Mitochondrial Dysfunction in Bronchopulmonary Dysplasia

To the Editor:

We read with great interest the study by Kandasamy and colleagues (1), wherein the authors describe the important role of mitochondrial function in the development of bronchopulmonary dysplasia (BPD). We congratulate the authors for conducting this study, in which they concluded that the vascular endothelial mitochondrial dysfunction seen in premature infants contributes to early mortality and the development of BPD.

In this excellent study, Kandasamy and colleagues (1) isolated human umbilical vein endothelial cells (HUVECs) from umbilical cords of preterm infants who died or developed BPD, and infants who survived without BPD. They cultured HUVECs and measured mitochondrial bioenergetics (oxygen consumption rate and ATP), mitochondrial reactive oxygen species, and mitochondrial DNA damage. However, they ignored some well-known potential risk factors for mitochondrial dysfunction, such as the mitochondrial membrane potential, peroxisome proliferator-activated receptor- γ coactivator 1 α (which stimulates mitochondrial biogenesis) (2), and the nicotinamide adenine dinucleotide (NAD)/reduced NAD ratio, all of which are essential for mitochondrial function (3). The measurement of mitochondrial biogenesis may be vital to support the result that there was no difference in the mitochondrial content of HUVECs from infants who died or developed BPD compared with infants who survived without BPD. Further, the authors reported that there was an accumulation of mitochondrial DNA damage in HUVECs from infants who died or developed BPD. This may have been due to impaired mitophagy (the autophagy-dependent degradation of mitochondria), which may lead to the accumulation of reactive oxygen species-producing damaged mitochondria as reported in their study (4). These issues should be resolved in future studies. ■

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Reply to Shah *et al.*

From the Authors:

We thank Shah and colleagues for their thoughtful comments on our study (1). In response, we note the following:

1. We used fluorescent dyes that use changes in the mitochondrial membrane potential (MMP) to enter and label the mitochondria, such as MitoTracker and rhodamine-based dyes (2). However, we did not measure MMP directly. We found that mitochondrial bioenergetic function was decreased (suggesting a lower MMP), whereas oxidant generation was increased (suggesting a higher MMP) in human umbilical vein endothelial cells (HUVECs) from premature infants who later died or developed bronchopulmonary dysplasia (BPD), compared with those who survived without BPD. Therefore, we agree that it is important to obtain direct MMP measurements using dyes such as JC-1 (5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide) to determine MMP differences between these infant groups (3).
2. We did not find differences in HUVEC mitochondrial DNA content between infants with and without BPD, although we noted that mitochondrial DNA damage was greater in the former group. These findings indicate that differences in mitophagy or mitogenesis could be associated with differential risk for BPD, as Shah and colleagues suggest.
3. We agree that peroxisome proliferator-activated receptor- γ coactivator activity and the nicotinamide adenine dinucleotide (NAD)/reduced form of NAD (NADH) ratio are valid and important measures to assess mitochondrial biogenesis and functional differences between infants who are BPD-susceptible and those who are BPD-resistant.

We are currently conducting studies to test for differences in MMP, NAD/NADH, mitophagy, and mitogenesis (using peroxisome proliferator-activated receptor- γ coactivator content) in murine models of lung injury and HUVECs obtained from preterm infants. We hope to publish our findings in the near future. ■

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Amphetamine Derivatives and the Risk of Pulmonary Arterial Hypertension: A Missing Chapter of the Story?

To the Editor:

Zamanian and colleagues (1) should be commended for their study of patients with pulmonary arterial hypertension (PAH) secondary to methamphetamine use, which helps to establish the role of amphetamine derivatives in PAH. They point out the similarities to cases of PAH secondary to the use of anorexigens (i.e., aminorex fumurate, 5-methyl-aminorex, and fenfluramine) whose molecular structure is similar to that of methamphetamine. However, they do not mention the recent epidemics of PAH related to benfluorex, a benzoate ester that shares similar structural and pharmacologic characteristics with fenfluramine, which, with the exception of North America, was marketed over 33 years worldwide in more than 50 countries for treatment of diabetes and metabolic syndrome. Similarly, in the accompanying editorial, Simonneau and Humbert briefly summarize the history of PAH triggered by exposure to derivatives of amphetamine (2). They point out that a new chapter is opening today with the accumulation of concordant elements that makes it possible to classify methamphetamine, a widely used psychostimulant drug, as a “definite” (not just “likely”) risk factor for PAH. However, in their brief summary, they neglect to mention benfluorex as an important chapter of this deplorable story. Indeed, not all fenfluramines were withdrawn from the worldwide market in 1997: benfluorex was only withdrawn in 2009 (3), despite a first report to the French pharmacovigilance authorities as early as 1999 (4). This delay was due to the drug not being marketed as an anorexigen and to the manufacturer denying its similarities to amphetamines (5). After the publication of a study describing a small series of patients with PAH who had prior exposure to benfluorex (6), benfluorex was established as a definite risk factor for PAH (7). The characteristics of PAH related to benfluorex exposure were later studied in more detail in a large series (8).

As another example of iatrogenic complications in medicine, the full history of PAH induced by anorexigens and related agents is essential to remember so that practitioners can be alert to all possible forms of exposure to amphetamine derivatives—marketed, hidden, diverted from their use, or consumed illegally. ■

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Reply to Frachon

From the Editorialists:

In the most recent update of the classification for drug- and toxin-induced pulmonary arterial hypertension, several anorectic agents sharing with amphetamines the same phenylethylamine structure are listed as “definite” risk factors (aminorex, benfluorex, dexfenfluramine, and fenfluramine) (1). Among them, benfluorex has some specificities that should be emphasized. Benfluorex has been approved in Europe as an agent for the treatment of diabetes and as a hypolipidemic agent but, surprisingly, not as an anorectic substance. However, benfluorex shares similar structural and pharmacological characteristics with dexfenfluramine and fenfluramine, and these drugs all form norfenfluramine as a metabolite. Given its properties, benfluorex would obviously be expected to have toxic effects similar to the