ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 6, 2007

DOI: 10.1089/ars.2007.1580

Forum Editorial

From Oxygen Sensing to Heart Failure

YUICHIRO J. SUZUKI

INTRODUCTION

THE OBJECTIVE of the Forum on "From Oxygen Sensing to Heart Failure" and associated Integrative Cardio-Pulmonary Biology Workshop "From Oxygen Sensing to Heart Failure" that was held on October 11–13, 2006, in Bethesda, Maryland, was to promote an integrative approach in solving health problems which involve cardiopulmonary interactions. Specifically, the issues on the influence of chronic and intermittent hypoxia on the pathogenesis of systemic and pulmonary hypertension, cardiac hypertrophy, and heart failure were addressed, with a focus on the relationship between oxygen sensing mechanisms, redox signaling, and cardiovascular diseases. This Forum consists of ten interdisciplinary articles on both basic science and clinical aspects of hypoxic diseases, oxygen sensing, redox signaling, and heart failure (1, 14, 19, 20, 22, 32, 34, 37, 53, 60). Figure 1 describes the organization of this Forum.

Heart failure is a condition in which the heart cannot supply adequate blood flow to tissues and organs. Some of the causes of heart failure include coronary artery disease, hypertension, valvular disease, and myocardial infarction. Conditions that are associated with respiratory dysfunctions and hypoxia can also lead to heart failure. For example, hypoxic pulmonary hypertension, which can be caused by lung diseases such as chronic obstructive pulmonary disease (COPD), promotes right ventricular hypertrophy and right heart failure. Intermittent hypoxia, which occurs in obstructive sleep apnea syndrome, appears to cause hypertension of both systemic and pulmonary circulatory systems, resulting in left- and right-sided cardiac hypertrophy and heart failure. Obstructive sleep apnea may also cause increased incidence of coronary artery disease and myocardial infarction. Other conditions, which could promote hypoxia-associated cardiovascular alterations, include first-hand and second-hand tobacco smoke. Mechanisms of heart failure during hypoxic conditions, however, have not been defined. Lack of such knowledge interferes with therapeutic strategies to prevent and/or treat heart failure. Redox signaling events may play important roles in the pathogenesis of hypoxia-associated heart failure by promoting vascular and cardiac hypertrophy, regulating apoptosis, and mediating oxygen sensing mechanisms.

OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR DISEASES

Obstructive sleep apnea is a condition characterized by the occurrence of repetitive episodes of airflow obstruction during sleep. Obstructive sleep apnea is a common disorder in the United States and other Western countries, with prevalence of 4% in males and 2% in females (63). Obstructive sleep apnea has been implicated in pathogenesis of systemic hypertension, pulmonary hypertension, congestive cardiac failure, cardiac arrhythmias, atherosclerosis, ischemic heart disease, and stroke (2, 12, 24, 33, 35, 36, 39–41, 44).

It appears that obstructive sleep apnea symptom is heterogeneous and resultant consequences differ accordingly. For example, an early study by Bradley *et al*. (4) identified that 12% of obstructive sleep apnea patients had right heart failure and these patients had a substantially lower awake arterial pO_2, suggesting that sustained hypoxia activates signals to promote pulmonary hypertension and right ventricular heart failure. In contrast, the majority of obstructive sleep apnea patients do not have daytime hypoxemia, and nighttime intermittent hypoxia appears to elicit systemic hypertension. Accumulating evidence suggests the occurrence of oxidative stress in obstructive sleep apnea patients (49).

Intermittent hypoxia is characterized by repeated episodes of hypoxia/reoxygenation cycles, which likely produce reactive oxygen species (ROS). Substantial evidence points to the role of oxidant-mediated signal transduction in the

Department of Pharmacology, Georgetown University Medical Center, Washington, District of Columbia.

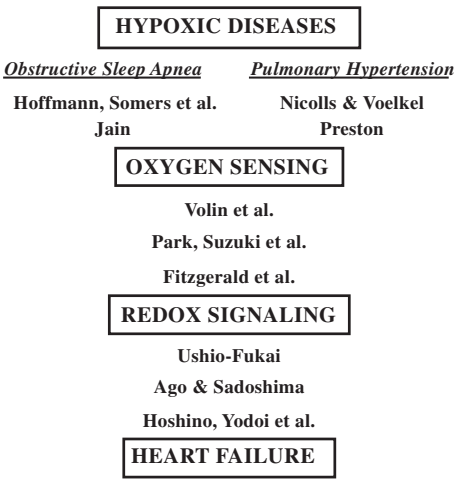

FIG. 1. The Organization of the Forum on "From Oxygen Sensing to Heart Failure".

promotion of systemic hypertension (16, 45–47, 52, 58). Thus, although the proposed mechanism of obstructive sleep apnea-mediated hypertension may involve sensing of oxygen by the carotid body and the subsequent activation of the renin–angiotensin axis (15), ROS produced directly by hypoxia/reoxygenation cycles might also play a role in the development of systemic hypertension. Recent evidence also suggests that ROS may directly affect the heart during intermittent hypoxia (10). In this Forum, Somers and co-workers provide experimental results from human samples showing that obstructive sleep apnea alters gene expression of antioxidant enzymes (19), and Jain summarizes clinical literature on obstructive sleep apnea-associated cardiovascular complications (22).

HYPOXIC PULMONARY HYPERTENSION AND RIGHT HEART FAILURE

Pulmonary hypertension can occur secondary to various hypoxic diseases including acute lung injury, chronic obstructive pulmonary disease, lung fibrosis, and obstructive sleep apnea syndrome. Pathologic characteristics of pulmonary hypertension include histological abnormalities of the vascular wall with hypertrophy of smooth muscle, resulting in a mean pulmonary arterial pressure of >25 mm Hg at rest or >30 mm Hg during exercise, and the progressively increased pulmonary arterial impedance (9). The increased pulmonary arterial blood pressure ultimately produces right ventricular hypertrophy, heart failure, and death (13, 21, 31).

Pulmonary hypertension involves abnormalities of vascular biology in each compartment of the pulmonary circulation. The endothelium excessively produces vasoconstrictors, and smooth muscle cells are depolarized and overloaded with Ca^{2+}, due to reduced expression of voltage-gated potassium channels (28, 50). These events cause vasoconstriction and vascular smooth muscle cell growth. By the time patients with pulmonary hypertension obtain clinical attention, pathologic lesions have developed, which include pulmonary artery medial hypertrophy, adventitial thickening, and neointimal lesions. Abnormal growth of smooth muscle cells is a main component of vascular remodeling, and appears to be regulated by vasoactive factors such as endothelin-1 and serotonin, both of which have been shown to use ROS as second messengers for cell growth signaling (25, 26, 56, 57). In this Forum, Nicolls and Voelkel introduce the idea of the effects of hypoxia on the lung beyond hypoxic vasoconstriction (32), and Preston reviews clinical literature on hypoxia-mediated pulmonary hypertension (37).

OXYGEN SENSING MECHANISMS

Hypoxia elicits various biologic events, which might lead to heart failure. For example, in the case of sustained hypoxic conditions, mean blood pressure of pulmonary circulation rises due to hypoxic vasoconstriction and vascular narrowing. Increased pulmonary vascular resistance imposes pressure overload to the right ventricle, resulting in initial concentric hypertrophy, followed by dilated cardiomyopathy. During hypoxic vasoconstriction, it is well established that pulmonary artery smooth muscle directly serves as the oxygen-sensing organ and constricts the vessels. Molecular mechanisms of oxygen sensing, however, have not been defined. Various theories have been proposed, including the mitochondria theory (8) and the NAD(P)H oxidase theory (23). More recently, hemoxygenase-2 has been shown to act as an oxygen sensor (59). Hypoxia-inducible factor 1 (HIF-1) plays an important role in sensing oxygen and regulates gene transcription via the activation of prolyl and asparaginyl hydroxylases (42, 43). In this Forum, Wolin *et al.* describe redox-regulated mechanisms of oxygen sensing in vascular smooth muscle (60).

Do cardiac myocytes have oxygen-sensing mechanisms, which might influence the course of the development of cardiac hypertrophy and transition to heart failure? Schumacker and co-workers have shown that cardiac myocytes do sense low oxygen tension via the activation of the production of reactive oxygen species from mitochondria (6, 11, 54). Cataldi *et al*. (7) reported that protein kinase C alpha is involved in sensing intermittent hypoxia in the rat heart. Wright *et al*. (61) showed that prolyl hydroxylation is the oxygen sensing mechanism in cardiac myocytes, which in turn regulates HIF-1, hemoxygenase-1, and GLUT1. While the roles of NADPH oxidase in oxygen sensing processes in cardiac myocytes have not yet been reported, this enzyme has been shown to be expressed in the heart and to serve roles in the development of cardiac hypertrophy and transition to heart failure (3, 5, 18, 27, 30, 38, 62). In this Forum, Park *et al.* address the mechanisms of the effects of intermittent hypoxia on the heart (34).

Oxygen sensing mechanisms in central and peripheral nervous systems have been well studied, and these mechanisms also regulate cardiovascular/pulmonary functions. Integrative studies which consider both neuroscience and cardiovascular/respiratory science should promote better understanding of how heart and lung diseases might occur. In this Forum, Fitzgerald *et al.* addresses the oxygen sensing mechanisms in the carotid body (14).

TABLE 1. AGENDA FOR INTEGRATIVE CARDIO-PULMONARY BIOLOGY WORKSHOP "FROM OXYGEN SENSING TO HEART FAILURE" OCTOBER 11–13, 2006; BETHESDA, MD

Discussion Session on Pulmonary Hypertension and Right Heart Failure

Introduction: *Clinical Problems in Pulmonary Hypertension*
Vivek Jain, M.D. (George Washington University)

Brief Discussion on *Medical Education & Pulmonary Hypertension*
"Should early medical education cover therapeutic strategies for pulmonary hypertension?"
Discussion Leader: Yuichiro Suzuki, Ph.D. (Georgetown University)

Special Presentation: *Differential Innervation to Right and Left Ventricles*
Martha Davila–Garcia, Ph.D. (Howard University)

Special Presentation: *Molecular Mechanism of Right Heart Failure in Severe Pulmonary Hypertension*
Michael Crow, Ph.D. (Johns Hopkins University)

Keynote Lecture on *Right Heart Failure*
Paul Forfia, M.D. (University of Pennsylvania)

Discussion on *Pulmonary Hypertension and Right Heart Failure*
Chairs: Paul Hassoun, M.D. (Johns Hopkins University) and Norbert Voelkel, M.D. (University of Colorado)

Opening Ceremony at Masur Auditorium, National Institutes of Health

Vassilios Papadopoulos, Ph.D. (Georgetown University)
Opening Remarks: Oxygen Sensing Mechanisms

Elizabeth Denholm, Ph.D. (NHLBI/NIH)
NHLBI Strategies for Promoting Right Heart Failure Research

Vivek Jain, M.D. (George Washington University)
Clinical Problems in Obstructive Sleep Apnea

Scientific Session I Hypoxia and Cardio-Pulmonary Disease

Chairs: Yuichiro Suzuki (Georgetown University) and James Sham (Johns Hopkins University)

Virend Somers, M.D.,Ph.D.(Mayo Clinic)
Obstructive Sleep Apnea and Heart Failure

Ioana Preston, M.D. (New England Medical Center)
Mechanisms of Hypoxic Pulmonary Hypertension

Paul Hassoun, M.D. (Johns Hopkins University)
Molecular Determinants of Right Ventricular Failure in Pulmonary Arterial Hypertension

Norbert Voelkel, M.D. (University of Colorado)
Right Ventricle in Severe Pulmonary Hypertension

Dipak Das, Ph.D. (University of Connecticut)
Oxygen Sensing and Hypoxic Preconditioning

Yuichiro Suzuki, Ph.D. (Georgetown University)
Effects of Intermittent Hypoxia on the Heart

Scientific Session II Oxygen Sensing: Cancer to Neuroscience

Chairs: Michael Espey (NCI/NIH) and Ajay Verma (Uniformed Services University of the Health Sciences)

Paul Kemp, Ph.D. (Cardiff University)
Oxygen Sensing by Potassium Channels: Protein Partners and 'Gas' Transmitters

Isaac Pessah, Ph.D. (University of California, Davis)
Ryanodine Receptors: A Multiprotein Redox-Sensor

Murali Krishna, Ph.D. (National Cancer Institute/NIH)
Real-Time Oxygen and Redox Imaging

Oxygen Club of Greater Washington DC Young Investigator Presentation
Douglas Thomas, Ph.D. (NCI/NIH)
Under Normoxic Conditions Nitric Oxide-Mediated HIF-1α Accumulation is Regulated by Superoxide Fluxes

Gregg Semenza, M.D.,Ph.D. (Johns Hopkins University)
Role of HIF-1 in Cardio-Pulmonary Responses to Continuous and Intermittent Hypoxia

Ajay Verma, M.D.,Ph.D. ((Uniformed Services University of the Health Sciences)
Oxygen Sensing in Brain

(Continued)

TABLE 1. *(Continued)*

Robert Fitzgerald, Ph.D. (Johns Hopkins University)
Neurochemical Processes in the Carotid Body Chemotransduction of Low Oxygen

Discussion on *How Do Oxygen Sensing Mechanisms Influence the Development of Heart Failure?*
(Discussion Leaders: Robert Fitzgerald and Gregg Semenza)

Daniel L. Gilbert Memorial Lecture:
Junji Yodoi, M.D.,Ph.D. (Kyoto University)
Redox Regulation by Thioredoxin

Scientific Session III Oxygen and Redox Signaling

Chairs: Junji Yodoi (Kyoto University) and Chandan Sen (Ohio State University)

Chandan Sen, Ph.D. (Ohio State University)
Perceived Hyperoxia: Oxygen-Induced Remodeling of the Reoxygenated Heart

Junichi Sadoshima, M.D.,Ph.D. (University of Medicine and Dentistry of New Jersey)
Dnajb5 Mediates Anti-Hypertrophic Actions of Thioredoxin 1

Chuang Chiueh, Ph.D. (Taipei Medical University)
Role of Thioredoxin in Neuronal Differentiation following Anoxic Preconditioning

Oxygen Club of Greater Washington DC Young Investigator Presentation

Tetsuro Ago, M.D.,Ph.D. (University of Medicine and Dentistry of New Jersey)
Thioredoxin1 Upregulates PGC-1α and NRF1, and Enhances Mitochondrial Functions, thereby Exerting Cardioprotective Roles

Connie Noguchi, Ph..D (NIDDK/NIH)
Hypoxia, Erythropoietin and Cardiovascular System

Lisa Palmer, Ph.D. (University of Virginia)
S-Nitrosothiols, HIF and the Development of Pulmonary Hypertension

Masuko Ushio–Fukai, Ph.D. (University of Illinois, Chicago)
NADPH Oxidase in Vascular Signaling

Michael Wolin, Ph.D. (New York Medical College)
Cytosolic NAD(P)H Regulation of Redox Signaling and Vascular Oxygen Sensing

Discussion on *What Oxygen Levels Should We Use for Cell Culture Experiments?*

(Discussion Leaders: Chandan Sen and Connie Noguchi)

MOLECULAR MECHANISMS OF LEFT AND RIGHT CARDIAC HYPERTROPHY AND HEART FAILURE

In response to vascular resistance and pressure overload, the heart adapts to thicken the ventricular walls to increase the force of blood ejection. In the case of increased systemic vascular blood pressure, the left ventricle is affected; and the increased pulmonary vascular resistance affects the right ventricle. As the ventricular mass increases, the ventricular chamber size might be reduced to a level that is not sufficient to hold enough blood for sustaining appropriate stroke volume. These events are followed by the reduction of the thickness of ventricular walls and enlargement of the heart, leading to the dilated heart with weak contractile functions. There has been ample information generated by research concerning left ventricular hypertrophy and failure; however, knowledge of the right side of the heart is limited (55). Further, it is not yet clear whether molecular mechanisms of cardiac hypertrophy and failure are different between right and left sides of the heart. As right ventricular hypertrophy is often associated with sustained hypoxic conditions, the direct effects of hypoxia might alter pressure overload-mediated signaling in the heart. Thus, understanding biology of the hypoxic right ventricle may help in developing effective therapeutic strategies against this condition. Similarly, systemic hypertension-mediated left cardiac hypertrophy in obstructive sleep apnea might be influenced by changes in oxygen tension and the production of reactive oxygen species.

Hypoxia can directly influence cardiac gene regulation and functions. Hypoxia has been shown to induce the shift in myosin heavy chain isoforms (17). Hypoxia also downregulates gene expression of alpha-adrenergic receptors (29). Thus, alpha-receptor signaling might not contribute significantly to the development of hypoxic pulmonary hypertension-mediated right cardiac hypertrophy, whereas alpha-receptor-mediated signaling may play important roles in the development of pressure overload-induced left ventricular hypertrophy. Since hypoxia induces myocardial histone acetylation (51) and the inhibition of histone deacetylases and the promotion of protein acetylation induce right and left ventricular hypertrophy (64), hypoxia may influence hypertrophic signaling mechanisms.

Redox signaling events play important roles in the development of vascular and cardiac remodeling. In this Forum, Ushio–Fukai summarizes the roles of NAD(P)H oxidase and reactive oxygen species in vascular signaling (53). Reactive oxygen species have also been shown to mediate hypertrophic signaling of cardiac muscle (48). In this Forum, Ago and

FIG. 2. Photographs from Integrative Cardio-Pulmonary Biology Workshop "From Oxygen Sensing to Heart Failure" (October 11–13, 2006). *Top row (from left):* Vassilios Papadopoulos, Elizabeth Denholm, Vivek Jain, Virend Somers, Ioana Preston, Paul Hassoun, Norbert Voelkel; *Second row (from left):* Dipak Das, refreshment break, Shilpa and Ah-Mee at reception desk, Michael Espey; *Third row (from left):* Paul Kemp, Isaac Pessah, Murali Krishna, Douglas Thomas, James Sham, Gregg Semenza, Ajay Verma; *Fourth row (from left):* Oxygen Club of Greater Washington DC Annual Meeting, Robert Fitzgerald, Junichi Sadoshima; *Fifth row (from left):* Junji Yodoi, Oxygen Club of Greater Washington DC Poster Session, Chuang Chiueh, Tetsuro Ago, Lisa Palmer; *Sixth row (from left):* Yuichiro Suzuki, Junji Yodoi and Martin Morad, Chandan Sen and Connie Noguchi, Masuko Ushio–Fukai, Michael Wolin.

Sadoshima describe a novel role of thioredoxin 1 in cardiac hypertrophy (1), and Yodoi and colleagues summarize the role of thioredoxin in cardiovascular system (20).

INTEGRATIVE CARDIO-PULMONARY BIOLOGY WORKSHOP

From October 11th through 13th, 2007, an Integrative Cardio-Pulmonary Biology Workshop "From Oxygen Sensing to Heart Failure" was held at the National Institutes of Health in Bethesda, MD. The Workshop was co-sponsored by Georgetown University, Oxygen Club of Greater Washington DC, and International Redox Network; and was funded by the National Heart, Lung, and Blood Institute and Flight Attendant Medical Research Institute. The Workshop was designed to bring together leading investigators from multiple disciplines to address the issues of the influence of chronic and intermittent hypoxia on the pathogenesis of systemic and pulmonary hypertension, cardiac hypertrophy, and heart failure. Specifically, the relationship between oxygen sensing mechanisms, redox signaling, and cardiovascular diseases were discussed. Interdisciplinary sessions included: (a) Hypoxia and Cardio-Pulmonary Disease, (b) Oxygen Sensing: Cancer to Neuroscience, and (c) Oxygen and Redox Signaling (Table 1).

In Session I: Hypoxia and Cardio-Pulmonary Disease (chaired by Yuichiro Suzuki and James Sham), Virend Somers described obstructive sleep apnea as a risk factor for heart failure, Ioana Preston gave an introduction to hypoxic pulmonary hypertension, and Paul Hassoun and Norbert Voelkel addressed the importance of right heart failure in pulmonary hypertension. These introductory talks on hypoxic diseases were followed by Dipak Das discussing the role of hypoxia as a preconditioning mediator. Yuichiro Suzuki later provided a link between obstructive sleep apnea and hypoxic preconditioning.

Session II: Oxygen Sensing: Cancer to Neuroscience (chaired by Michael Espey and Ajay Verma) began with Paul Kemp describing the mechanisms of oxygen sensing by carotid body potassium channels, and Isaac Pessah addressing the ryanodine receptor as a redox sensor. These lectures were followed by Murali Krishna's talk on real-time oxygen and redox imaging technology. Oxygen sensing by HIF-1 was discussed by Gregg Semenza and Ajay Verma with focus on cardiopulmonary responses and the brain, respectively. Robert Fitzgerald described the role of the carotid body as an oxygen sensor and led the discussion on "How do oxygen sensing mechanisms influence the development of heart failure?" During the discussion, Gregg Semenza emphasized the importance of the fact that all the organs sense oxygen and complex and integrative mechanisms are involved in the development of heart failure. In this Session, a Young Investigator Award recipient, Douglas Thomas discussed HIF regulation by nitric oxide.

Chandan Sen and Junji Yodoi chaired Session III: Oxygen and Redox Signaling. Chandan Sen talked about the effects of varied oxygen tension on the heart, and Junichi Sadoshima described the role of thioredoxin in regulating cardiac hypertrophy. Interdisciplinary thioredoxin talks continued with Chuang Chiueh's report on neuronal thioredoxin and the presentation on the mechanism of thioredoxin-mediated cardioprotection by a Young Investigator Award recipient, Tetsuro Ago. The vascular biology segment featured Connie Noguchi's talk on erythropoietin and endothelial cells, Lisa Palmer describing thiol regulation of pulmonary hypertension, Masuko Ushio–Fukai addressing the role of NAD(P)H oxidase in angiogenesis, and Michael Wolin summarizing the role of cytosolic NAD(P)H in redox regulation of vascular oxygen sensing. The Session was concluded by Discussion of "What oxygen levels should we use for cell culture experiments?" led by Chandan Sen and Connie Noguchi. It was concluded that this is a critical issue that requires further evaluations.

In addition, the Workshop featured the Discussion Session on Pulmonary Hypertension and Right Heart Failure and the 1st Daniel L. Gilbert Memorial Lecture of the Oxygen Club of Greater Washington DC by Junji Yodoi. Figure 2 shows photographs of some of the activities at this Workshop. The Workshop helped to stimulate currently under-studied fields, including hypoxic pulmonary hypertension-mediated right heart failure, obstructive sleep apnea-induced cardiovascular complications, and heart failure associated with environmental factors which promote chronic and intermittent hypoxia. Further, the Workshop fostered interdisciplinary interactions through the interests in redox and oxygen biology.

ACKNOWLEDGMENTS

This ARS Forum and Integrative Cardio-Pulmonary Biology Workshop "From Oxygen Sensing to Heart Failure" were supported by grants from National Institutes of Health (R13HL86004) and Flight Attendant Medical Research Institute. I thank Drs. Michael Espey (NIH), Vivek Jain (George Washington University), Venkataraman Srinivasan [Armed Forces Radiobiology Research Institute (AFRRI)], Regina Day [Uniformed Services University of the Health Sciences (USUHS)], Ajay Verma (USUHS), William Blakely (AFRRI), and other members of the Oxygen Club of Greater Washington DC for their significant contributions to the success of Integrative Cardio-Pulmonary Biology Workshop "From Oxygen Sensing to Heart Failure".

REFERENCES

1. Ago T and Sadoshima J. Thioredoxin1 as a negative regulator of cardiac hypertrophy. *Antioxid Redox Signal* 9: 679–687, 2007.
2. Bassetti C, Aldrich MS, and Quint D. Sleep-disordered breathing in patients with acute supra- and infratentorial strokes. A prospective study of 39 patients. *Stroke* 28: 1765–1772, 1997.
3. Bendall JK, Cave AC, Heymes C, Gall N, and Shah AM. Pivotal role of a gp91(phox)-containing NADPH oxidase in angiotensin II-induced cardiac hypertrophy in mice. *Circulation* 105: 293–296, 2002.
4. Bradley TD, Rutherford R, Grossman RF, Lue F, Zamel N, Moldofsky H, and Phillipson EA. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* 131: 835–839, 1985.
5. Browe DM and Baumgarten CM. Angiotensin II (AT1) receptors and NADPH oxidase regulate Cl^- current elicited by beta1 integrin stretch in rabbit ventricular myocytes. *J Gen Physiol* 124: 273–287, 2004.
6. Budinger GR, Duranteau J, Chandel NS, and Schumacker PT. Hibernation during hypoxia in cardiomyocytes. Role of mitochondria as the O_2 sensor. *J Biol Chem* 273: 3320–3326, 1998.

7. Cataldi A, Bianchi G, Rapino C, Sabatini N, Centurione L, Di Giulio C, Bosco D, and Antonucci A. Molecular and morphological modifications occurring in rat heart exposed to intermittent hypoxia: role for protein kinase C alpha. *Exp Gerontol* 39: 395–405, 2004.
8. Chandel NS and Schumacker PT. Cellular oxygen sensing by mitochondria: old questions, new insight. *J Appl Physiol* 88: 1880–1889, 2000.
9. Chemla D, Castelain V, Herve P, Lecarpentier Y, and Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J* 20: 1314–1331, 2002.
10. Chen L, Einbinder E, Zhang Q, Hasday J, Balke WC, and Scharf SM. Oxidative Stress and Left Ventricular Function with Chronic Intermittent Hypoxia in Rats. *Am J Respir Crit Care Med* 172: 915–920, 2005.
11. Duranteau J, Chandel NS, Kulisz A, Shao Z, and Schumacker PT. Intracellular signaling by reactive oxygen species during hypoxia in cardiomyocytes. *J Biol Chem* 273: 11619–11624, 1998.
12. Dyken ME, Somers VK, Yamada T, Ren ZY, and Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. *Stroke* 27: 401–407, 1996.
13. Farber HW and Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 351: 1655–1665, 2004.
14. Fitzgerald RS, Shirahata M, Balbir A, and Grossman CE. Oxygen sensing in the carotid body and its relation to heart failure. *Antioxid Redox Signal* 9: 745–749, 2007.
15. Fletcher EC. Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. *J Appl Physiol* 90: 1600–1605, 2001.
16. Griendling KK, Minieri CA, Ollerenshaw JD, and Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res* 74: 1141–1148, 1994.
17. Hashimoto T, Sugiyama A, and Taguchi S. Hypoxia-induced adaptational shift in MHC-beta isoform expression in rat ventricles. *Jpn J Physiol* 55: 109–115, 2005.
18. Heymes C, Bendall JK, Ratajczak P, Cave AC, Samuel JL, Hasenfuss G, and Shah AM. Increased myocardial NADPH oxidase activity in human heart failure. *J Am Coll Cardiol* 41: 2164–2171, 2003.
19. Hoffmann MS, Singh P, Wolk R, Romero–Corral A, Raghavakaimal S, and Somers VK. Microarray studies of genomic oxidative stress and cell cycle responses in obstructive sleep apnea. *Antioxid Redox Signal* 9: 661–669, 2007.
20. Hoshino Y, Shioji K, Nakamura H, Masutani H, and Yodoi J. From oxygen sensing to heart failure: role of thioredoxin. *Antioxid Redox Signal* 9: 689–699, 2007.
21. Humbert M, Sitbon O, and Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 351: 1425–1436, 2004.
22. Jain V. Clinical perspective of obstructive sleep apnea-induced cardiovascular complications. *Antioxid Redox Signal* 9: 701–710, 2007.
23. Jones RD, Hancock JT, and Morice AH. NADPH oxidase: a universal oxygen sensor? *Free Radic Biol Med* 29: 416–424, 2000.
24. Lavie P, Herer P, and Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *Br Med J* 320: 479–482, 2000.
25. Lee SL, Wang WW, and Fanburg BL. Superoxide as an intermediate signal for serotonin-induced mitogenesis. *Free Radic Biol Med* 24: 855–858, 1998.
26. Lee SL, Simon AR, Wang WW, and Fanburg BL. H_2O_2 signals 5-HT-induced ERK MAP kinase activation and mitogenesis of smooth muscle cells. *Am J Physiol* 281: L646–L652, 2001.
27. Li JM, Gall NP, Grieve DJ, Chen M, and Shah AM. Activation of NADPH oxidase during progression of cardiac hypertrophy to failure. *Hypertension* 40: 477–484, 2002.
28. Mandegar M and Yuan JX. Role of K^+ channels in pulmonary hypertension. *Vascul Pharmacol* 38: 25–33, 2002.
29. Michelotti GA, Bauman MJ, Smith MP, and Schwinn DA. Cloning and characterization of the rat alpha 1α-adrenergic receptor gene promoter. Demonstration of cell specificity and regulation by hypoxia. *J Biol Chem* 278: 8693–8705, 2003.
30. Nakagami H, Takemoto M, and Liao JK. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. *J Mol Cell Cardiol* 35: 851–859, 2003.
31. Nauser TD and Stites SW. Pulmonary hypertension: new perspectives. *Congest Heart Fail* 9: 155–162, 2003.
32. Nicolls MR and Voelkel NF. Hypoxia and the lung: beyond hypoxic vasoconstriction. *Antioxid Redox Signal* 9: 741–743, 2007.
33. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, and Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 283: 1829–1836, 2000.
34. Park A-M, Nagase H, Kumar SV, and Suzuki YJ. Effects of intermittent hypoxia on the heart. *Antioxid Redox Signal* 9: 723–729, 2007.
35. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, and Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J* 14: 179–184, 1999.
36. Peppard PE, Young T, Palta M, and Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *New Engl J Med* 342: 1378–1384, 2000.
37. Preston IR. Clinical perspective of hypoxia-mediated pulmonary hypertension. *Antioxid Redox Signal* 9: 711–721, 2007.
38. Privratsky JR, Wold LE, Sowers JR, Quinn MT, and Ren J. AT1 blockade prevents glucose-induced cardiac dysfunction in ventricular myocytes: role of the AT1 receptor and NADPH oxidase. *Hypertension* 42: 206–212, 2003.
39. Qureshi A and Ballard RD. Obstructive sleep apnea. *J Allergy Clin Immunol* 112: 643–651, 2003.
40. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, and McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 149: 416–422, 1994.
41. Schafer H, Koehler U, Ewig S, Hasper E, Tasci S, and Luderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. *Cardiology* 92: 79–84, 1999.
42. Schofield CJ and Ratcliffe PJ. Oxygen sensing by HIF hydroxylases. *Nat Rev Mol Cell Biol* 5: 343–354, 2004.
43. Semenza GL. HIF-1, O_2, and the 3 PHDs: how animal cells signal hypoxia to the nucleus. *Cell* 107: 1–3, 2001.
44. Shamsuzzaman AS, Gersh BJ, and Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 290: 1906–1914, 2003.
45. Suzuki YJ and Ford GD. Superoxide stimulates IP_3-induced Ca^{2+} release from vascular smooth muscle sarcoplasmic reticulum. *Am J Physiol* 262: H114–H116, 1992.
46. Suzuki YJ and Ford GD. Redox regulation of signal transduction in cardiac and smooth muscle. *J Mol Cell Cardiol* 31: 345–353, 1999.
47. Suzuki YJ, Forman HJ, and Sevanian A. Oxidants as stimulators of signal transduction. *Free Radic Biol Med* 22: 269–285, 1997.
48. Suzuki YJ, Nagase H, Nie K, and Park AM. Redox control of growth factor signaling: recent advances in cardiovascular medicine. *Antioxid Redox Signal* 7: 829–834, 2005.
49. Suzuki YJ, Jain V, Park AM, and Day RM. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. *Free Radic Biol Med* 40: 1683–1692, 2006.
50. Sweeney M, and Yuan JX. Hypoxic pulmonary vasoconstriction: role of voltage-gated potassium channels. *Respir Res* 1: 40–48, 2000.
51. Taylor PB and McDonald GW. Hypoxia stimulates myocardial RNA synthesis and histone acetylation. *Res Commun Chem Pathol Pharmacol* 40: 349–352, 1983.
52. Ushio–Fukai M, Zafari AM, Fukui T, Ishizaka N, and Griendling KK. $p22^{phox}$ is a critical component of the superoxide-generating NADH/NADPH oxidase system and regulates angiotensin II-induced hypertrophy in vascular smooth muscle cells. *J Biol Chem* 271: 23317–23321, 1996.
53. Ushio–Fukai M. VEGF signaling through NADPH oxidase-derived ROS. *Antioxid Redox Signal* 9: 731–739, 2007.
54. Vanden Hoek TL, Becker LB, Shao Z, Li C, and Schumacker PT. Reactive oxygen species released from mitochondria during brief hypoxia induce preconditioning in cardiomyocytes. *J Biol Chem* 273: 18092–18098, 1998.
55. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smark FW, Suzuki YJ, Gladwin M, Denholm EM, and Gail DB. Right ventricular function and failure: The need to know more. Report of a National

Heart, Lung and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation* 114: 1883–1891, 2006.
56. Wedgwood S, Dettman RW, and Black SM. ET-1 stimulates pulmonary arterial smooth muscle cell proliferation via induction of reactive oxygen species. *Am J Physiol* 281: L1058–L1067, 2001.
57. Wedgwood S and Black SM. Role of reactive oxygen species in vascular remodeling associated with pulmonary hypertension. *Antioxid Redox Signal* 5: 759–769, 2003.
58. Wilcox CS. Reactive oxygen species: roles in blood pressure and kidney function. *Curr Hypertens Rep* 4: 160–166, 2002.
59. Williams SE, Wootton P, Mason HS, Bould J, Iles DE, Riccardi D, Peers C, and Kemp PJ. Hemoxygenase-2 is an oxygen sensor for a calcium-sensitive potassium channel. *Science* 306: 2093–2097, 2004.
60. Wolin MS, Ahmad M, Gao Q, and Gupte SA. Cytosolic NAD(P)H regulation of redox signaling and vascular oxygen sensing. *Antioxid Redox Signal* 9: 671–678, 2007.
61. Wright G, Higgin JJ, Raines RT, Steenbergen C, and Murphy E. Activation of the prolyl hydroxylase oxygen-sensor results in induction of GLUT1, heme oxygenase-1, and nitric-oxide synthase proteins and confers protection from metabolic inhibition to cardiomyocytes. *J Biol Chem* 278: 20235–20239, 2003.
62. Xiao L, Pimentel DR, Wang J, Singh K, Colucci WS, and Sawyer DB. Role of reactive oxygen species and NAD(P)H oxidase in alpha(1)-adrenoceptor signaling in adult rat cardiac myocytes. *Am J Physiol* 282: C926–C934, 2002.
63. Young T, Palta M, Dempsey J, Skatrud, J, Weber S, and Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 328: 1230–1235, 1993.
64. Zhang CL, McKinsey TA, Chang S, Antos CL, Hill JA, and Olson EN. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. *Cell* 110: 479–488, 2002.

Address reprint requests to:
Dr. Yuichiro J. Suzuki
Department of Pharmacology
Georgetown University Medical Center
Room NW403, Medical-Dental Building
3900 Reservoir Road NW
Washington, DC 20057

E-mail: ys82@georgetown.edu

Date of first submission to ARS Central, January 22, 2007; date of acceptance, January 27, 2007.