pulmonary hypertension. As it has been shown in multiple series, most of the time patients with SAPH have parenchymal lung disease and chronic hypoxemia. However, probably in about 20% to 30% of the people in each series reported, there is another pathophysiologic mechanism besides pulmonary fibrosis involved. For example, many years ago, Robyn Barst reported a small series with patients with SAPH with pulmonary arteriopathy, fairly similar to iPAH. Subsequently, there were a lot of other series describing the SAPH histopathology in explanted lungs or postmortem examinations. We started to identify this process of granulomatous inflammation, in the arterioles but mainly in the venules of the pulmonary vasculature, a mechanism similar to pulmonary vaso-occlusive disease (PVOD). In addition, a small percent of people with SAPH has significant extrinsic compression of the pulmonary vasculature by the mediastinal and hilar adenopathy of fibrotic disease.

Some people, in theory at least, have granulomatous hepatitis from sarcoid and can develop portal hypertension, and consequently porto-pulmonary hypertension. About one-third of them will have pulmonary hypertension due to left heart disease, as Bob Baughman has shown in one series. It is very important to identify the dominant phenotype to help guide further medical management.

Dr Bob Baughman: I primarily work in a sarcoidosis clinic, although I have had a strong interest in pulmonary hypertension and have collaborated with Dr Peter Engel at University of Cincinnati for many years.

Dr Shlobin: Bob, maybe you can mention or comment on disease prevalence given that you mostly see patients with sarcoidosis versus Roxana and Stacy, who mostly see patients with pulmonary hypertension.

Dr Baughman: I think you have to think in terms of where you're coming from. In a tertiary clinic like ours, which includes a lot of patients with refractory parenchymal disease, it's around 7 to 10%. In some published series, it is as high as 20%. In Athol Wells' group in London, where mostly fibrotic sarcoidosis patients are seen, nearly a quarter have PH. In general, I think it's somewhere between 5% and 20%.

Dr Shlobin: Thank you Bob. A follow-up question is for Stacy and also Anjali. As advanced heart failure cardiologists, can you comment on the various mechanisms the sarcoidosis can affect the heart and cause PH, as well as the importance of right and left heart catheterization in teasing out a specific diagnosis, and why it is especially important in sarcoidosis population?

Dr Stacy Mandras: As a heart failure specialist, we do see a small percentage of patients who come to us with an underlying diagnosis of cardiac sarcoidosis. I'd say less than 10% of our referrals with advanced heart failure have cardiac sarcoidosis. In the general sarcoidosis

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population, cardiac disease is often subclinical, and we may not even make the diagnosis until the time of transplantation when we review the pathology after the heart has been explanted. At least a third of these patients will have pulmonary hypertension due to elevated left sided pulmonary pressures associated with diastolic dysfunction. Often these patients also present with ventricular arrhythmias, which will ultimately lead to their need for transplantation, as they tend to be very difficult to control despite antiarrhythmic drugs and ablations. Even sympathectomy can be completely ineffective in these situations, and in such cases, the management corners on treatment of the underlying LV dysfunction (rather than treatment of the pulmonary hypertension), and often ultimately leads to cardiac transplantation.

In my pulmonary hypertension practice, I see all of the mentioned mechanisms of SAPH—everything from WHO group 1 to group 5—the patients with concomitant left sided heart disease, fibrocystic lung disease, the patients who have extrinsic pulmonary artery compression, and the patients who truly do look like they have WHO group 1 pathophysiology.

Dr Shlobin: I wanted to ask the group if any of you use any kind of provocative maneuvers while doing the right heart catheterization in these patients.

Dr Sulica: Yes, I do as I always contemplate how to treat their PH. As you very well know, it is very difficult to get PAH-specific medications approved without a vasoreactivity maneuver. Obviously, patients with precapillary SAPH, even with positive vasoreactive maneuver, are not true *vasoreactors*, at least not by the definition that incorporates long-term response to calcium channel blockers.

Dr Vaidya: I agree with contemplating treatment. I think that's a whole other discussion and something that we all, in the PH space, have our minds open to. I always appreciate talking to colleagues from different places, because the insurance payer patterns are very different. I haven't done a vasoreactive study in years for the purpose of getting medications approved, and it probably depends what the payers require in your specific geographic area.

From a purely clinical purpose of understanding pathophysiology and its affecting management, I actually don't do vasoreactive studies in the sarcoid PH patients. But from a broader sense, in terms of provocative maneuvers, I do often include exercise physiology into the right heart catheterizations in these patients to identify their true cause of dyspnea. This ties into Stacy's point about the mixed left heart failure phenotype, which often actually can coexist with a PAH phenotype in the sarcoid PH patient. These are some of the most challenging patients that we are facing that have the mixed physiology, precapillary and postcapillary PH.

I'll use provocative maneuvers in the Cath Lab with rest and perform an exercise RHC with simultaneous CPET (aka invasive CPET) to get a sense as to what their true underlying physiology and limitation with exertion is. From a hemodynamic perspective, if they have mixed physiology and their wedge pressure goes up by two-fold or three-fold while the right atrial pressure goes up only minimally and their pulmonary vascular resistance falls, that indicates that this is more of a WHO group 2 left heart failure PH phenotype. Whereas, if their VE/VCO_2 climbs to 45 with exercise and their PVR does not fall, or it goes up and the right atrial pressure goes up to a magnitude greater than left atrial pressure, then I might say, "The phenotype of this patient is more clearly that of pulmonary vascular disease or more resembling the iPAH patient." These provocative maneuvers can be quite helpful.

Dr Shlobin: Stacy, do you also prefer exercise right heart catheterization with CPET versus fluid loading in this patient population?

Dr Mandras: Absolutely agree with Anjali. I like to exercise patients in the Cath Lab to attempt to unmask diastolic dysfunction. We use an *under the desk* exercise bike pedal exerciser that we literally put on the Cath table once the pulmonary artery catheter is in place and we have obtained baseline hemodynamic measurements. We have the patients pedal for exercise, and we record what happens to their systemic pressure, their filling pressures, PA pressure, and cardiac output. I prefer doing that to fluid loading. I have partners that do fluid challenge their patients, but I feel that we get more information from having them exercise and try to simulate what happens when they're active to try to understand why it is that they're getting short of breath with activity.

Dr Vaidya: Exercise cath is much more physiologic than a fluid challenge. If I can build off of what Stacy said, going back to the left heart failure component of the conversation, I want to bring it even to the next level in terms of the transplant consideration, because in the lung transplant world, sarcoid is a big player. In the heart transplant world, sarcoid is a big player. We have a large exposure to the combined heart-lung transplant world, relative to our other left heart failure partners or other lung transplant partners.

I find the sarcoid population is the most commonly represented diagnosis in this population of combined heart-lung transplant. I also find it to be very challenging sometimes, because the isolated indication for lung transplant might not be as obvious, and the isolated indication for heart transplant may not be as strong. In other words, their fibrotic lung disease might not be as severe or their PAH might not be as severe or their left heart failure might not be as severe, but when you combine them together, a heart-lung transplantation is the indicated treatment.

Sometimes the lung disease will preclude PH management, or the left heart involvement will preclude PH management, and the additive sum component of infiltrative granulomatous disease causing arrhythmia, diastolic dysfunction, systolic dysfunction, right heart failure from PH, gas exchange limitation is often a rapid accelerator driver to combined heart-lung transplant. I'd like to hear what the rest of the group has experienced in that regard?

Dr Baughman: I'm probably the only non-"transplanter" here. I think a lot of the time that sarcoidosis PH can be medically managed, but I think it's an evolution management. Often patients present with a combined precapillary and postcapillary PH, which is initially managed with diuretic therapy. Once their volume status is well controlled, if the patient is still short of breath, they may benefit from treatment of the precapillary component of their pulmonary hypertension as well. I agree that it's very good to do the exercise challenge in Cath Lab to try to uncover the predominant phenotype in these mixed PH cases.

In our original paper with Peter Engel, of 120 sarcoidosis patients that underwent catheterization, a significant number of patients had diastolic dysfunction. We weren't doing routine cardiac MRIs at that time and we've never had an opportunity to analyze another large group of dyspneic sarcoidosis patients to determine how many may have myocardial involvement by cardiac MRI.

Has any of you seen any data on how often a cardiac MRI uncovers potential causes for diastolic dysfunction in these sarcoid patients?

Dr Shlobin: I have not. In my experience, patients with significant cardiac sarcoid do not usually have precapillary pulmonary hypertension and vice versa. In our experience, it's either severe PH (with or without parenchymal disease) or bad cardiac sarcoid. To follow up on Anjali's question, you're absolutely right. Other than congenital heart diseases, sarcoidosis is the most common indication for combined heart-lung transplant. In my experience it's a combination of end stage burnt out parenchymal lung disease and active cardiac sarcoidosis causing arrhythmias that cannot be controlled medically, or significant left systolic ventricular dysfunction that is the most common indication. Per our lung transplant work up protocol, we always look for cardiac sarcoidosis with a combination of cardiac MRI and PET.

Dr Shlobin: I wanted to go back to the basics and ask Bob and Roxana, when do you suspect pulmonary hypertension in patients with sarcoidosis, and then how do you work them up?

Dr Baughman: Our clinic approach was initially driven by Roxana's publication, when she was at Mount Sinai and analyzed a large number of patients referred for echo. We then began looking at our persistently dyspneic patients, those failing anti-inflammatory therapy such as prednisone, methotrexate, and/or infliximab, and found that over half of these patients had pulmonary hypertension. So when I see someone in sarcoidosis clinic who I'm treating for lung disease with anti-inflammatory therapy and they're just not getting better, I start the work up for pulmonary hypertension.

The other clues there that helped me include a reduced six-minute walk test (6MWT) distance. Certainly somebody who walks under 300 meters or who desaturates during their 6MWT needs a screening echo and probably right heart catheterization to look for either precapillary or postcapillary PH. An elevated BNP is another clue. The Dutch have actually suggested that a sarcoidosis patient with fibrosis on chest imaging should get an annual ECHO. The term *parenchymal fibrosis* is a bit difficult in sarcoid, because there are a lot of people with a little bit of fibrosis on their imaging. Therefore I would modify that to say that patients with at least 20% fibrosis on CT scan should be considered for screening ECHOs.

I still think that the main trigger for work up is persistent or out-of-proportion shortness of breath. The other factor that I don't use as much as others is an enlarged pulmonary artery (PA) or PA/aorta diameter ratio on chest CT scan. There is interesting data in sarcoidosis showing the denominator should not be the aorta diameter but the body surface area. Two large series (1 from Holland, 1 from France) showed that the PA diameter when corrected for the body surface area was a better predictor of SAPH.

Dr Sulica: How about diffusing lung capacity (DLCO)?

Dr Baughman: A reduced DLCO is probably much more useful than a reduced forced vital capacity. The things that should bring PH for consideration are: a reduced DLCO (probably less than 60% or predicted), a 6MWT distance of less than 300 meters, new or worsening desaturation with exercise, more than 20% fibrosis on high-resolution CT scan, or dyspnea that seems out of proportion to their clinical presentation and the amount of lung disease. Those patients should be further worked up for pulmonary hypertension.

Dr Vaidya: That's great. Roxana, what about the next step in the work up algorithm?

Dr Sulica: My workup is very similar to what most of us do for patients with PH in general. In addition, you need to determine the specific and dominant mechanism of pulmonary hypertension it is, as we just said at the very beginning that the mechanisms of pulmonary hypertension in sarcoid are multifactorial. I tend to do a cardiac MRI, because I want to see how the myocardium looks. Sometimes we use PET scans as well if we want to tease out how much active inflammation there is. We do exercise right heart catheterizations fairly often, although we don't have the capability of doing simultaneous CPET during RHCs.

Otherwise, we do everything else that you do for PH patients: VQ scans, CAT scans, and full pulmonary function test, because the DLCO, as Bob was saying, is important in the diagnosis and prognosis for these patients. We also look for sarcoidosis liver involvement, test for HIV, and screen for concomitant connective tissue disorders. Throughout the years we had a small number of patients that had more than one risk factor for pulmonary hypertension besides sarcoid; we had patients with both sarcoidosis and HIV or lupus.

Dr Shlobin: What about chronic clots in patients with SAPH?

Dr Sulica: We do get VQ scans and CT with PE protocol, absolutely. Sometimes in sarcoidosis a VQ scan may

show perfusion defects that are sizeable and mismatched. Then the differential becomes more extensive with extrinsic compression versus intrinsic chronic thromboembolic disease. We do have a very good radiology department with excellent postprocessing for the CT with PE protocols. Less and less we are using the pulmonary angiograms, but obviously in situations when you're really not clear if it's intrinsic CTEPH-like disease or not, you will need to get a formal pulmonary angiogram.

Dr Shlobin: Anjali, given that you co-direct a major CTEPH center, what has your experience been?

Dr Vaidya: Yes, I'm glad to hear this discussion. I agree completely. I would say the concomitant presence of clinically significant CTEPH that warrants advanced CTEPH intervention along with intrinsic sarcoid is on the lower side. However, I always say anybody with chronic heart failure or chronic lung disease can also have recurrent venous thromboemboli. Although this does exist, it's a very common scenario for the abnormal VQ scan to lead us down the CTEPH evaluation in patients with sarcoid, and it's a fake-out, a CTEPH mimicker, and there actually is not a truly intravascular thromboembolic disease.

As Roxana nicely stated, often abnormal VQ scans are caused by extrinsic compression of pulmonary segmental or sub-segmental branches by bulky lymphadenopathy or fibrotic scarring granulomatous disease, and it gives the impression of perfusion defects on the VQ scan. There's a nuance I think in the evaluation from that perspective where we're always hearing that the gold standard diagnostic study for CTEPH is an invasive pulmonary angiogram. I think I'd like to continue to question that in the modern era, because it really is only a luminogram, and the CTA really is the most informative comprehensive study. It's particularly valuable in our sarcoid patients, because you can then visualize that compression and get that appreciation which the invasive angiogram would not provide and would only lead us down a false impression of CTEPH. I just had a patient like that in the last couple of weeks.

I think there's an important concept - in CTEPH at least - even in the presence of significant thromboembolic disease. Let's say the patient has CTEPH and it is deemed proximal and operable and accessible. There's an important concept of "not perfusing bad lung," so to speak. We don't want to generate ventilatory inefficiency and worsen dead space ventilation. This is the case for anyone—be it advanced sarcoid lung disease or other chronic lung disease.

I just wanted to mention that if there is a patient that has significant lung scarring via parenchymal involvement by sarcoidosis with concomitant true thromboembolic disease, it's extremely complicated. One always has to question if CTEPH treatment will result in reperfusion of an area affected by advanced scarring and actually harm the patient. A little restraint in treatment sometimes goes a long way.

One may also raise a question about balloon pulmonary angioplasty (BPA). Our program has done over 100 BPAs. In sarcoidosis patients with significantly hemodynamically severe PH related to distal thromboembolic disease, staged BPA may be a very reasonable consideration, rather than PTE.

Dr Shlobin: Sounds like a paper in making.

Dr Vaidya: Yes. I'll add it to the list.

Dr Shlobin: Thanks Anjali. Another question to the whole group: When you have someone with significant extrinsic compression, what factors do you consider for intervention for either pulmonary arterial or pulmonary venous constriction by bulky lymphadenopathy?

Dr Mandras: There are a couple of case series of small numbers of patients—5 to 8 patients—of angioplasty with or without stenting for patients who have extrinsic compressions not related to thromboembolic disease, which did demonstrate an improvement in hemodynamics and did not come with an increase in morbidity and mortality. Again, these are very small numbers. There's definitely more information that's needed for that patient population.

Dr Shlobin: Stacy, maybe while you're answering that question, what about pulmonary venous stenting?

Dr Mandras: Similar results. Again, from small case series.

Dr Shlobin: I agree, this area definitely needs more research. In someone who has bulky lymphadenopathy, one does need to think about both the arterial and venous strictures due to extrinsic compression. Sometimes it can really change one's treatment approach, because if you can stent the artery or vein with a resultant drop in pulmonary pressures, a patient may not need as much diuretics or pulmonary arterial vasodilators.

Dr Baughman: The French registry of 160 SAPH patients found 9 patients who had an improvement in PA pressure after giving corticosteroids to reducing the adenopathy. There is also a prospective study from China**,** which Stacy alluded to, demonstrating that almost 10% of their SAPH patients improved with stenting.

In our clinic, we've only had 1 patient that we've ever stented for pulmonary hypertension, and I have over 2500 sarcoidosis patients and nearly 100 patients with SAPH. I would like to make a general comment on treatment of SAPH. If you are a PH specialist, you need to make sure that the underlying parenchymal lung disease has been aggressively managed with anti-inflammatory therapy (such as steroids, methotrexate, infliximab), as patients' hemodynamics and symptoms may improve with appropriate treatment. If you are a sarcoidosis specialist and you have managed to control the inflammatory parenchymal component, or your patient has burnt out fibrotic parenchymal disease, if they have evidence of PH, they should be considered for further pulmonary vascular evaluation and treatment with pulmonary vasodilator medications, stenting, etc.

Dr Vaidya: That's an excellent segue into our last series of questions. In the current era of PAH medical therapy, we have over a dozen treatment options. Sarcoid-associated PH spans across, as Stacy nicely said, all 5 WHO groups in terms of phenotype and physiology. Roxana mentioned that she considers PAH medical therapy and follow them thoroughly for that.

With that in mind, how do you determine if a patient may be appropriate for medical therapy? I think that's one of the hardest decisions. Then we'll segue into what classes of drugs or approaches to treatments themselves. How do you initially consider a patient being appropriate for consideration of PH medical therapy?

Dr Mandras: I think you have to take each patient on a case-by-case basis. I think that what Roxana said, that the first step is to try to figure out what the underlying etiology for the patient's pulmonary hypertension is, ie, which WHO group they fall into. Often it's not straightforward. They may fall into one or two or three or more of these groups.

I inherited a pulmonary hypertension practice in 2009 that originally was started in the 1990s. I had SAPH patients that were initiated on a 3 drug therapy at that time, and remained stable and did very well for over a decade on therapy. Likewise, I had newly incident cases that seemed very straightforward without significant parenchymal lung disease and with normal left-sided filling pressure, so very much a WHO group 1 PAH-like phenotype. Yet the way these patients are managed in the current era may be very different because now, often pulmonary vasodilators are not paid for by insurance if the diagnosis of sarcoidosis is present, and this can make things very challenging. As soon as the diagnosis of sarcoidosis appears on the chart, no form of a prostacyclin will be approved. You may be caring for a high-risk patient who you feel strongly would benefit from parenteral therapy, and the payer denies coverage. It's very challenging to manage the sicker sarcoid patient. For the patients that are lower risk, treatment is fairly straightforward. We have data from a handful of mixed trials—some prospective, some retrospective—that show benefits of ERAs and PDE5s and combination therapy in this patient population, which demonstrated improvement in 6MWT, functional capacity, and improved hemodynamics without worsening in oxygenation, and for the most part we are able to obtain insurance authorization for these drugs.

Dr Shlobin: Well said. Roxana, what do you think?

Dr Sulica: Yes, one always has to take into account the payer situation. As Stacy mentioned, there are a couple of smaller and larger studies that looked at the effect of PAH specific therapies in SAPH. Unfortunately, they are small studies, some of them with a high drop-out rate, but they did show improvement. Until recently, the one placebo-controlled trial of bosentan showed no increase in 6-minute walk distance despite clear hemodynamic improvement. I am not very surprised of the dichotomy given the multiple comorbidities that may have led to decreased exercise capacity in SAPH. As Stacy mentioned, there are also case series as well as anecdotical reports in which PAH advanced therapies have been used in SAPH on a compassionate basis. Interestingly, some of those patients have responded beautifully to therapy, even with hemodynamic normalization. We do not know if that response translates into long-term survival benefit. When we plan SAPH trials, we have to be very careful to rule out pathology that can potentially lead to harmful effect from PAH drugs use (such as left heart disease). In addition, we do have to learn more about the type of endpoints that are meaningful in SAPH treatment trials.

Dr Shlobin: There is certainly a spectrum of diseases, just very much like interstitial lung diseases, where there is a more vascular phenotype and a more parenchymal phenotype of sarcoidosis. An ideal trial patient is the one with a vascular phenotype. Having said that, a recent trial of inhaled treprosinil in ILD-PH targeted all-comers with fibrotic lung disease and showed improvement in 6MWT distance, markers of right heart failure and delay in clinical worsening. With that, I wanted to ask Bob to comment on the recently submitted data on riociguat in SAPH.

Dr Vaidya: The only one comment I'll say before we open it to Bob on his perspective as well is that, in the growing interest—rapidly growing interest—in the pulmonary hypertension field and all of our young trainees going out into the community with so much more interest to treat these patients, I would emphasize the PH associated with sarcoid, as Stacy said, has many faces. It's one of the specific diagnoses that I think still very much should be referred to expert centers, to individuals such as all of you, to do that very high-level assessment that Roxana described beautifully.

Dr Shlobin: Bob, the Rioci-guat data will be presented at ATS, can you comment on the results of the RioSAPH trial?

Dr Baughman: While I've done several trials in SAPH, there have been limitations to all of these trials to date. One issue is that we do not have really good endpoints. Up until a few years ago, we really had struggled about whether we should be looking at the 6MWT or hemodynamics. Our group became intrigued by the idea of time to clinical worsening, because we thought that this would still be a good endpoint in SAPH given its multifactorial nature. Steve Nathan and Oksana Shlobin have worked with us on a recently completed trial, and we were able to demonstrate a difference in time to clinical worsening between the patients treated with riociguat therapy compared to placebo. This was the first long-term trial of SAPH patients, and I think that contributed to a clearer outcome of therapy. This is all preliminary data, which needs to be further validated. There's a larger SAPH study being currently conducted looking at time to clinical worsening as

a secondary endpoint after intervention with selexipag. I do think this approach should be a standard for outcomes in SAPH—these endpoints have become the standard in group 1 PAH.

My bias, of course, is that we should treat precapillary phenotype of SAPH. SAPH is an independent factor predicting mortality in sarcoidosis. Oksana led the recently published analysis of survival of 215 patients in our Registry for Sarcoid-Associated Pulmonary Hypertension (ReSAPH) and found only a 72% transplant-free survival at 3 years. Overall in ReSAPH, a third of the US patients were not treated for their SAPH at the time of entry into the registry, including patients with moderate to severe pulmonary hypertension.

Dr Vaidya: There's so much more we could discuss but we are at the top of the hour. On behalf of Oksana and myself, thank you so much, Stacy, Roxana, Bob, for taking the time and sharing your expertise for this discussion. We really enjoyed it.