Physiol. Res. 44: 361–367, 1995

Acute Hypoxic Pulmonary Vasoconstriction: A Model of Oxygen Sensing

E. D. MICHELAKIS, S. L. ARCHER, E. K. WEIR

Department of Medicine, Veterans Administration Medical Center and University of Minnesota, Minneapolis, USA

Received July 20, 1995

Accepted August 7, 1995

Summary

One explanation of the mechanism of hypoxic pulmonary vasoconstriction (HPV) suggests that hypoxia shifts the redox status of the pulmonary artery smooth muscle cell towards a more reduced state, through changes in the redox couples and the activated oxygen species generation. The outward K^+ current is then reduced and the membrane depolarized, leading to Ca^{++} influx through the voltage dependent Ca^{++} channels and vasoconstriction. The response of both pulmonary and systemic vessels to hypoxia may depend on the expression of different K^+ channels in the two sites. While the oxygen sensor in pulmonary artery smooth muscle cells may be the delayed rectifier K^+ channel, in the systemic arteries, hyperpolarization of the smooth muscle cell membrane, leading to vasodilatation, probably represents the effect of hypoxia in opening ATP-sensitive and Ca^{++}-dependent K^+ channels. The similarities between oxygen sensing mechanisms in several oxygen sensing cells (pulmonary artery smooth muscle cell, carotid body type I cell, neuroepithelial body) are striking. It is very likely that the mechanisms by which hypoxia is sensed at the molecular level are highly conserved and tightly regulated.

Introduction

One of the most intriguing challenges for modern physiology is to explain the mechanism by which oxygen is sensed in the pulmonary vasculature and by which acute hypoxic pulmonary vasoconstriction (HPV) is elicited. Since the first detailed description by von Euler and Liljestrand (1946), the mechanism by which hypoxia is sensed and that signal is translated into vasoconstriction in the lung has remained elusive.

HPV is important both in the foetus and in the adult. In the foetus hypoxic vasoconstriction contributes to the high pulmonary artery (PA) resistance which shunts blood through the ductus arteriosus. In the adult HPV ensures that atelectatic or underventilated areas of the lung are not perfused (Zasslow *et al.* 1982). HPV directs blood to adequately oxygenated alveoli improving the V/Q match and thus reducing systemic hypoxaemia.

The pathogenesis of chronic hypoxic pulmonary hypertension, including vascular remodelling, is not considered here. This review examines the mechanism of oxygen sensing and acute hypoxic vasoconstriction in the adult lung.

Characteristics of HPV

A number of characteristics of HPV have become apparent. Any putative mediator or theory of HPV should explain these features.

1) *HPV is intrinsic to the lung,* as it can be demonstrated in isolated lungs (McMurtry *et al.* 1976) and isolated small pulmonary arteries ($< 300\,\mu m$) (Madden *et al.* 1985). Since PA rings denuded of endothelium, as well as isolated PA smooth muscle cells (Madden *et al.* 1992), can constrict in response to acute hypoxia, the oxygen sensor appears to reside in the PA smooth muscle cell (Fig. 1). It is recognized that many substances from the endothelium and elsewhere, such as nitric oxide, prostanoids and leukotrienes, can modulate HPV.

Presented at the International Symposium "Pulmonary Circulation VI", Prague, July 26–29, 1994.

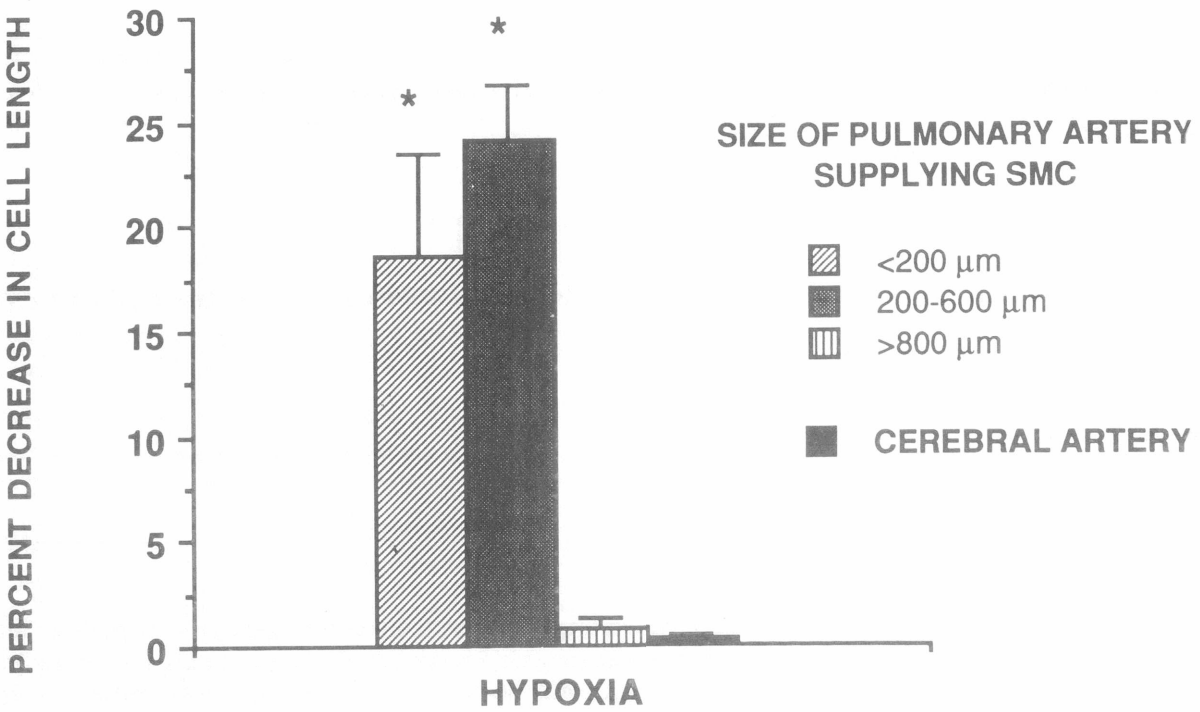

Fig. 1
Percent decrease in length of smooth muscle cells isolated from three sizes of pulmonary artery and from cerebral arteries during exposure to hypoxia (* $p<0.05$) (from Madden *et al.* 1992, with permission)

2) *Requirement for extracellular Ca^{++}:* HPV is inhibited by Ca^{++} channel blockers (McMurtry *et al.* 1976, Archer *et al.* 1985) and is enhanced by Ca^{++} channel agonists, like Bay K 8644 (McMurtry 1985, Tolins *et al.* 1986). As discussed below, these observations make it likely that extracellular Ca^{++} is important in HPV.

3) *Hypoxia decreases the resting membrane potential* of smooth muscle cells in small pulmonary arteries (Madden *et al.* 1985) and in isolated PA smooth muscle cells (Post *et al.* 1992).

4) *Rapid onset of HPV:* the start of HPV occurs within seven seconds of the onset of hypoxia in the perfused lungs (Jensen *et al.* 1992). Furthermore, in a well characterized model of oxygen sensing, the type I cell of the carotid body, it has been shown that the effect of hypoxia on K^+ currents starts within a few hundred milliseconds (Lopez-Lopez and Gonzalez 1992). However, phase two of HPV, which develops slowly over 45 minutes, appears to be endothelium-dependent at least in the rat (Jin *et al.* 1992).

A number of substances have been demonstrated to cause pulmonary vasoconstriction (e.g. histamine, serotonin, angiotensin II, catecholamines, prostaglandins, leukotrienes) but none of them has proved to be essential for HPV (Archer *et al.* 1989). Attention is now focused on the direct effect of oxygen on the pulmonary vasculature.

The role of calcium

Every theory attempting to explain HPV must account for the increased delivery of calcium to the contractile apparatus, either from outside the cell (through voltage-dependent or receptor-activated Ca^{++} channels) or from intracellular pools (sarcoplasmic reticulum or mitochondria).

Although the importance of the influx of extracellular Ca^{++} in the initiation of the hypoxic vasoconstriction has been questioned (Salvaterra and Goldman 1993, Vadula *et al.* 1993), it seems likely that Ca^{++} enters the PA smooth muscle cell early in HPV through voltage-dependent Ca^{++} channels. This concept is supported by the enhancing effect of Ca^{++} channel agonists on HPV and the reduction of HPV by calcium channel blockers (as described above) and by the fact that removal of Ca^{++} from the perfusate inhibits HPV in ferret lungs (Farrukh *et al.* 1992) and small cat PA rings (Harder *et al.* 1985). In the type I cell of the carotid body, which bears many similarities to the PA smooth muscle cell in its response to hypoxia, the increase in cytosolic Ca^{++} comes entirely

from outside the cell (Urena *et al.* 1994, Buckler and Vaughan-Jones 1994).

The potassium channel

K^+ channels are essential in the control of smooth muscle cell membrane potential. K^+ channel blockers, such as tetraethylammonium and 4-amino-pyridine, inhibit the outward K^+ current, depolarize the membrane, permit Ca^{++} influx through the voltage-dependent Ca^{++} channels, and increase tension in PA rings (Post *et al.* 1992) and PA pressure in perfused lungs (Hasunuma *et al.* 1991).

Inhibition of the outward K^+ current by hypoxia is an attractive hypothesis to explain the onset of HPV. In the carotid body type I cell, hypoxia inhibits the K^+ current, depolarizing the membrane and leading to an increase in the influx of extracellular Ca^{++} (Lopez-Barneo *et al.* 1993). If confirmed, this would indicate that the sensor mechanism is intrinsic to the cell membrane or potassium channel. The same workers have reported K^+ current inhibition by hypoxia and this has also been shown in single channel studies with excised patches.

In the lungs, hypoxia inhibits whole cell K^+ current and depolarizes the membrane in freshly isolated (Post *et al.* 1992) and cultured PA smooth muscle cells (Yuan *et al.* 1993). In the latter study, the reducing agent dithionite was used to induce hypoxia. In these studies, hypoxia failed to reduce the K^+ current in renal and mesenteric vascular smooth muscle cells respectively.

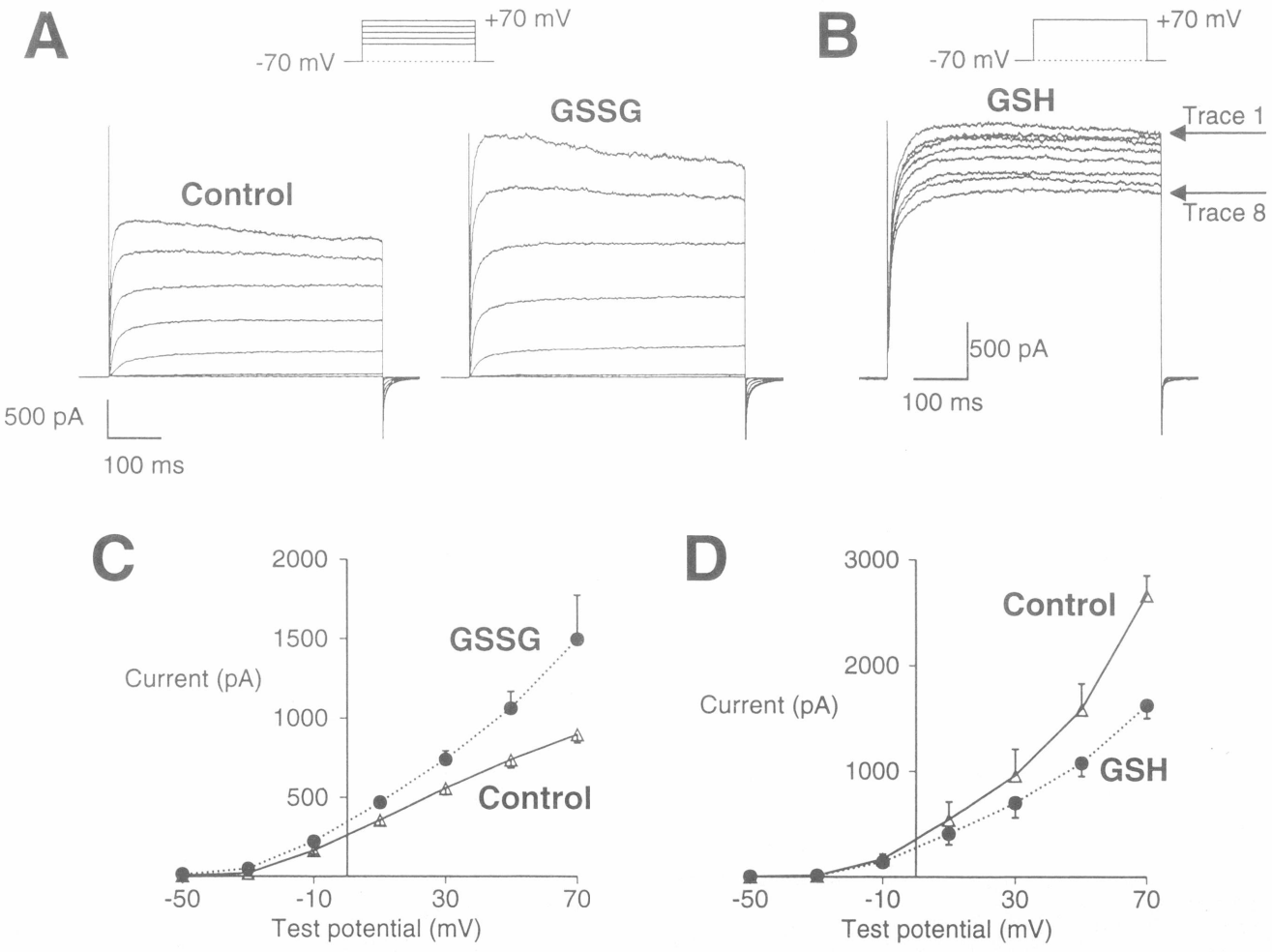

Fig. 2
Effect of intracellular oxidized and reduced glutathione on whole-cell potassium currents in rat pulmonary artery smooth muscle cells. A: K^+-currents (elicited by voltage steps) before and after 5 min dialysis of 2 mM GSSG into the cell, showing an increase in outward current. B: Series of K^+-currents elicited by a repetitive voltage step from −70 to +70 mV every 20 seconds after the start of dialysis of 2 mM GSH into the cell, showing a decrease in the outward current. C and D: Current-voltage relationship for mean K^+-current in the presence and absence of GSSG (2 mM) and GSH (2 mM) (from Weir and Archer 1995, with permission).

The gating of the K^+ channel and the redox theory

If hypoxia triggers the mechanism of HPV by inhibiting the K^+ current in PA smooth muscle cells, how are the K^+ channels gated? Several theories have been developed on the gating of the oxygen-sensitive K^+ channels which emphasize the role of ATP/high energy phosphates, P450, oxygen radicals and sulfhydryl redox status (Archer *et al.* 1989). The link between hypoxia, the smooth muscle cell redox status and the gating of the K^+ channel is an active area of investigation.

Redox control of K^+ channels has been demonstrated in several cell types. Oxidation of a critical cysteine residue in the β-subunit of the K 1-type K^+ channel, expressed in *Xenopus* oocytes, can enhance the activity of the channel (Rettig *et al.* 1994). Using whole cell and single channel patch clamping in PA smooth muscle cells it has been demonstrated that physiologic reducing agents, such as reduced glutathione (GSH) and NADH, inhibit the K^+ current while oxidized glutathione (GSSG) and NAD increase the current and the opening frequency of the channel (Weir and Archer 1995, Lee *et al.* 1994) (Fig. 2). The ratio of redox couples such as GSH/GSSG and NAD(P)H/NAD(P) reflect the redox state of the cytoplasm and may serve as a signal for changes in the gating of potassium channels.

A similar observation is that diamide, a sulfhydryl oxidant which reversibly reduces the ratio of cellular GSH/GSSG and NAD(P)H/NAD(P), increases the whole cell K^+ current (Post *et al.* 1992). Another sulfhydryl oxidant, t-butyl hydroperoxide does the same (Archer *et al.* 1993b). This could lead to hyperpolarization and be the mechanism for the inhibition of HPV seen following the administration of diamide *in vivo* (Weir *et al.* 1983). The antioxidant N-acetylcysteine (a sulfhydryl donor) conversely decreases the whole cell K^+ current (Post *et al.* 1993). Dithionite, a powerful reducing agent (Lambeth and Palmer 1973), decreases the K^+ current and causes depolarization and vasoconstriction (Yuan *et al.* 1993). These reports indicate that both endogenous and exogenous redox-active agents can alter K^+ channel gating in pulmonary vascular smooth muscle. Could hypoxia alter the redox status of the smooth muscle cell membrane?

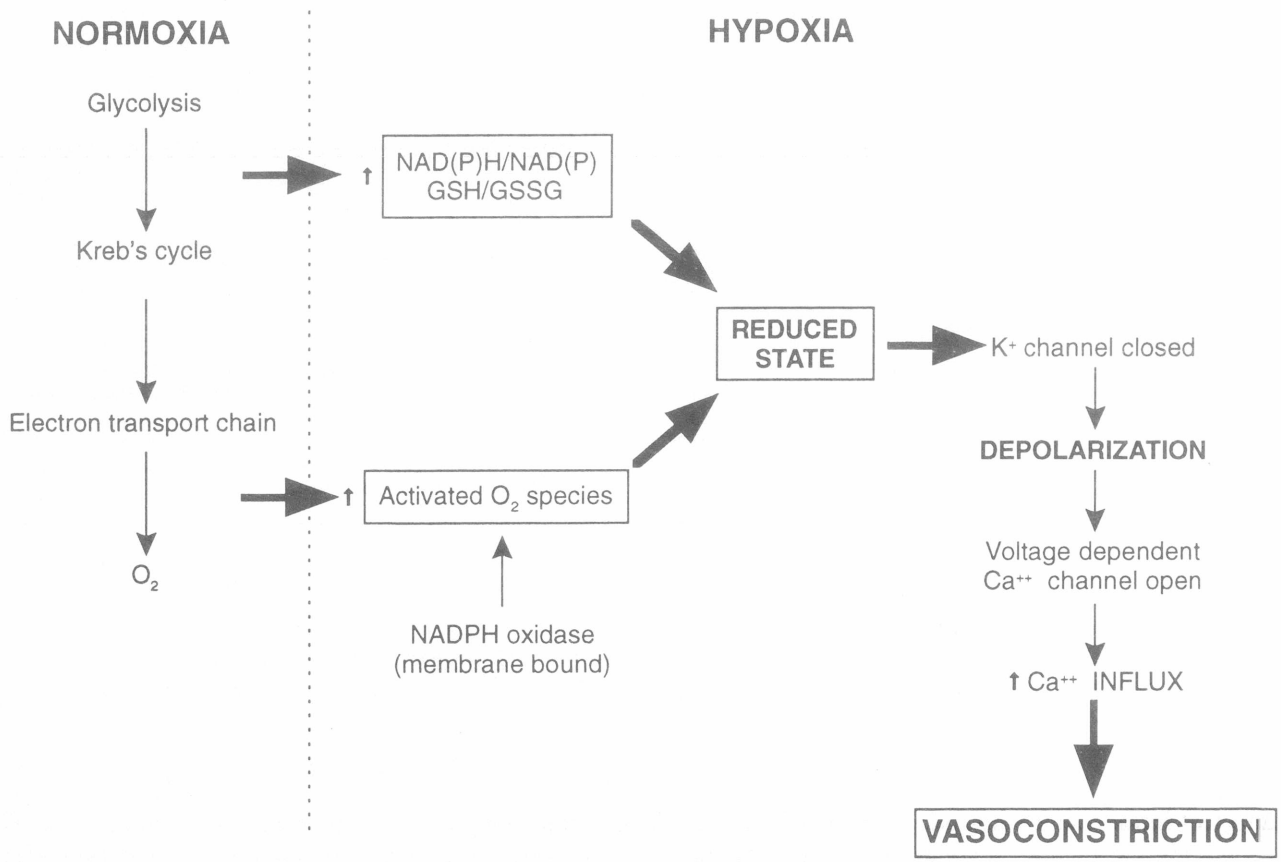

Fig. 3
Acute hypoxic pulmonary vasoconstriction and the redox theory.

Hypoxia and redox status

Hypoxia increases the GSH/GSSG ratio in the lung and decreases the superoxide anion and hydrogen peroxide production in lung mitochondria (Archer *et al.* 1989). Metabolic inhibitors, such as 2-deoxyglucose or iodoacetate (inhibitors of glycolysis) and rotenone or antimycin (inhibitors of oxidative phosphorylation) reduce the K^+ current in PA smooth muscle cell (Archer *et al.* 1993a). It might be thought that this reduction in current could be the result of ATP depletion. However, 5 mM ATP was dialysed into the smooth muscle cell along with the metabolic inhibitors from the microelectrode. The provision of ATP ensures that the rapid reduction of the K^+ current is not the result of the depletion of high energy phosphates. Like hypoxia, rotenone and antimycin have previously been shown to cause pulmonary vasoconstriction (Rounds and McMurtry 1981, Stanbrook and McMurtry 1983).

Hypoxic and pharmacologic inhibition of the aerobic metabolic pathways leads to accumulation of reducing equivalents which, along with the decreased production of oxygen radicals and peroxides (activated oxygen species, AOS), shift the redox status of the lung towards a more reduced state. These changes provide a potential mechanism for the signalling of hypoxia (Fig. 3). The hypothesis that the K^+ channel senses hypoxia through the redox status of the PA smooth muscle cell (Archer *et al.* 1986) is supported by the fact that strikingly similar mechanisms have been proposed for the carotid body type I cell and the neuroepithelial body (NEB) (discussed in detail in Weir and Archer 1995).

Which K^+ channel is modulated by hypoxia?

ATP-sensitive K^+ channels (KATP) have been identified in the PA (Clapp and Garney 1993). These channels mediate, at least in part, the hypoxic vasodilatation in systemic vascular smooth muscle cells (hyperpolarizing the membrane, through an increase in outward K^+ current, when ATP levels fall) (Daut *et al.* 1990). KATP channels are not considered to be essential in the control of the normoxic low PA pressure, as KATP channel blockers do not increase the normoxic pressure (Wiener *et al.* 1991). A fall in ATP levels is unlikely to mediate HPV as ATP levels show either no change or increase shortly after the onset of hypoxia in the porcine lung (Buescher *et al.* 1991). After prolonged and severe hypoxia the pulmonary pressure, which rose initially, begins to decline. This fall can be prevented by glybenclamide, a KATP channel blocker, suggesting that a reduction of ATP may open these channels late in the hypoxic response (Wiener *et al.* 1991).

There has been a recent interest in the role of Ca^{++}-dependent K^+ channels (KCa) in the regulation of vasomotor tone in systemic arteries (Brayden and Nelson 1992). Opening of a KCa channel in response to hypoxia, with resulting vasodilatation, has been recently shown in isolated smooth muscle cells from cerebral vessels (Harder *et al.* 1993). Both KCa and delayed rectifier (KDR) channels have been found in the pulmonary vessels. Both of these channels can be gated by redox changes (Post *et al.* 1993, Lee *et al.* 1994, Yuan *et al.* 1994). Because it opens at a more negative potential than the other two, the KDR channel was recently proposed to be the major determinant of resting membrane potential in the PA smooth muscle cell (Sheehan *et al.* 1994). It is likely to be the primary sensor in HPV.

Potential sensors other than mitochondria

The effects of hypoxia on single K^+ channels in the carotid body type I cell (Lopez-Barneo *et al.* 1993) raise the possibility of a direct effect of oxygen on the K^+ channel protein. However, the presence of an oxygen sensor in the membrane, close to the K^+ channel, cannot be excluded. In fact, a membrane bound haeme-linked NADPH oxidase has been proposed to have oxygen sensing abilities and, through the production of hydrogen peroxide, to alter the redox gating mechanism of the K^+ channel (Cross *et al.* 1990). A possible role of NADPH oxidase has also been proposed in the NEB (Youngson *et al.* 1993). Interestingly, a haemeprotein oxygen sensor has been proposed in the erythropoietin producing cells (Goldberg *et al.* 1988). Unfortunately, much of the evidence for involvement of NADPH oxidase is based on the use of its inhibitor, diphenyleneiodonium, which turns out to be a non-specific blocker of Ca^{++} and K^+ channels (Weir *et al.* 1994).

Acknowledgements

E. K. Weir and S.L. Archer are supported by VA Merit Review funding and by the Minnesota Medical Foundation. S.L. Archer is also supported by NIH HL-45735. The work illustrated in Figure 2 was performed by J.M.C. Huang, Ph.D.

References

ARCHER S.L., YANKOVICH R.D., CHESLER E., WEIR E.K.: Comparative effects of nisoldipine, nifedipine, and bepridil on experimental pulmonary hypertension. *J. Pharmacol. Exp. Ther.* **233:** 12–17, 1985.

ARCHER S.L., WILL J.A., WEIR E.K.: Redox status in control of pulmonary vascular tone. *Herz* **11:** 127–141, 1986.

ARCHER S.L., MCMURTRY I.F., WEIR E.K.: Mechanisms of acute hypoxic and hyperoxic changes in pulmonary vascular reactivity. In: *Pulmonary Physiology and Pathophysiology*. E.K. WEIR, J. REEVES (eds), Marcel Dekker, New York, 1989, pp. 241–290.

ARCHER S.L., HUANG J., HENRY T., PETERSON D., WEIR E.K.: A redox-based O_2 sensor in rat pulmonary vasculature. *Circ. Res.* **73:** 1100–1112, 1993a.

ARCHER S.L, HUANG J., POST J.M., HUME J.R., WEIR E.K.: t-butyl hydroxyperoxide and glutathione modulate an outward K^+ current in rat pulmonary vascular smooth muscle cells. *Circulation* **88** (Suppl. I): I-143, 1993b.

BRAYDEN J.E., NELSON M.T.: Regulation of arterial tone by activation of calcium-dependent potassium channels. *Science* **256:** 532–535, 1992.

BUCKLER K.J., VAUGHAN-JONES R.D.: Effects of hypoxia on membrane potential and intracellular calcium in rat neonatal carotid body type 1 cells. *J. Physiol. Lond.* **476:** 423–428, 1994.

BUESCHER P.C., PEARSE D.B., PILLAI R.P., LITT N.C., MITCHEL M.C., SYLVESTER J.T.: Energy state and vasomotor tone in hypoxic pig lungs. *J. Appl. Physiol.* **70:** 1874–1881, 1991.

CLAPP L., GARNEY A.: ATP sensitive K^+ channels in the pulmonary vasculature. In: *Ion Flux in Pulmonary Vascular control*. E.K. WEIR, J.R. HUME, J. REEVES (eds), Plenum Press, New York, 1993, 129–139..

CROSS A.R., HENDERSON L., JONES O.T, DELPIANO M.A., HENTSCHEL J., ACKER H.: Involvement of an NAD(P)H oxidase as a pO_2 sensor protein in the rat carotid body. *Biochem. J.* **272:** 743–747, 1990.

DAUT J., MAIER-RUDOLP H.W., VON BECKERATH N., MEHRKE G., GUNTHER G., GOEDEL-MEINEN L.: Hypoxic dilatation of coronary arteries is mediated by ATP sensitive K^+ channels. *Science* **247:** 1341–1344, 1990.

FARRUKH I.S., MICHAEL J.R.: Cellular mechanisms that control pulmonary vascular tone during hypoxia and normoxia. Possible role of Ca^{2+}-ATPases. *Am. Rev. Respir. Dis.* **145:** 1389–1397, 1992.

GOLDBERG M.A., DUNNING S.P., BUNN H.F.: Regulation of the erythropoietin gene: evidence that the oxygen sensor is a heme protein. *Science* **242:** 1412–1415, 1988.

HARDER D.R., MADDEN J.A., DAWSON C.: Hypoxic induction of Ca^{2+}-dependent action potentials in small pulmonary arteries of the cat. *J. Appl. Physiol.* **59:** 1389–1393, 1985.

HARDER D.R., GEBREMEDHIN D., ROMAN R.: Influence of physical and environmental factors on ion channels in arterial muscle. In: *Ion Flux in Pulmonary Vasculature*. E.K. WEIR, J.R. HUME., J. REEVES (eds), Plenum Press, New York, 1993, 105–110.

HASUNUMA K., RODMAN D.M., MCMURTRY I.F.: Effects of K^+ channel blockers on vascular tone in the perfused rat lung. *Am. Rev. Respir. Dis.* **144:** 884–887, 1991.

JENSEN K.S., MICCO A.J., CZARTOLOMNA J., LATHAM L., VOELKEL N.F.: Rapid onset of hypoxic vasoconstriction in isolated lungs. *J. Appl. Physiol.* **72:** 2018–2023, 1992.

JIN N., PACKER C.S., RHOADES R.A.: Pulmonary arterial hypoxic contraction: signal transduction. *Am. J. Physiol.* **263:** L73–L78, 1992.

LAMBETH D.O., PALMER G.: The kinetics and mechanism of reduction of electron transfer proteins and other compounds of biological interest by dithionite. *J. Biol. Chem.* **248:** 6095–6103, 1973.

LEE S., PARK M., SO I., EARM Y.E.: NADH and NAD modulates Ca^{2+}-activated K^+ channels in small pulmonary arterial smooth muscle cells of the rabbit. *Pflügers Arch.* **427:** 378–380, 1994.

LOPEZ-LOPEZ J.R, GONZALEZ C.: Time course of K^+ current inhibition by low oxygen in the chemoreceptor cells of adult rabbit carotid body. Effects of carbon monoxide. *FEBS Lett.* **299:** 251–254, 1992.

LOPEZ-BARNEO J., BENOT A.R., URENA J.: O_2 sensing and the electrophysiology of arterial chemoreceptor cells. *News Physiol. Sci.* **8:** 191–195, 1993.

MADDEN J.A., DAWSON C.A., HARDER D.R.: Hypoxia-induced activation in small isolated pulmonary arteries from the cat. *J. Appl. Physiol.* **59:** 113–118, 1985.

MADDEN J.A., VADULA M.S., KURUP V.P.: Effects of hypoxia and other vasoactive agents on pulmonary and cerebral artery smooth muscle cells. *Am. J. Physiol.* **263:** L384–L393, 1992.

MCMURTRY I.F.: BAY K 8644 potentiates and A23187 inhibits hypoxic vasoconstriction in rat lungs. *Am. J. Physiol.* **249:** H741–H746, 1985.

MCMURTRY I.F DAVIDSON A.B., REEVES J.T., GROVER R.F.: Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. *Circ. Res.* **38:** 99–104, 1976.

POST J.M. HUME J.R., ARCHER S.L. WEIR E.K.: Direct role for potassium channel inhibition in hypoxic pulmonary vasoconstriction. *Am. J. Physiol.* **262:** C882–C890, 1992.

POST J.M., WEIR E.K., ARCHER S.L., HUME J.R.: Redox regulation of potassium channels and hypoxic pulmonary vasoconstriction. In: *Ion Flux in Pulmonary Vascular Control*. E.K. WEIR, J.R. HUME, J. REEVES (eds), Plenum Press, New York, 1993.

RETTIG J., HEINEMANN S., WUNDER F., LORRA C., PARCEJ D.N., DOLLY J.O., PONGS O.: Inactivation properties of voltage gated K^+ channels altered by presence of β-subunit. *Nature* **369:** 289–294, 1994.

ROUNDS S., MCMURTRY I.F: Inhibitors of oxidative ATP production cause transient vasoconstriction and block subsequent pressor responses in rat lungs. *Circ. Res.* **48:** 393–400, 1981.

SALVATERRA C., GOLDMAN W.F.: Acute hypoxia increases cytosolic calcium in cultured pulmonary arterial myocytes. *Am. J. Physiol.* **264:** L323–L328, 1993.

SHEEHAN D., SYLVESTER J., SHAM J.: 4-aminopyridine sensitive, delayed-rectifier K^+ current is the major K^+ current controlling resting membrane potential in porcine vascular smooth muscle. *Am. J. Resp. Crit. Care Med.* **149:** A293, 1994.

STANBROOK H.C., MCMURTRY I.F.: Inhibition of glycolysis potentiates hypoxic vasoconstriction in rat lungs. *J. Appl. Physiol.* **55:** 1467–1473, 1983.

TOLINS M., WEIR E.K., CHESLER E., NELSON D.P., FROM A.H.: Pulmonary vascular tone is increased by a voltage-dependent calcium channel potentiator. *J. Appl. Physiol.* **60:** 942–948, 1986.

URENA J., FERNANDEZ-CHACON R., BENOT A.R., ALVAREZ DE TOLEDO G.A., LOPEZ-BARNEO J.: Hypoxia induces voltage-dependent Ca^{2+} entry and quantal dopamine secretion in carotid body glomus cells. *Proc. Natl. Acad. Sci. USA* **91:** 10208–10211, 1994.

VADULA M.S., KLEIMMAN J.G., MADDEN J.A.: Effect of hypoxia and norepinephrine on cytoplasmic free Ca^{2+} in pulmonary and cerebral arterial myocytes. *Am. J. Physiol.* **265:** L591–L597, 1993.

VON EULER U., LILJESTRAND G.: Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol. Scand.* **12:** 301–320, 1946.

WEIR E.K., ARCHER S.L.: The mechanism of acute hypoxic pulmonary vasoconstriction: the tale of two channels. *FASEB J.* **9:** 183–189, 1995.

WEIR E.K., WILL J.A., LUNDQUIST L.J., EATON J.W., CHESLER E.: Diamide inhibits pulmonary vasoconstriction induced by hypoxia or PG $F_{2\alpha}$. *Proc. Soc. Exp. Biol. Med.* **173:** 96–103, 1983.

WEIR E.K., WYATT C.N., REEVE H.L., HUANG J., ARCHER S.L., PEERS C.: Diphenyleneiodonium inhibits both potassium and calcium currents in isolated pulmonary artery smooth muscle cells. *J. Appl. Physiol.* **76:** 2611–2615, 1994.

WIENER C.M., DUNN A., SYLVESTER J.T.: ATP-dependent K^+ channels modulate vasoconstrictor responses to severe hypoxia in isolated ferret lungs. *J. Clin. Invest.* **88:** 500–504, 1991.

YOUNGSON C., NURSE C., YEGER H., CUTZ E.: Oxygen sensing in airway chemoreceptors. *Nature* **365:** 153–155, 1993.

YUAN X.-J., GOLDMAN W.F., TOD M.L., RUBIN L.J., BLAUSTEIN M.P.: Ionic currents in rat pulmonary and mesenteric arteriolar myocytes in primary culture and subculture. *Am. J. Physiol.* **264:** L107–L115, 1993.

YUAN X.-J., TOD M.L., RUBIN L.J., BLAUSTEIN M.P.: Deoxyglucose and reduced glutathione mimic effects of hypoxia on K^+ and Ca^{2+} conductances in pulmonary artery cells. *Am. J. Physiol.* **267:** L52–L63, 1994.

ZASSLOW M.A., BENUMOF J.L., TROUSDALE F.R.: Hypoxic pulmonary vasoconstriction and the size of hypoxic compartment. *J. Appl. Physiol.* **53:** 626–630, 1982.

Reprint Requests

E. Kenneth Weir, M.D., Professor of Medicine, University of Minnesota, VA Medical Center (111C), One Veteran Drive, Minneapolis, Minnesota 55417, USA.