Pulmonary Arterial Hypertension in Adults with Congenital Heart Disease


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This discussion was moderated by Robyn J. Barst, MD, Professor of Pediatrics, Divisions of Pediatric Cardiology at Columbia University College of Physicians and Surgeons and Cornell Medical Center, and Director of New York Presbyterian Pulmonary Hypertension Center at Columbia University Medical Center, New York, New York. Panel members included Jeffrey R. Fineman, MD, Pediatric Critical Care Specialist and Associate Investigator of the Cardiovascular Research Institute, University of California, San Francisco; John Granton, MD, Assistant Professor of Medicine, University of Toronto, Pulmonary Arterial Hypertension Programme, University Health Network, Toronto, Ontario; Michael A. Gatzoulis, MD, PhD, Professor of Cardiology, Congenital Heart Disease, and Consultant Cardiologist and Director of the Adult Congenital Heart Centre at the Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College School of Medicine, London, UK; and Richard A. Krasuski, MD, Director of Adult Congenital Heart Disease Services, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio.

Dr Barst: This discussion will focus on treatment of adult pulmonary arterial hypertension (PAH) patients with congenital heart disease (CHD). Is there evidence-based data for us to recommend guidelines or are our recommendations based on consensus of experience only? As we look at the risks and benefits of treatment, how does this compare to the natural history of untreated Eisenmenger syndrome? PAH patients with classic Eisenmenger syndrome have a far more favorable natural history than those with all other forms of PAH. However, there are also other patients with smaller congenital heart defects who are clinically and physiologically more like patients with idiopathic PAH (iPAH) than those with Eisenmenger syndrome. The natural history of these iPAH-CHD patients is similar to that of iPAH without CHD, and thus the risks and benefits of treatment may be different from those of classic Eisenmenger patients. Thus, how do we decide which patients with CHD have classic Eisenmenger syndrome? Or is the CHD, that is, the atrial or ventricular septal defect, merely a trigger for iPAH?

Dr Fineman: Classification of these patients is difficult. It depends on the size and the location. It is hard to ignore a good-sized ventricular septal defect in a young adult and say that this was an incidental finding, because the natural history is that a patient with a large unrepaired ventricular septal defect will have a significant likelihood of developing advanced pulmonary vascular disease.

Dr Barst: But does it matter which it is, Eisenmenger syndrome versus iPAH with an associated CHD? Patients come to us and want to know whether the ventricular or atrial septal defect is the cause of their pulmonary hypertension, or an associated finding, or a trigger. However, from a treatment standpoint, does it really matter? Do you treat these patients the same?

Dr Fineman: I suppose that depends on why you believe an Eisenmenger patient would do better, whether it's due to a pop-off for the right ventricle, or in the setting of perhaps a high-pressure, high-flow lesion, the right ventricle never gets a chance to maladapt at its peak, and therefore the right ventricle does better over time.

Dr Barst: The natural history data with Eisenmenger patients is an 80% 5-year survival and a 40% 25-year survival, which is substantially better than for iPAH patients with trivial CHDs, where the median survival would be approximately 2½ years for adult patients and less than 1 year for children.

Dr Fineman: I think this distinction is important for counseling patients about prognosis.

Dr Granton: If I can just offer some thoughts initially about the prognosis. I also have trouble with the prognosis for these patients, and with when a hole in the heart is contributory and causative versus "associated." You mentioned right ventricular function, and I think that is critical. There are some prognostic indices that have been published

looking at ventilatory equivalents that have been reasonably helpful in assessing functional performance. I think it is critical, perhaps, for the timing of one-way therapy with transplantation and surgical intervention, but is perhaps less critical when we discuss medical therapies. Irrespective of what the cause of the pulmonary hypertension is, most therapies that we currently have seem to work at the same magnitude.

Dr Gatzoulis: Well, one can criticize us for that, but so far we have a class III basis for therapy in Eisenmenger patients based on the data that exist. Obviously there is a move toward considering class II patients in other forms of pulmonary hypertension. I think data are emerging with the Eisenmenger cohort as well. Is the practice different at your end in that you are treating functional class II patients?

Dr Barst: We do treat patients who are in functional class II. We treat them based on the risks and benefits of the therapeutic modalities. Our goal in treating any patient with pulmonary hypertension is to make that patient class II even if it means parenteral therapy.

Dr Gatzoulis: Sure.

Dr Barst: The question is, if they are in functional class II when we initially see them, is it beneficial to start treatment to maintain their class, or should we try to make them class I? Does starting treatment earlier make a difference with the Eisenmenger patient, as it appears to with iPAH patients?

Dr Gatzoulis: Yes, this is very true, mimicking what we have seen in other forms of pulmonary hypertension. I think in a very simplistic way, the more I look into this in terms of the lungs and the response to therapy, there are major similarities, but of course, Eisenmenger patients have a well-trained right ventricle because of the chronicity of this, well adapted to systemic pressures. There is also the intriguing right-to-left shunting and the ability to maintain systemic cardiac output at the expense of cyanosis.

Dr Barst: Point well taken. Can we now turn our attention to how we should be treating these patients, whether with classic Eisenmenger syndrome or iPAH with a small CHD?

Dr Gatzoulis: I think the first thing, and perhaps it's a strong comment to make, is to stop making mistakes. There has been a lot of iatrogenic damage if you look at patients with cyanosis with regard to a shunt. Inappropriate venisection is still harming patients.

Dr Barst: This is a very important point. The other issue we should talk about is physicians' often not understanding why we treat these patients with supplemental iron even if it increases their hemoglobin and hematocrit.

Dr Gatzoulis: If we look at previous reports and studies, clearly there is an association between an increased incidence of transient ischemic attacks and stroke, and iron deficiency anemia/venisections. And then there is the question as to whether it was the iron deficiency anemia or another mechanism, such as a different shape and size of red cells causing mechanical obstruction. Again, that does not seem to be the case. We did some work looking at blood viscosity. It is probably very simple, that when patients are iron depleted in this setting, they have reduced transport capacity for oxygen and that compromises their oxygen tissue delivery, so the brain and other organs are more predisposed to hypoxia and hypoxic crises. If you look at patients who are not iron-depleted, they have levels of secondary erythrocytosis in keeping with the degree of cyanosis and can perform better than those who are iron-depleted. That is, with a respectable blood viscosity. So, I am not suggesting that this is just a simple mechanism, but I think there is little evidence or justification that venisection has a role to play in the majority of patients.

The first thing we do with patients who come to our service with cyanosis is to ensure that they are not iron depleted. Some traditional markers such as mean red cell volume are not helpful in this setting. We use transferrin saturation and serum ferritin for a stable patient. We have a study to look at the effect of restoring iron levels on exercise capacity.
– Dr Gatzoulis

Dr Barst: Could you clarify your recommendation? Do you treat patients if they are iron deficient to make sure they are iron replete?

Dr Gatzoulis: The first thing we do with patients who come to our service with cyanosis is to ensure that they are not iron depleted. Some traditional markers such as mean red cell volume are not helpful in this setting. We use transferrin saturation and serum ferritin for a stable patient. We have a study to look at the effect of restoring iron levels on exercise capacity. One of the major problems, of course, is that cardiologists are not the only ones who see these patients. When they go to a hematologist, and they see this markedly elevated hematocrit, their gut reaction is to venisect. We need to raise awareness about needless venisections.

Dr Barst: Could venisection result in ischemic stroke? Do you ever consider a phlebotomy if the patient has signs and symptoms of hyperviscosity?

Dr Gatzoulis: If a patient has a trial of phlebotomy and relief of symptoms, it is imaginary because the symptoms of hyperviscosity are mimicking the symptoms of iron deficiency anemia. Furthermore, if you take patients who are venisection naïve and they don't know about it, they hardly ever come to you giving you symptoms of hyperviscosity syndrome, particularly if they are not iron depleted. There is the occasional patient who may benefit from this, and it is very difficult to undo a practice or pattern of repeat venisection in patients who have had serial venisections as the only medical intervention. So, whether or not there is a placebo effect, I think it is not easy.

Dr Barst: Let me push you. What would make you do a phlebotomy?

Dr Gatzoulis: I think I would make sure the patient is not dehydrated and is iron replete. And then, I still struggle to find indications for elective phlebotomy, particularly in a phlebotomy-naïve patient.

Dr Barst: Are there any symptoms, such as a sudden increase in headaches or a sudden change in vision, that make you consider a phlebotomy?

Dr Granton: Sometimes it is hard in those who are iron replete. They start having increasing symptoms and you have no other cause and their hematocrit has been climbing. We would consider those patients.

Dr Krasuski: I have recently had a few patients who acutely presented with headache and visual changes in the context of Eisenmenger physiology. I think it is very important to exclude another neurologic event, in particular a stroke, as opposed to ascribing it to sludging from hyperviscosity. In such cases I have sent patients for imaging, but it wasn't predominantly to look for some manifestation of sludging, but mainly to rule out a true stroke.

I feel very differently about catheterization. I think in the proper hands the risk of a right heart catheterization to assess hemodynamics is low, even in this high-risk patient population. If I am planning to initiate therapy, I like to have every patient I see undergo catheterization unless I can find a contraindication or the patient refuses. It helps me to select the type of therapy.
– Dr Krasuski

Dr Gatzoulis: Absolutely, particularly when there are atypical or focal neurologic symptoms.

Dr Krasuski: We frequently have a completely negative neurologic image and I think that is very reassuring.

Dr Fineman: These are MRIs that you are talking about?

Dr Krasuski: Yes.

Dr Barst: Have you been looking at this or is this something you think we should be looking at?

Dr Fineman: I think this is something we should be looking at because it seems the technology is there where we can start thinking about characterizing the potential changes associated with hyperviscosity.

Dr Barst: It is interesting that you say that. If we look at patients with hemolytic anemias, such as sickle cell disease, hematologists consider intracranial hemorrhage an indication for a hypertransfusion regimen to minimize sludging. That may be what we want to look at in patients with Eisenmenger syndrome and erythrocytosis.

Dr Gatzoulis: I agree. I am not suggesting for a moment that we have all the answers on this. What I am saying is that routine venisection to protect these patients from strokes and relieve symptoms is seriously challenging some of the data we have.

Dr Barst: Can we turn to the role of anticoagulation?

Dr Gatzoulis: The data to guide us are very limited. Other groups and we more recently published our experience with intrapulmonary thrombosis in this setting. Looking at the Eisenmenger patients, about 20% of our patients have extensive intrapulmonary thrombus, which is inside the thrombosis. It is not thromboembolic. In many ways intrapulmonary thrombosis reflects disease state and disease progression. At what point in time that occurs, and what particular patients are at risk, remains unknown, and furthermore, how to prevent this, and what therapy to provide and at what point to start, remains unknown.

Dr Krasuski: I think we can make a blanket statement that we would not recommend therapeutic phlebotomy prophylactically in anybody with Eisenmenger syndrome. And if you are going to use continuous intravenous prostaglandin therapy, then patients should receive anticoagulation because of the potential stroke risk from a catheter-related thromboembolic complication in the setting of a right-to-left shunt.

Dr Barst: Do you consider intravenous epoprostenol less readily in Eisenmenger syndrome patients than in patients with iPAH, or do you decide based on the PAH severity regardless of whether the patient has right-to-left shunting secondary to Eisenmenger syndrome?

Dr Krasuski: We presented an abstract at the last American College of Cardiology meeting where we retrospectively compared our therapeutic approach to the Eisenmenger patient with our approach to the iPAH patient. We found that we were less likely to treat Eisenmenger patients with the more aggressive medical therapies, despite the fact that their stage of disease and their disability were just as great as those of the iPAH patients. I think this reluctance may be due to our fears of complications from lines, etc.

Dr Barst: I think we all agree that in patients with right heart failure we use anticoagulation because of low flow and sludging. But what about the Eisen-menger patient without right heart failure and the role of anticoagulation? Do we see more hemoptysis in Eisenmenger patients than we do in iPAH patients, and does anticoagulation have adverse effects in patients who have a history of hemoptysis?

Dr Granton: In Eisenmenger patients, the right ventricle doesn't usually dilate. It just becomes dysfunctional and hypertrophied, and I'm not certain that most centers subscribe to treating these patients with dysfunctional or dilat-

ed right ventricles with anticoagulation because of the fear, as you said, of hemoptysis. And although, as Michael said, approximately 25% of our patients have in situ thrombosis, I am not certain that, although we do it, use of anticoagulants in these patients has any bearing on outcome. I think it is difficult to make any firm statements about anticoagulation, even more so than with iPAH patients, which is walking a tight line. The level of anticoagulation is even problematic, so I think this is an area for study. I don't think, quite honestly, that there could be a reasonable consensus, certainly no consensus based on fact or evidence, regarding anticoagulation in the Eisenmenger patient.

Dr Barst: If we had a large observational registry, do you think we could look at this as one of the covariants for therapeutic modality?

Dr Gatzoulis: This is an area that needs further attention. To reflect the small data set from here, which echoes what John said, in the study that was published this summer, of about 50 patients, there was no link between anticoagulation and in situ thrombosis.

Dr Barst: Overall, for Eisenmenger patients who have a bidirectional or right-to-left shunt, do you routinely anticoagulate with warfarin?

Dr Gatzoulis: Not routinely. However, if there are other indications for doing so, such as a sustained atrial arrhythmia or more advanced ventricular dysfunction, we would consider empiric anticoagulation. We would engage a hematologist on this because titrating can be challenging; I have seen disasters in patients who have been given anticoagulants running into problems with major bleeding. We haven't seen, again, the discussion of the question that we are asking Robyn, any link between anticoagulation and the incidence of hemoptysis, so whether anticoagulation is a good thing or bad for hemoptysis is still an open question. About 45% to 50% of adults with Eisenmenger physiology who are followed up here eventually undergo anticoagulation therapy.

Dr Granton: Well, I'm not a cardiologist or a congenital heart person, but when they are sent to me, my only indication, as Michael said, is for other indications such as very poor right ventricular function or atrial fibrillation.

Dr Fineman: I am going to waffle on this one because I don't really see adult patients, and I think that in pediatric patients we generally find a reason to anticoagulate, but we look for a reason.

Dr Krasuski: I am pretty wary of anticoagulation in Eisenmenger patients. I discuss it very carefully with them and let them know that the decision is based on very little actual clinical data and more just on clinical experience. If there are indications otherwise for anticoagulation, such as arrhythmias, a pacemaker lead in place, or an indwelling line, it tends to push me in the direction of anticoagulation. But, as a routine, I don't treat all my patients with warfarin. I can tell you as an adult cardiologist who sees mostly adult congenital heart disease, but who also sees patients with other structural heart disease, that patients almost always try to find reasons why they can't be given anticoagulants, because in the end no one really likes warfarin therapy. We have even less data on the role of antiplatelet therapy, and it's unclear whether there is any benefit from aspirin or other antiplatelet drugs in these patients.

Dr Barst: Let's move on to the role of cardiac catheterization with acute vasodilator drug testing in these patients. Do you recommend it? Do they acutely respond? Is it worthwhile from a prognostic standpoint?

Dr Gatzoulis: We don't catheterize routinely. We will have at least a diagnosis established, noninvasively. But, if one were to catheterize, there are some data, and you are probably aware of this from a few years ago, from a Belgian trial in catheterized patients. They did acute vasoreactivity studies with nitric oxide in a small group of about 50 patients. Several years later a report on the same group showed that those who were reactive acutely had better survival prospects, which is a nice thing to see and be able to say. But we would not subject patients to cardiac catheterization unless there is a specific reason for this, assuming that the diagnosis was firm on the noninvasive expertise here.

Dr Krasuski: I feel very differently about catheterization. I think in the proper hands the risk of a right heart catheterization to assess hemodynamics is low, even in this high-risk patient population. If I am planning to initiate therapy, I like to have every patient I see undergo catheterization unless I can find a contraindication or the patient refuses. It helps me to select the type of therapy. Again, I am applying guidelines designed not for patients with Eisenmenger syndrome, but more for the idiopathic cases, but I still like to know whether they are responsive or not. I am aware of the same study examining vasodilator testing in Eisenmenger patients. There was actually an even smaller number of patients studied, less than 30, so it was a very tiny series of patients. I believe there is a similarity in the pathophysiology here, and that is important. The biggest limitation we have regarding vasodilator testing is that we have no single definition of a positive response that has been repeatedly correlated with survival. Our currently accepted definition is a drop in the mean pulmonary arterial pressure of 10 mmHg or more to less than 40 mmHg, but I have to be honest with you, that is not what I use in routine critical practice for risk stratification. Certainly if I see a large drop in pulmonary pressures during testing, I am encouraged. The other thing to mention is that in some of these advanced patients I don't expect to see a tremendous drop in pressure, but I have seen significant shifts in the degree of shunting. In fact, some of the patients who are perfectly matched from a shunt perspective may develop more left-to-right shunting and have almost no right-to-left shunting during testing. Their hypoxia therefore improves, but they actually develop more left-to-right shunting. The long-term effects on the right heart are unclear in these cases. I don't know what this means to

them therapeutically, but it's data that I think that need to be collected for future reference to be certain that we are doing the right thing for these patients.

Dr Barst: I agree. I find that the hemodynamic data are valuable, from a prognostic standpoint. I do not do a cardiac catheterization unless the data are useful in initiating or changing therapy. Even though in our database the acute vasodilator response in Eisenmenger patients is much lower than that in iPAH patients, for the rare patient who is very reactive it is worth knowing and something we can all do safely.

Dr Gatzoulis: I respect your point of view, of course, but a great question about this is whether an acute response in the catheterization lab influence the type of therapy you consider for these patients.

Dr Krasuski: That is very interesting. I have had these questions asked of me before and had a hard time struggling through to the answer. I think when you get all the information you can start to put things into perspective. Certainly, if the patients are in class IV in terms of their symptoms, that is to me a warning sign that they need aggressive medical therapy. I also think that if their cardiac index is low, although this is rare, I would treat aggressively. If they are not vasoresponsive, or if their shunts don't improve, I am going to have much lower expectations for a favorable response to long-term therapy. Plus it makes me feel more comfortable if I see the right-to-left shunting diminish. I have a greater sense that I am going to positively influence the quality of life of patients and that they will be able to detect a difference with therapy.

Dr Barst: Michael, I know what you are saying. Being a devil's advocate, as long as we have patients who are iron replete, what do we need to know other than their resting systemic arterial oxygen saturation and how much they desaturate for a given workload? I do the test because if I see some reactivity, it has been helpful for the long-term prognosis.

Dr Gatzoulis: Good point.

Dr Barst: Why don't we move on to whether we should treat these patients with supplemental oxygen. There have been two studies, one a very small series of Eisenmenger patients from the UK published in the mid 80s with 9 patients in one group and 11 in the other. Half of the patients were on supplemental oxygen at least 12 hours a day and the other patients did not receive any supplemental oxygen; there was improved survival in the patients treated with oxygen at for least 12 hours a day. However, Julio Sandoval in the 1990s looked at that as well and found no difference. What do you recommend routinely for your patients who have Eisenmenger syndrome with regard to sleeping with supplemental oxygen?

Dr Granton: I think it is important to ensure that they don't have concomitant pulmonary disease. As you know, many of these patients have underlying restrictive or obstructive disease and they are entitled to get everything other people have, so certainly there may be a component of intrapulmonary shunting that may be oxygen responsive that one needs to consider, as well as sleep disturbances. So, either central or obstructive sleep apnea also needs to be excluded in patients with concomitant cardiac disease, so we can treat our patients with CPAP and oxygen as needed. Certainly if they have any demonstrable pulmonary parenchymal disease, and we can demonstrate that they respond to oxygen both physiologically and symptomatically, we will do a blinded walk test off and on oxygen. If we can show that they improve, then we recommend that they use it. As a routine, I think the burden of data suggests that it is not efficacious. Again, in the catheterization lab, when we put someone on 100% oxygen, we occasionally do demonstrate that the intrapulmonary shunting or relative shunt fraction changes. This may be something, but I am not sure it is clinically meaningful to patients.

Dr Barst: Michael, what do you do?

Dr Gatzoulis: I am not against oxygen. Again, I talk to patients and if it is oxygen all the time that keeps them wheelchair or bed bound, I don't want it. If oxygen is used at night, with patients who are obviously in functional class III or IV, in trouble, as add-on therapy, sure. I would prefer, though, and patients do as well, to give oral therapy twice a day if you are in class III, as opposed to being prescribed indefinite oxygen therapy around the clock. Some patients benefit, but this is very empiric. I agree with John. It would not be the first line of therapy for us. We have seen in BREATHE-5 the use of oxygen as part of the protocol, and as John says, some patients respond dramatically to it.

Dr Barst: One thing I have found over the years is that patients want to know when they come to see me that my primary goal is to improve their quality of life today. If you can get patients off supplemental oxygen, no matter how complicated the medical therapy is, including parenteral prostacyclin, it is often the best thing you can do for them, from an overall quality of life standpoint, to no longer have them tied to a tank of oxygen. Have you seen that?

Dr Gatzoulis: Yes, I agree, absolutely. Physical conditioning within their abilities is also necessary and helpful. We have restricted many of these patients, again, not knowing that may be harmful. It is necessary to assess each patient individually, how he or she copes with this, but I think there is oral medication that tends to give symptomatic and hemodynamic benefits. This is the first line of therapy for us so far.

Dr Barst: Moving to targeted PAH drugs, how do you decide whether to start with a prostanoid, an endothelin receptor antagonist, or a PD5 inhibitor?

Dr Granton: In our country and our provinces we are limited

by availability and the government is quite restrictive, as are third-party payers, as to what we are able to use. In general, I would follow the current guidelines. I think the only data out there are for oral therapy and that is an endothelin receptor antagonist, whether you believe it works or not. We currently do not have an indication for the use of PD5 inhibitors in Canada in Eisenmenger patients. Certainly, if people have repaired defects, we can use it. Nor do we have an indication for a prostanoid, so we are quite restricted. When I work around it, my current approach is an endothelin receptor antagonist, sildenafil, and then a prostanoid.

Dr Gatzoulis: Identical, I would say here. We have to respect the data, although there are more data emerging. Seeing an individual patient, will the patient cope with the level of monitoring that is required with one drug versus the other? In the Eisenmenger cohort, I would follow what the data suggest. So, this is a very similar approach to John's.

Dr Fineman: I agree. I think the only difference is that we tend to use a bit more sildenafil in younger patients because of the issues with dosing and availability, otherwise, I would start with an endothelin receptor antagonist.

Dr Barst: Does it matter whether the endothelin receptor antagonist is ET_A-selective or nonselective?

Dr Fineman: I don't know. I think a side-by-side study is never going to be done, and with the data that are out there, it's hard to say there is a difference. I believe there are some theoretical differences in more advanced disease where a selective endothelin A receptor blocker would be beneficial. But without data, I think either one is probably acceptable.

Dr Krasuski: I would like to readdress the prostanoid aspect of therapy. Again, I agree with the other panelists. Obviously the best study we have is BREATHE-5. It is the only study that was randomized and done in proper fashion. There are series of patients receiving prostanoid therapy that have been reported, and some of those are fairly old, from the late 90s and early 2000s, where there was significant improvement in 6-minute walk test distance and in functional capacity. So again, if I have someone with very advanced symptoms, truly class IV, I would look in that direction. The endothelial antagonist, however, is the drug with the most data at this time. We tend to use sildenafil as well, because of its selective properties for the pulmonary vasculature and lack of systemic hemodynamic effect. If you use nitric oxide in the catheterization lab it is very interesting to see Eisenmenger patients' saturations improve. One of the end points of BREATHE-5 was to make sure there was no worsening of oxygen saturations, which there was not. But in general you don't see much improvement in saturations with endothelin receptor antagonists. You tend to see more, in my experience, with the PD5 inhibitors. But, I agree, you want the best outcomes for your patients, and the best published outcomes and safety data at this time are with the endothelin receptor antagonists. Let me ask a question of the panel. Has anyone had any significant experience with considering closure of a CHD, let's say an atrial septal defect, if a patient with Eisenmenger physiology has a substantial improvement with medical therapy? And, when is it safe to do so? There are at least two or three papers, case reports, showing that this was a feasible strategy. How many people have had experience in this area?

To summarize, although there remains no cure for patients with Eisenmenger syndrome, appropriate management has decreased morbidity and mortality and improved overall quality of life. With tertiary care and counseling on risks such as pregnancy, surgery, pulmonary infections, exposure to high altitude, extreme exercise, and psychological stress, patients with Eisenmenger syndrome may enjoy a better quality of life with increased survival. – Dr Barst

Dr Gatzoulis: Very few patients would benefit from such an approach based on what we know. There is very little evidence in the literature, just a few case reports here and there. You need to make sure you are not harming the patient by closing the atrial or extracardiac communication. The occasional patient with an atrial septal defect may have a dramatic response to advanced therapy. These patients, once the advanced therapy has been employed for some time and has been tolerated well, may benefit from elective closure, but I don't think it's going to be a huge number of patients. We just don't have the data. That is my impression.

Dr Barst: This is probably another misperception in the medical community. When is it appropriate to close a defect such as an atrial septal defect? During cardiac catheterization, the data at rest are for the largest left-to-right shunt, but what happens when the patient exercises? If there is any degree of systemic arterial oxygen desaturation, and the overall resting shunt is less than 2:1, I think those patients are getting a disservice if the defect is repaired. However, a select few patients may develop a large left-to-right shunt with aggressive medical treatment, and I would consider these patients for complete or partial (fenestrated) closure of the defect. Do others agree with that?

Dr Gatzoulis: Yes.

Dr Barst: What do you do with regard to timing of lung or heart/lung transplantation? And, an area that is often neglected, what do you do with regard to treatment of the other multiorgan systems involved in these patients, which from a quality-of-life standpoint can be significant.

Dr Gatzoulis: From experience in transplantation on the London end, most patients, by the time they are transplant candidates, sadly, are really not transplant candidates because of significant comorbid conditions.

Dr Barst: Why?

PH Roundtable

(continued from page 147)

Dr Gatzoulis: Because of their age and the very small number of lung transplantations taking place in the UK. I think on the organ side, perhaps you are right. This chronic cyanosis may be a good thing with the right-to-left shunting, but it is a multiorgan disease. I think, again, that any opportunity to improve organ perfusion and tissue oxygen delivery is bound to have some effect on organ function, whether it is renal or the brain, and if you can address that early in the course of the disease, and reverse the shunt, you may be able to repair the lung fields, but not many patients are suitable for this route.

Dr Krasuski: My experience has been that Eisenmenger patients can live for quite a while, and obviously it is hard to predict who is going to live and who is going to die. Unfortunately lung transplantation may not be a good exchange. Giving them a lung transplant may not give them a better survival, in fact survival could be worse, though their quality of life may improve somewhat. Timing of transplantation is a pretty tough decision.

Dr Barst: This group of patients is more difficult to compare to patients who have iPAH. But, when I discuss transplantation with patients, if they answer yes when I ask if they would ever consider transplantation, I recommend active listing when they have a poor quality of life. To me, as long as patients are able to live with their limitations and enjoy what they have in life, even if they seem sicker than other patients, I recommend they continue to do that because we don't know if they will be better or worse off after a transplant, and transplantation is a one-way street, not a panacea. Thus, overall, the timing of transplantation often becomes subjective and related to quality of life and to whether the patient wants it or not. I know that's not a good answer.

Dr Krasuski: Actually that is a great answer. I feel the same way.

Dr Barst: To summarize, although there remains no cure for patients with Eisenmenger syndrome, appropriate management has decreased morbidity and mortality and improved overall quality of life. With tertiary care and counseling on risks such as pregnancy, surgery, pulmonary infections, exposure to high altitude, extreme exercise, and psychological stress, patients with Eisenmenger syndrome may enjoy a better quality of life with increased survival. Current practice is to avoid interventions that may destabilize the delicately balanced physiology between the systemic and pulmonary circulations in these patients. In most cases, treatment has focused on symptomatic patients and has been directed at avoiding or ameliorating the complications associated with chronic hypoxia, hematologic abnormalities, pulmonary infection, and congestive heart failure. Prostanoids and lung or heart/lung transplantation have been shown to be effective in improving functional class and pulmonary hemodynamics. Selection criteria, however, remain problematic and the procedures are both invasive and associated with significant complications. More selective pulmonary vasodilators with antiproliferative effects hold promise in leading to improvement and better prognosis by altering the natural history of PAH associated with CHD (with or without Eisenmenger syndrome). Further investigation is needed in this patient population as extrapolation from various other forms of PAH may in fact not be applicable to PAH associated with CHD. ■

Profile - Joseph K. Perloff, MD

(continued from page 108)

edition of *Congenital Heart Disease in Adults* with John Child and Joseph Perloff, I came to appreciate other aspects of this great man: his friendship, his consideration for the creativity and ideas of younger colleagues, and his unwavering focus and determination to complete a given task. Despite a lifetime of accomplishment, Joseph Perloff is not the type of man to sit back and enjoy his numerous accolades; he remains a highly productive researcher, lecturer, and writer. He is a truly inspirational individual. ■

— *Jamil Aboulhosn, MD*