COMBINED TRAINING PROGRAM IN CARDIOVASCULAR RESEARCH AND MEDICINE

Division of Cardiovascular Diseases
University of Tennessee Health Science Center
Memphis, Tennessee

2002–2010

March 3, 2009

TRAINEE: Linus A. Wodi, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2002–2003

We use a model of chronic mineralocorticoid excess to simulate one component of human congestive heart failure, namely aldosteronism. **Linus Wodi, MD** found a reduction in cytosolic-free $[Mg^{2+}]_i$ in circulating peripheral blood mononuclear cells (PBMC) and which was accompanied by intracellular Ca^{2+} loading. In response to this rise in total and cytosolic-free Ca^{2+} was the appearance of oxidative stress in these cells, expressed as a rise in lymphocyte and monocyte H_2O_2 production, and a fall in plasma α_1-antiproteinase activity. In addition, there was evidence of an autoactivation of PBMC based on their transcriptome with up- and downregulated genes related to a proinflammatory phenotype (*Circ Res* 2003;93:e124-e135 and *Am J Physiol Heart Circ Physiol* 2003;285:H813-H821). At the time, our working hypothesis centered around a potential direct role played by aldosterone in modifying the divalent composition of PBMC and which was responsible for the induction of oxidative stress and their activation.

Publications (Abstracts included):

1. Gerling IC, Sun Y, Ahokas RA, Wodi LA, Bhattacharya SK, Warrington KJ, Postlethwaite AE, Weber KT. Aldosteronism: an immunostimulatory state precedes the proinflammatory/fibrogenic cardiac phenotype. *Am J Physiol Heart Circ Physiol.* 2003;285:H813-H821.
2. Ahokas RA, Warrington KJ, Gerling IC, Sun Y, Wodi LA, Herring PA, Lu L, Bhattacharya SK, Postlethwaite AE, Weber KT. Aldosteronism and peripheral blood mononuclear cell activation. A neuroendocrine-immune interface. *Circ Res.* 2003;93:e124-e135.
3. Weber KT, Sun Y, Wodi LA, Munir A, Jahangir E, Ahokas RA, Gerling IC, Postlethwaite AE, Warrington KJ. Toward a broader understanding of aldosterone in congestive heart failure. *J Renin Angiotensin Aldosterone Syst.* 2003;4:155-163.
4. Wodi LA, Ahokas RA, Sun Y, Weber KT. Oxidative stress and peripheral blood mononuclear cell free cytosolic magnesium in rats treated with aldosterone/salt [abstr]. *J Investig Med.* 2003;51 (Suppl 1):S283.
5. Wodi LA, Sun Y, Ahokas RA, Gerling IC, Bhattacharya SK, Weber KT. Oxi/nitrosative stress and aldosteronism. Role of peripheral blood mononuclear cells divalent cations in vascular remodeling [abstr]. *J Mol Cell Cardiol.* 2003;35:A29.
6. Wodi LA, Ahokas RA, Warrington KJ, Gerling IC, Sun Y, Bhattacharya SK, Postlethwaite AE, Weber KT. The proinflammatory coronary vascular phenotype of aldosteronism: role of cytosolic free $[Mg^{2+}]_i$ and $[Ca^{2+}]_i$ in peripheral blood mononuclear cell activation [abstr]. *J Investig Med.* 2004;52 (Suppl 1):S264.
7. Zagol BW, Wodi LA, Davis RC, Jr., Weber KT. A hyperactive pulmonary vasculature in response to mitral regurgitation in a patient with aortic stenosis [abstr]. *J Investig Med.* 2005;53 (Suppl 1):S269.
8. Zagol BW, Wodi LA, Davis RC, Newman KP. A hyperactive pulmonary vasculature in response to chronic mitral regurgitation. *Am J Med Sci.* 2007;333:390-393.

Awards:

Young Investigator Award, Southern Society for Clinical Investigation, 2004

TRAINEE: Vikram S. Chhokar, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2003–2004

Despite the attractiveness and simplicity of the direct effect of ALDOST hypothesis, we explored yet another scenario responsible for the shift in these important intracellular cations. These studies were conducted by **Vikram Chhokar, MD**, who used a metabolic cage to address urinary and fecal excretion of Ca^{2+} and Mg^{2+}. This approach was based on the original work of J. W. Conn as he proved a role of aldosterone, acting at multiple sites that included colon, kidneys, sweat, and salivary glands, in leading to increased K^+ excretion and which was derived from an aldosterone-producing adrenal adenoma. In our rat model of aldosteronism, Dr. Chhokar's studies identified marked losses of Ca^{2+} and Mg^{2+} in urine and feces and which led to a fall in plasma-ionized $[Ca^{2+}]_o$ and $[Mg^{2+}]_o$ and, in turn, to the increased secretion of parathyroid hormone (PTH) with increased plasma PTH levels. The presence of secondary hyperparathyroidism (SHPT) was confirmed by bone resorption, manifest as a reduction in bone mineral density and bone Ca^{2+} and Mg^{2+} concentrations, and fall in bone strength. In addition, this revised hypothesis led us to suspect PTH was responsible for intracellular Ca^{2+} overloading of diverse tissues, including PBMC, heart, and skeletal muscle. Cotreatment of these rats with spironolactone, an aldosterone receptor antagonist, prevented the heightened losses of Ca^{2+} and Mg^{2+} in urine and feces and therefore prevented the fall in plasma-ionized concentrations of these cations and loss of bone mineral density (*Am J Physiol Heart Circ Physiol* 2004:287:H2023-H2026 and *Circulation* 2005;111:871-878).

Publications (Abstracts included):

1. Chhokar VS, Sun Y, Bhattacharya SK, Ahokas RA, Myers LK, Xing Z, Smith RA, Gerling IC, Weber KT. Loss of bone minerals and strength in rats with aldosteronism. *Am J Physiol Heart Circ Physiol.* 2004;287:H2023-H2026.
2. Chhokar VS, Sun Y, Bhattacharya SK, Ahokas RA, Myers LK, Xing Z, Smith RA, Gerling IC, Weber KT. Hyperparathyroidism and the calcium paradox of aldosteronism. *Circulation.* 2005;111:871-878.
3. Law PH, Sun Y, Bhattacharya SK, Chhokar VS, Weber KT. Diuretics and bone loss in rats with aldosteronism. *J Am Coll Cardiol.* 2005;46:142-146.
4. Runyan AL, Chhokar VS, Sun Y, Bhattacharya SK, Runyan JW, Weber KT. Bone loss in rats with aldosteronism. *Am J Med Sci.* 2005;330:1-7.
5. Runyan AL, Sun Y, Bhattacharya SK, Ahokas RA, Chhokar VS, Gerling IC, Weber KT. Responses in extracellular and intracellular calcium and magnesium in aldosteronism. *J Lab Clin Med.* 2005;146:76-84.
6. Chhokar VS, Bhattacharya SK, Ahokas RA, Martinez A, Postlethwaite AE, Sun Y, Weber KT. Oxi/nitrosative stress and bone loss in aldosteronism [abstr]. *J Mol Cell Cardiol.* 2004;36:627.
7. Chhokar VS, Kiani MF, Sun Y, Weber KT. Endothelial activation and a proinflammatory vascular phenotype in aldosteronism [abstr]. *J Mol Cell Cardiol.* 2004;36:627-628.
8. Chhokar VS, Sun Y, Bhattacharya SK, Ahokas RA, Myers LK, Xing Z, Smith RA, Gerling IC, Weber KT. Hyperparathyroidism and the calcium paradox of aldosteronism [abstr]. *J Investig Med.* 2005;53 (Suppl 1):S265-S266.

Awards:

Trainee Research Award, Southern Society for Clinical Investigation, 2005

TRAINEE: Alex Vidal, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2004–2005

Alex Vidal, MD undertook studies to validate the role of PTH and parathyroid glands in promoting intracellular $[Ca^{2+}]_i$ overloading. Toward this end, he performed a surgical parathyroidectomy (PTx) to thereby remove circulating PTH. In rats with aldosteronism and PTx, there still appeared the loss of Ca^{2+} and Mg^{2+} in urine and feces and the fall in plasma-ionized $[Ca^{2+}]_o$ and $[Mg^{2+}]_o$. However, there was no PTH response and in this setting there was no rise in $[Ca^{2+}]_i$ in PBMC, heart, and skeletal muscle, and no increase in H_2O_2 production by PBMC to confirm the role played by PTH in intracellular Ca^{2+} overloading and its role in inducing oxidative stress. Interestingly, the expression of oxidative stress (NADPH oxidase) and presence of inflammatory cells invading the intramural coronary vasculature was attenuated by PTx (*Am J Physiol Heart Circ Physiol* 2006;290:H286–H294).

The studies of Wodi, Chhokar, and Vidal underscored the importance of intracellular Ca^{2+} overloading in the induction of oxidative stress and which was enforced with several pharmacologic interventions that included spironolactone, an aldosterone receptor blocker, which prevented the loss of Ca^{2+} and Mg^{2+} in urine and feces, and by parathyroidectomy.

Publications (Abstracts included):

1. Vidal A, Sun Y, Bhattacharya SK, Ahokas RA, Gerling IC, Weber KT. The calcium paradox of aldosteronism and the role of the parathyroid glands. *Am J Physiol Heart Circ Physiol.* 2006;290:H286–H294.
2. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with aldosteronism. Response to spironolactone. *Am J Physiol Heart Circ Physiol.* 2007;293:H2361-H2366.
3. Vidal A, Ahokas RA, Sun Y, Bhattacharya SK, Weber KT. Aldosteronism: a proinflammatory phenotype secondary to calcium overload [abstr]. *J Investig Med.* 2005;53 (Suppl 1):S318.
4. Vidal A, Sun Y, Bhattacharya SK, Ahokas RA, Gerling IC, Weber KT. Parathyroidectomy prevents calcium loading and oxidative stress in rats with aldosteronism [abstr]. *J Investig Med.* 2006;54 (Suppl 1):S279.
5. Thomas M, Vidal A, Bhattacharya SK, Sun Y, Weber KT. Sustained secondary hyperparathyroidism and the recovery of fallen extracellular calcium and magnesium in rat with chronic aldosteronism [abstr]. *J Investig Med.* 2006;54 (Suppl 1):S285.
6. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Johnson PL, Sun Y, Gerling IC, Weber KT. Hypozincemia and oxidative stress in rats with chronic aldosteronism [abstr]. *J Investig Med.* 2006;54 (Suppl 1):S264.
7. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with aldosteronism: response to spironolactone [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S274 | S276.

Awards:

Young Investigator Award, Southern Society for Clinical Investigation, 2006

TRAINEE: Manesh Thomas, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2005–2006

Endogenous antioxidant defenses, such as Cu/Zn-superoxide dismutase (SOD), are called upon to counteract reactive oxygen intermediates. Little is known about Zn homeostasis in aldosteronism although hypozincemia has been found in patients with CHF, where secondary aldosteronism is expected. **Manesh Thomas, MD** undertook his study to address Zn balance, Zn tissue distribution, and plasma and tissue Cu/Zn-SOD activities in rats receiving aldosterone/salt treatment (ALDOST). As with Ca^{2+} and Mg^{2+}, urinary Zn losses increased early and were persistent with aldosteronism leading to negative Zn balance with hypozincemia and a fall in plasma Cu/Zn-SOD activity, each of which could be blocked with spironolactone. Myocardial injury first appears at wk 4 of ALDOST and is accompanied by activation of NADPH oxidase at these sites, where increased tissue Zn and metallothionein expression and tissue Cu/Zn-SOD activity were found. These responses were not found in the liver, which was not injured, nor in skeletal muscle, but which had become atrophic during ALDOST. Thus increased urinary Zn losses, together with its preferential translocation to sites of injury, contribute to Zn dyshomeostasis in rats with aldosteronism and which can be prevented by spironolactone.

Publications (Abstracts included):

1. Thomas M, Vidal A, Bhattacharya SK, Sun Y, Weber KT. Sustained secondary hyperparathyroidism and the recovery of fallen extracellular calcium and magnesium in rat with chronic aldosteronism [abstr]. *J Investig Med.* 2006;54 (Suppl 1):S285.
2. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Johnson PL, Sun Y, Gerling IC, Weber KT. Hypozincemia and oxidative stress in rats with chronic aldosteronism [abstr]. *J Investig Med.* 2006;54 (Suppl 1):S264.
3. Selektor Y, Sun Y, Thomas M, Weber KT. Structural remodeling of the heart in rats with aldosteronism: response to spironolactone or dietary zinc supplement [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S255.
4. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with aldosteronism: response to spironolactone [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S274 | S276.
5. Thomas M, Vidal A, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with aldosteronism. Response to spironolactone. *Am J Physiol Heart Circ Physiol.* 2007;293:H2361-H2366.
6. Amin AA, Thomas M, Selektor Y, Parker RB, Bhattacharya SK, Sun Y, Weber KT. Excretory zinc losses and bone zinc resorption in rats with aldosteronism [abstr]. *J Investig Med.* 2008;56 (Suppl 1):363.
7. Thomas M, Davis RC. Asymptomatic extensive coronary cameral fistulae involving the left ventricle. *Can J Cardiol.* 2008;24:e46.

Awards:

Young Investigator Award, Southern Society for Clinical Investigation, 2007
Young Clinical Scientist Award, International Academy of Cardiovascular Sciences/North America, 2007

TRAINEE: Yelena Selektor, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2006–2007

Yelena Selektor, MD conducted and completed two studies. The first was related to the cotreatment of rats receiving ALDOST with the calcimimetic cinacalcet. With this approach and despite the appearance of reduced plasma-ionized $[Ca^{2+}]_o$, the rise in plasma PTH levels were much attenuated. Correspondingly, there was no rise in intracellular $[Ca^{2+}]_i$ in heart tissue and PBMC, and no evidence of increased oxidative stress. This included a prevention to the fall in plasma α_1-antioproteinase activity, no increase in lymphocyte H_2O_2 production, and no increase in cardiac malondialdehyde levels.

Her other project addressed ^{65}Zn studies in rats with ALDOST for 1 and 4 wks. Findings indicated: a fall in plasma Zn at these time points and which is related to an early (wk 1) and persistent (wk 4) rise in the fecal and urinary excretion of Zn and a redistribution of Zn to selected tissues. This includes the heart, where a coronary vasculopathy and microscopic scarring are found. Of further interest, Zn levels in bone and skin fell and where SHPT with PTH-mediated bone mineral resorption contributes to the reduction in bone Zn. Tissues in which Zn levels did not change during ALDOST included spleen and skeletal muscle.

Publications (Abstracts included):

1. Selektor Y, Sun Y, Thomas M, Weber KT. Structural remodeling of the heart in rats with aldosteronism: response to spironolactone or dietary zinc supplement [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S255.
2. Selektor Y, Ahokas RA, Bhattacharya SK, Sun Y, Gerling IC, Weber KT. Cinacalcet and the prevention of secondary hyperparathyroidism in rats with aldosteronism. *Am J Med Sci.* 2008;335:105-110.
3. Selektor Y, Parker RB, Sun Y, Zhao W, Bhattacharya SK, Weber KT. Tissue ^{65}zinc translocation in a rat model of chronic aldosteronism. *J Cardiovasc Pharmacol.* 2008;51:359-364.
4. Selektor Y, Weber KT. The salt-avid state of congestive heart failure revisited. *Am J Med Sci.* 2008;335:209-218
5. Selektor Y, Zia AA, Munir A. A case of mitral and tricuspid regurgitation during diastole [abstr]. *J Investig Med.* 2008;56 (Suppl 1):379-380.
6. Amin AA, Thomas M, Selektor Y, Parker RB, Bhattacharya SK, Sun Y, Weber KT. Excretory zinc losses and bone zinc resorption in rats with aldosteronism [abstr]. *J Investig Med.* 2008;56 (Suppl 1):363.
7. Selektor Y, Ahokas RA, Bhattacharya SK, Sun Y, Gerling IC, Weber KT. Cinacalcet and the prevention of secondary hyperparathyroidism in rats with aldosteronism [abstr]. *J Investig Med.* 2008;56:425.
8. Selektor Y, Parker RB, Sun Y, Zhao W, Bhattacharya SK, Weber KT. Tissue ^{65}zinc distribution in a rat model of chronic aldosteronism [abstr]. *J Investig Med.* 2008;56:454.

Awards:

Finalist, Young Clinician Scientist Award, Southern Society for Clinical Investigation, 2008
Finalist, Basic Science Award, International Academy of Cardiovascular Sciences/North America, 2008

TRAINEE: Malay S. Gandhi, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2007–2008

The progression to our studies into pathogenic origins and pathophysiologic expressions of the divalent cation dyshomeostasis that occurs in rats receiving aldosterone/salt treatment (ALDOST), has revealed the importance of intracellular $[Ca^{2+}]_i$ overloading, as a prooxidant, and increased $[Zn^{2+}]_i$ as antioxidant. **Malay Gandhi, MD** addressed causes and consequences of Zn^{2+} dyshomeostasis. Compared to untreated control rats, he found an acidification of urine and metabolic alkalosis associated with increased urinary Zn excretion and hypozincemia, each of which were prevented by acetazolamide, a carbonic anhydrase inhibitor. A rise in cardiac tissue Zn^{2+} was also found, further confirmation of previous findings, and which included cardiomyocyte cytosolic free $[Zn^{2+}]_i$ and mitochondrial $[Zn^{2+}]_m$, which were associated with: increased tissue metallothionein, a Zn^{2+}-binding protein; 8-isoprostane and malondialdehyde, markers of lipid peroxidation; and activation of $gp91^{phox}$ subunit of NADPH oxidase, a source of superoxide, together with markers of oxidative stress in urine and plasma. Cotreatment with $ZnSO_4$ prevented hypozincemia, but not ionized hypocalcemia and attenuated oxidative stress and attenuated oxidative stress and microscopic scarring without preventing the vasculitis and perivascular fibrosis and intramural coronary arteries. Thus, the hyperzincuria seen with ALDOST is due to urinary acidification. The oxidative stress that appears in the heart is accompanied by increased tissue Zn^{2+} serving as an antioxidant. Cotreatment with $ZnSO_4$ attenuated cardiomyocyte necrosis, however, a polynutrient supplement will be required to counterbalance the dyshomeostasis of both Ca^{2+} and Zn^{2+} that accompanies ALDOST and contributes to cardiac injury and pathology.

Publications (Abstracts included):

1. Gandhi MS, Deshmukh PA, Kamalov G, Zhao T, Zhao W, Whaley JT, Tichy JR, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Causes and consequences of zinc dyshomeostasis in rats with chronic aldosteronism. *J Cardiovasc Pharmacol.* 2008;52:245-252.
2. Khan BQ, Gandhi MS, Edmonds H, Ahmad K, Rasberry RD, Corbett C, Jukkola AF, Carbone LC. Lymphoma mimicking carcinoma erysipeloides. *Int J Dermatol.* 2008;47:269-271.
3. Ahmad K, Gandhi MS, Smith WC, Weber KT. Bilateral pleural effusions in congestive heart failure. *Am J Med Sci.* 2008;335:484-488.
4. Gandhi MS, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Calcium and zinc dyshomeostasis and oxidative stress in rats with aldosteronism [abstr]. *J Investig Med.* 2008;56 (Suppl 1):368-369.
5. Gandhi MS, Deshmukh PA, Kamalov G, Zhao T, Zhao W, Tichy JR, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with chronic aldosteronism. Response to zinc supplement [abstr]. *J Investig Med.* 2009;57:364.
6. Green KD, Gandhi MS, Sun Y, Weber KT. Recovery from muscle wasting and prevention of progressive cardiac fibrosis in rats with aldosteronism treated with eplerenone [abstr]. *J Investig Med.* 2009;57:370-371.
7. Elam MB, Cowan GS, Jr., Rooney RJ, Hiler ML, Yellaturu C, Deng X, Howell GE, Park EA, Gerling IC, Patel D, Corton JC, Cagen LM, Wilcox HG, Gandhi MS, Bahr M, Allan C, Wodi L, Cook GA, Hughes TA, Raghow R. Hepatic gene expression in morbidly obese women: implications for disease susceptibility. *Obesity.* 2009 (In press).
8. Kamalov G, Deshmukh PA, Baburyan NY, Gandhi MS, Johnson PL, Ahokas RA, Bhattacharya SK, Sun Y, Gerling IC, Weber KT. Coupled calcium and zinc dyshomeostasis and oxidative stress in cardiac myocytes and mitochondria of rats with chronic aldosteronism. *J Cardiovasc Pharmacol.* 2009 (In press).

Awards:

Young Clinician Scientist Award, Southern Society for Clinical Investigation, 2009

TRAINEE: German Kamalov, MD, PhD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2008–2009

In separate studies, the extra- and intracellular dyshomeostasis of Ca^{2+} and Zn^{2+} seen during aldosterone/salt treatment (ALDOST) was identified and which respectively contributes to an imbalance of prooxidant and antioxidant. **German Kamalov, MD** hypothesized this to be a coupled dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} and its relationship to oxidative stress as related to the redox state of cardiac myocytes and mitochondria harvested from rat myocardium at 4 wks ALDOST alone or cotreatment with spironolactone (Spiro), an ALDO receptor antagonist, or amlodipine (Amlod), a Ca^{2+} channel blocker. Compared to controls, he found increased cytosolic free $[Ca^{2+}]_i$ and $[Zn^{2+}]_i$ in cardiomyocytes coupled to increased $[Ca^{2+}]_m$ and $[Zn^{2+}]_m$ in mitochondria, each of which could be prevented by Spiro and attenuated with Amlod. Increased levels of 3-nitrotyrosine and 4-hydroxy-2-nonenal in cardiomyocytes, together with increase H_2O_2 production, malondialdehyde and oxidized GSSG in mitochondria that were coincident with increased activities of Cu/Zn-superoxide dismutase and glutathione peroxidase. Increased expression of metallothionein-1, Zn transporters (Zip-1 and ZnT1), and metal-response element transcription factor (MTF)-1 that were attenuated by Spiro. Thus in cardiomyocytes and mitochondria, an intrinsically coupled dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} serves to alter redox state through their respective induction of oxidative stress and generation of antioxidant defenses. These findings call into question the potential for therapeutic strategies that would uncouple these two crucial cations and modulate their ratio in favor of sustained antioxidant defenses. Toward this end, responses to $ZnSO_4$ supplement and PDTC, a dithiocarbamate Zn^{2+} ionophore, to uncouple the intracellular Ca^{2+} and Zn^{2+} will be examined with respect to manipulating oxidative stress in favor of antioxidant defenses.

Publications (Abstracts included):

1. Kamalov G, Varma BR, Lu L, Sun Y, Weber KT, Guntaka RV. Expression of the multifunctional Y-box protein, YB-1, in myofibroblasts of the infarcted heart. *Biochem Biophys Res Commun.* 2005;334:239-244.
2. Kamalov G, Deshmukh PA, Bhattacharya SK, Ahokas RA, Sun Y, Weber KT. Cytosolic and mitochondrial calcium in rat cardiomyocytes: response to aldosteronism and cotreatment with spironolactone or amlodipine [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S255.
3. Kamalov G, Deshmukh PA, Baburyan N, Ahokas RA, Sun Y, Weber KT. Cardiomyocyte expression of metallothionein and zinc transporter 1 in rats with aldosteronism: response to spironolactone or amlodipine [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S255-S256.
4. Deshmukh PA, Kamalov G, Bhattacharya SK, Ahokas RA, Sun Y, Weber KT. Cytosolic calcium and zinc in cardiomyocytes of rats with aldosteronism: response to spironolactone and amlodipine cotreatment [abstr]. *J Investig Med.* 2007;55 (Suppl 1):S280.
5. Gandhi MS, Deshmukh PA, Kamalov G, Zhao T, Zhao W, Whaley JT, Tichy JR, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Causes and consequences of zinc dyshomeostasis in rats with chronic aldosteronism. *J Cardiovasc Pharmacol.* 2008;52:245-252.
6. Kamalov G, Deshmukh P, Ahokas RA, Sun Y, Bhattacharya SK, Weber KT. Increased oxidative stress in mitochondria harvested from rat hearts during chronic aldosteronism [abstr]. *J Investig Med.* 2008;56:370.
7. Deshmukh P, Kamalov G, Bhattacharya SK, Ahokas RA, Sun Y, Weber KT. Calcium and zinc dyshomeostasis of the heart, its cardiomyocytes and mitochondria in rats with aldosteronism [abstr]. *J Investig Med.* 2008;56:367.
8. Deshmukh PA, Kamalov G, Baburyan N, Ahokas RA, Sun Y, Bhattacharya SK, Gerling IC, Weber KT. Cardiomyocyte expression of metal response element transcription factor-1, metallothionein-1 and zinc transporters in rats with aldosteronism. Response to spironolactone or amlodipine [abstr]. *J Investig Med.* 2009;57:371.

9. Gandhi MS, Deshmukh PA, Kamalov G, Zhao T, Zhao W, Tichy JR, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Zinc dyshomeostasis in rats with chronic aldosteronism. Response to zinc supplement [abstr]. *J Investig Med.* 2009;57:364.
10. Kamalov G, Deshmukh PA, Ahokas RA, Sun Y, Bhattacharya SK, Gerling IC, Weber KT. Oxidative stress in cardiac mitochondria harvested from rats with aldosteronism. Response to spironolactone or amlodipine cotreatment [abstr]. *J Investig Med.* 2009;57:393.
11. Kamalov G, Deshmukh PA, Baburyan NY, Gandhi MS, Johnson PL, Ahokas RA, Bhattacharya SK, Sun Y, Gerling IC, Weber KT. Coupled calcium and zinc dyshomeostasis and oxidative stress in cardiac myocytes and mitochondria of rats with chronic aldosteronism. *J Cardiovasc Pharmacol.* 2009 (In press).

Awards:

Finalist, Basic Scientist Award, Southern Society for Clinical Investigation, 2009

TRAINEE: Atta U. Shahbaz, MD PRECEPTOR: Karl T. Weber, MD
PERIOD IN TRAINING: 2009–2010

The coupled dyshomeostasis of $[Ca^{2+}]_i$ and $[Zn^{2+}]_i$ relative to redox state of cardiac myocytes and mitochondria may serve as a fundamental pathophysiologic response leading to cardiomyocyte necrosis followed by tissue repair with microscopic scarring. A heterogeneity to this scarring is evident throughout the right (RV) and left (LV) ventricles without a predilection for a certain location within the myocardium. The basis for the susceptibility of a certain population of cardiomyocytes toward necrosis is uncertain. A propensity to greater intracellular $[Ca^{2+}]_i$ overloading is one possibility. Beginning July, 2009, **Atta Shahbaz, MD** will examine different areas of left and right ventricles for tissue $[Ca^{2+}]_i$ and $[Zn^{2+}]_i$ using atomic absorption spectroscopy following subcutaneous administration of isoproterenol, a synthetic catecholamine known to induce intracellular Ca^{2+} overloading. Tissue samples will be obtained at 6–8 h post dosing from the inner and outer half of the base, equator and apex of the LV and full thickness RV sections from these corresponding planes. Based on these findings, he is prepared to study the kinetics of ^{45}Ca in intact heart post dosing, the density and behavior of Ca^{2+} channels in isolated cardiomyocytes from "susceptible" sites, together with biomarkers of oxidative stress in these cells and mitochondria, and the response to cotreatment with either a Ca^{2+} channel blocker or PDTC, a Zn^{2+} ionophore. The findings of this preliminary study using the isoproterenol model will set the stage for the application of these principles and issues to the aldosterone/salt treatment model, where we have established intracellular Ca^{2+} overloading and oxidative stress as the basis for cardiomyocyte necrosis and scarring. A heterogeneity to cardiac mitochondria and oxidative stress will also be explored.

Publications (Abstracts included):

1. Zafarullah H, Shahbaz AU, Alturkmani R, LaGuardia SP, Paulus BM, Battin DL, Afzal MO, Davis RC, Smith JL, Weber KT. Elevated serum cobalamin in patients with decompensated biventricular failure. *Am J Med Sci.* 2008;336:383-388.
2. Alturkmani R, Zafarullah H, Shahbaz AU, Weber KT. Serial monitoring of serum cobalamin in patients with decompensated biventricular failure [abstr]. *J Investig Med.* 2008;56:363.
3. LaGuardia SP, Zafarullah H, Shahbaz AU, Alturkmani R, Davis RC, Weber KT. Serum cobalamin, not B-type natriuretic peptide, distinguishes decompensated biventricular failure from left heart failure [abstr]. *J Investig Med.* 2008;56:370-371.
4. Shahbaz AU, Munir A, Davis RC. Echocardiographic assessment of inferior vena cava dilation and tricuspid regurgitation severity in patients with and without decompensated biventricular failure [abstr]. *J Investig Med.* 2008;56:375.
5. Zafarullah H, Paulus BM, LaGuardia SP, Battin DL, Shahbaz AU, Alturkmani R, Davis RC, Smith JL, Weber KT. Elevated serum cobalamin in patients with decompensated heart failure [abstr]. *J Investig Med.* 2008;56:344-345.
6. Ali S, Shahbaz AU, Nelson MD, Munir A, D'Cruz IA, Weber KT. Lymphocytopenia in African-Americans with decompensated heart failure. Role of splanchnic congestion [abstr]. *J Investig Med.* 2009;57:371-372.
7. Shahbaz AU, Ali S, Nelson MD, Davis RC, Weber KT. Reversible lymphocytopenia in African-Americans with decompensated biventricular failure [abstr]. *J Investig Med.* 2009:57:320.
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