Diabetes and the pulmonary circulation

Brian Fouty

Center for Lung Biology and Division of Pulmonary and Critical Care Medicine, University of South Alabama School of Medicine, Mobile, Alabama

Diabetes is an epidemic in the United States, affecting ~8% of the population. The hallmark of diabetes is hyperglycemia due to either insulin deficiency or insulin resistance. Systemic vascular dysfunction is a central part of the pathophysiology of both type I insulin-dependent and type II non-insulin-dependent diabetes and involves both the micro- and macrocirculation (11). Coronary heart disease is the leading cause of morbidity and mortality in diabetics and accounts for ~60% of deaths in this patient group. Peripheral vascular disease, retinopathy, and nephropathy are all more common in diabetics and lead to significant morbidity. Yet, despite the fact that the pulmonary circulation sees the same levels of glucose and insulin as the systemic circulation, the detrimental effects of diabetes in the lung, in general, and the pulmonary vasculature, in particular, are less clinically apparent.

Many studies dating back decades have identified pathological effects of diabetes in the lung. Isolated lungs from rats with streptozotocin-induced diabetes demonstrate altered prostaglandin (12) and leukotriene production (10), and triglyceride deposition has been identified in the walls of pulmonary arteries of diabetic rats (9). Thickening of the fused endothelial and epithelial basal laminae and an increased abundance of Weibel-Palade bodies in the pulmonary venules can be identified in streptozotocin-treated diabetic hamsters using electron microscopy (8). Autopsy studies in humans with diabetes have also demonstrated thickened alveolar epithelial and pulmonary capillary basal laminae (13). Pulmonary function tests in diabetics have demonstrated varied, and frequently conflicting, results with some studies indicating a reduction in lung volumes, whereas others have demonstrated no change compared with healthy controls. Given the autopsy findings of thickened alveolar-endothelial basement membranes in diabetics, a decrease in gas exchange as measured by changes in the diffusion of carbon monoxide (DLCO) might be expected, but multiple studies have also produced varied and conflicting results. A more sensitive measure of alveolar-capillary permeability using technetium 99m-diethyltriaminepentaacetacid (99mTc-DTPS) aerosol scintigraphy did demonstrate evidence of alveolar-capillary injury in different subsets of diabetics, even when DLCO was normal (7), however, suggesting that gas-exchange defects are likely present, but that DLCO is insufficient sensitive to detect it in many cases.

In sum, animal experiments, combined with anatomic and physiologic data in humans, suggest that diabetes adversely impacts the lung and the pulmonary circulation, but the pathological manifestations appear to vary, likely due to differences in experimental methods (in animal models) and on the type and severity of disease (in humans). Because diabetes manifests primarily as a systemic disease, though, the pulmonary circulation is relatively understudied, and the effects of diabetes in this vascular bed remain poorly defined.

In this issue of AJP-Lung, Lopez-Lopez and colleagues (3a) examine the effect of diabetes on an important component of endothelial function, the release of nitric oxide (NO) in response to acetylcholine (ACh). Impaired endothelial function is a common finding in patients with diabetes, and many animal studies have demonstrated impaired ACh-mediated relaxation of isolated aortic and other systemic vascular rings in experimental models of diabetes, but no such studies (to our knowledge) have directly examined this effect on pulmonary artery rings. The authors find that the endothelial dysfunction previously observed by others in the aorta of (streptozotocin-induced) diabetic rats is also present in the pulmonary artery. Using standard vascular ring studies, the investigators demonstrate a decrease in ACh-mediated vasorelaxation in phe- nylephrine-constricted pulmonary artery rings compared with controls and demonstrate that this is not due to defective guanylate cyclase/cGMP signaling in vascular smooth muscle by documenting equivalent relaxation to the NO donor, sodium nitroprusside. Blocking superoxide anion production with apocynin or scavenging it with superoxide dismutase restored normal ring relaxation to ACh. The authors conclude that in this model of diabetes, increased superoxide anion production, presumably via the NADPH oxidase pathway, scavenges NO (to form peroxynitrite), thus reducing its availability in the pulmonary vasculature.

This study is important because it demonstrates that hyperglycemia has a similar detrimental effect on ACh-mediated NO release in the pulmonary circulation as it does in the systemic circulation. It also highlights the important role of reactive oxygen species (ROS), particularly superoxide anion, in the pathological effect of hyperglycemia on endothelial function. Glucose is an inflammatory agent and has been demonstrated to increase ROS production when endothelial cells are exposed to high levels of glucose in vitro. Nishikawa and colleagues (6) demonstrated that glucose loading of endothelial cells increased the mitochondrial generation of ROS. These ROS led to the activation of three potentially detrimental pathways in bovine aortic endothelial cells: activation of diacyl glycerol/protein kinase C, generation of advanced glycosylation end products, and the generation of sorbitol due to activation of aldolase reductase. Inhibiting ROS production in the mitochondria blocked all three pathways. Subsequent papers have supported these findings (1), and pathological activation of these pathways has been implicated in the endothelial dysfunction associated with diabetes. The current paper did not examine whether these other pathways were activated in the pulmonary circulation, but it does support the central role of ROS production in the pathological effects of hyperglycemia on endothelial function.

Decreased NO production in the pulmonary circulation due to hyperglycemia might be expected to increase the risk of
pulmonary hypertension (PHTN) in diabetics. Although one paper has identified an increased incidence of PHTN in patients with type II diabetes (5) and another an increased incidence of PHTN in diabetics with COPD (4), such reports are few, and an epidemic of PHTN in individuals with diabetes has not been observed clinically. Possible reasons for the clinically disparate effects of diabetes on the pulmonary and systemic circulations are the differences in oxygen tension and pressure within each vascular bed. The low-resistance, high-capacitance pulmonary arteries experience lower oxygen tension than the systemic arteries. Given the apparent importance of ROS production on the pathological effects of diabetes on the vascular endothelium, this lower oxygen tension might lead to a decrease in ROS production (compared with the systemic arterial circulation) in vivo. Since the pulmonary artery rings studied in this paper were done in room air, rather than at the lower-oxygen tension seen by the proximal pulmonary artery in vivo, the production of ROS, and subsequent reduction of ACh-induced NO release in the intact pulmonary circulation, may be less impressive than these studies indicate. Future experiments that examine the potential effect of oxygen tension on ROS production in this model will be important.

An important limitation of this paper is that streptozotocin causes diabetes by destroying β-cells of the pancreas and as such is a better model of type I than type II diabetes. The effects of insulin resistance on pulmonary endothelial function may be of equal importance to those of hyperglycemia, since ~80% of diabetics in this country are not insulin deficient. Insulin resistance can lead to reduced NO release by inhibiting the phosphatidylinositol 3-kinase/AKT pathway (3), and a recent paper (2) demonstrated that a mouse model of insulin resistance, the apoE−/− mouse on a high-fat diet, develops pulmonary arterial hypertension. Another important question not addressed by this study is whether diabetes has a similar effect on endothelial function in the pulmonary microcirculation, vessels smaller than 100 μm in which the greatest resistance to pulmonary blood flow occurs and which is an important site of the pathology associated with PHTN.

Diabetes is arguably the most important medical problem in the United States today and will likely affect increasing numbers of Americans as the nation’s waistline continues to expand. While dysfunction of the systemic vascular bed will remain the major cause of morbidity in these patients, it is clear from this, and other studies, that the pulmonary circulation is not spared the toxic effects of hyperglycemia. Whether the increase in diabetes will be associated with an (delayed) increase in PHTN over the next few years and decades is not clear, but remains a possibility. Conversely, if the development of lung disease, in general, and pulmonary hypertension, in particular, remains an uncommon clinical finding despite the increased incidence of diabetes, closer examination of the pulmonary circulation might yield clues that will allow us to better understand why the systemic circulation is more severely affected in this disease and to design alternative therapeutic strategies to prevent these complications.

GRANTS
Support for this work was provided by National Heart, Lung, and Blood Institute/NIH RO1 award RO1-HL70273-01.

REFERENCES