The Endocrine Heart and Burns: Release of Natriuretic Peptides in Response to Burn Injuries

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ABSTRACT

In addition to being a pump, the heart also has an endocrine function. The peptides synthesized and secreted from the heart may exert endocrine, autocrine, and paracrine effects. The natriuretic peptides are a family of vasoactive hormones that play a dominant role in the regulation of cardiovascular and renal homeostasis. The 2 major hormones synthesized by the heart are the atrial and the brain natriuretic peptides, and elevated circulating levels of these substances have important prognostic and therapeutic implications. Although plasma natriuretic peptide measurements are helpful in excluding chronic heart failure in the ambulatory setting, many factors independent of heart failure may influence their levels. During the acute phase response of severe burn injuries, the severity of the cardiac stress can determine the postburn outcomes, and the pleiotropic effects exerted by the natriuretic peptide system play a key role in this process by activating compensatory mechanisms that promote systemic arterial dilatation, diuresis, natriuresis, and renin inhibition. Natriuretic peptides may also play a role in the wound healing process, which could be of clinical utility to reduce apparent scar formation in burn patients.

KEY WORDS: *Atrial natriuretic peptide, Brain natriuretic peptide, Cardiac biomarkers, Endocrine system, Severe burns*

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INTRODUCTION

The heart was always considered as an organ with a mechanical function, but this vision has changed since 1956, when secretory granules were found in the guinea pig atrium.[1] The exact role of these atrial granules remained elusive until 1981; it is now clear that the heart not only has a mechanical function but also an endocrine function, and this property has been extensively investigated since then.[1-5] The peptides synthesized and secreted from the heart may exert remote (endocrine) and local effects, (autocrine and paracrine effects)[5,6] and include colons adrenomedullins, angiotensins, apelin, endothelins, follistatin-like 1, natriuretic peptides, and others.[7-9] The proteins secreted from the cardiomyocytes, cardiac fibroblasts, endothelial cells, and smooth muscle are called "cardiokines," and the specific cardiomyocyte-derived peptides are called "cardiomyokines."[10]

Despite the numerous cardiac hormones discovered, such as those already mentioned, in this review, we have focused mainly on the natriuretic peptides, more specifically, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), and their effects in severe burn injuries, since these 2 peptides play a major role in cardiac endocrine function.

HOW DOES THE HEART RESPOND TO BURNS?

Burns covering 30% or more of the total body surface area induce the release of inflammatory mediators and lead to significant hypovolemia with a subsequent systemic effect on organs distant from the burn areas.[11,12] Severe burns trigger a cycle of inflammation, fibrosis, oxidative stress, and mitochondrial damage in the heart. The cardiac inflammatory response plays an important role in the pathogenesis of cardiac tissue damage[13]; increased mitochondrial uncoupling contributes to the hypermetabolic stress response and increased oxidative stress. All these cardiodynamic derangements contribute to multiple organ system failure, sepsis, and death.[14] Xiao and associates demonstrated how myocardial injury occurs before

hepatic, renal, and intestinal injuries, most likely due to the decrease in myocardial mechanical function after significant reduction of blood volume secondary to increased capillary permeability following the thermal injury.[15]

Immediately after burns, an ischemic/hypoxic myocardial damage with a functional myocardial impairment occurs.[15] During the acute phase response of severe burn injuries, the severity of the cardiac stress can determine the outcomes after the burn injury, and the pleiotropic effects exerted by the natriuretic peptide system play a key role in this process. Immediately after the injury, during the ebb phase, the cardiac function is severely depressed. A decrease in myocardial contractility starts immediately after the injury and continues for approximately 36 hours after burn. However, by 48 hours after the burn injury, when the flow phase starts, cardiac function rebounds and the myocardium becomes tachycardic and a hyperinflammatory process that can elevate the energy expenditure and cardiac work for over a year after injury evolves.[14,16]

Postburn cardiac dysfunction is the major cause of failed resuscitation, and it is characterized by slowed isovolumic relaxation, impaired contractility, and decreased diastolic compliance of the left ventricle. The mortality rate following the burn trauma is an important outcome parameter, and the percentage of total body surface area involved usually correlates with mortality, whereas the depth of the burn determines morbidity.[17]

ENDOCRINE FUNCTION OF THE HEART: THE NATRIURETIC PEPTIDE FAMILY

The natriuretic peptides are a family of vasoactive hormones that play an important role in regulation of cardiovascular and renal homeostasis.[18,19] Four natriuretic peptides have been described: types A, B, C, and D.[18-21] Among these, ANP and BNP are mainly synthesized and secreted by the heart (they can also be produced by many other tissues, but the amounts are too low to generate endocrine effects) in response to various stimuli and regulated by multiple signaling pathways[18-22] (Table 1). The GATA proteins play a pivotal role in cardiac gene expression, and several neuroendocrine factors can modulate the secretion of the ANPs and BNPs: acetylcholine, adrenergic agonists, angiotensin II, endothelin 1, glucagon-like peptide 1, glucocorticoids, prostaglandins, and thyroid hormones.[18,22,23]

The mechanisms of action of the natriuretic peptides are mediated by high-affinity natriuretic peptide receptors (NPR-A and NPR-B).[24] These peptides reflect cardiac stress and function. Although the cardiovascular effects of natriuretic peptides are well known, these proteins play a much broader role in physiology than previously recognized. They act on the kidney to promote diuresis and natriuresis and exert vasodilation on peripheral capacitance vessels to maintain water and sodium homeostasis and systemic blood pressure levels; they also have cardiac antifibrotic and antihypertrophic effects, antagonizing the renin-angiotensin-aldosterone system effects.[18-22] To reduce the blood volume, they restrain water reabsorption in the renal main collector via type 2 aquaporins by inhibiting salt intake, thirst, and the secretion of arginine vasopressin induced by angiotensin II in the pituitary gland.[18,25,26] Natriuretic peptides are rapidly cleared mainly by 2 mechanisms: extracellular proteases (neprilysin is the main enzyme) and receptor-mediated degradation via NPR-C.[21]

Because these peptides increase drastically in patients with heart failure, mainly in response to myocardial stretching, the use of both BNP and the N-terminal pro-brain natriuretic peptide (NT-pro-BNP) as diagnostic biomarkers of heart failure has brought significant improvements in treating these patients. However, several inflammatory states can act as confounding factors to stimulate BNP synthesis, including aging, anemia, obesity, sepsis, hypertension, myocardial infarction, cardiac hypertrophy, pulmonary hypertension, atrial fibrillation, diabetes mellitus, renal failure, liver cirrhosis, severe burns, and cancer chemotherapy. These factors underline a mode of BNP regulation that can be dissociated from any hemodynamic variation (Table 2).[27]

ATRIAL NATRIURETIC PEPTIDE

ANP was the first member of the natriuretic peptide family identified, occurring in 1983. It is a 28-amino acid

TABLE 1. Main Characteristics of the Atrial Natriuretic Peptide and Brain Natriuretic Peptide

	Atrial Natriuretic Peptide	Brain Natriuretic Peptide
Peptide length	28 amino acids	32 amino acids
Main synthesis location	Cardiac atria	Cardiac ventricle
Plasma half-life	2 to 4 minutes	20 minutes
Release stimulus	Increase in atrial wall stretching and tension	Increase in ventricular wall tension
Major effects	Decrease in plasma volume and blood pressure	Decrease in plasma volume and blood pressure
Plasma levels in burn patients	High	High

polypeptide mainly produced and stored in atrial granules, resulting from the C-terminal end of the prohormone pro-ANP. Small amounts are produced in the ventricle. mRNA of ANP is translated to pre-pro-ANP, a molecule of 151 amino acids and then cleaved into pro-ANP (126 amino acids), the main form of storage in atrial granules. The pro-ANP is rapidly cleaved by corin to form the biologically active ANP (composed of 28 amino acids and the biologically inactive NT-pro-ANP).[18] The half-life in healthy humans is 2 to 4 minutes and ranges from 0.5 to 4 minutes in dogs, monkeys, mice, rabbits, and rats.[28]

ANP has also been involved in thermal injuries. Its levels have been reported to be elevated within the first 48 hours after burn injury in patients with a mean total burn area of 22% total body surface area. The reason for this elevation has not yet been clarified, but it could be a stress-related response or due to the large amounts of intravenous fluid required by the burn patient. During the acute phase of burns, there is also a marked sodium retention with a highly positive water balance, which could lead to volume overload, causing atrial stretch and the subsequent ANP release. ANP in burn patients, unlike the vasoconstrictor neurohormones that are also activated in the setting of thermal injuries, such as the renin and angiotensin system, has been found to be beneficial through its activation of compensatory mechanisms that promote systemic arterial dilatation, diuresis, natriuresis, and renin inhibition[29] (Figure 1).

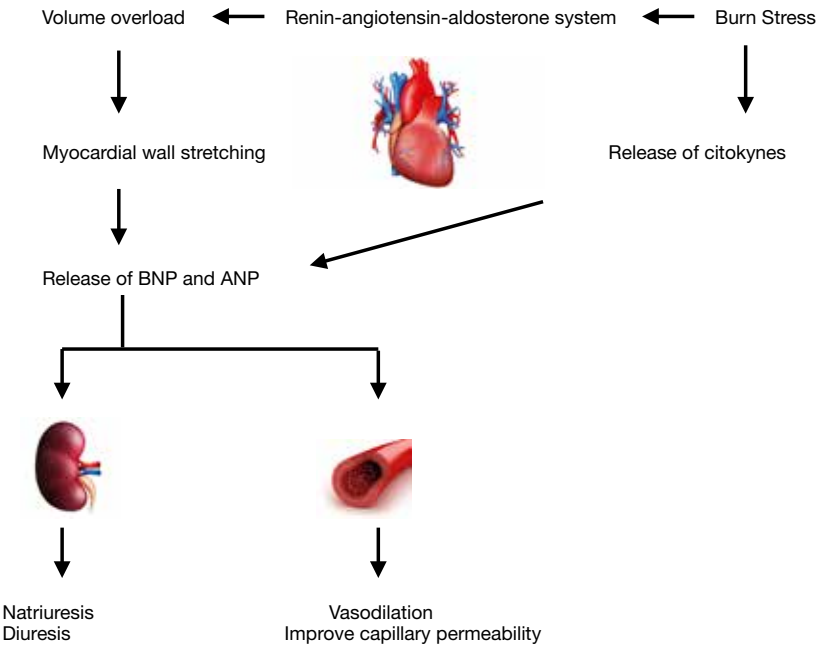
BRAIN NATRIURETIC PEPTIDE

The type B natriuretic peptide or BNP was first isolated from pig brains in 1988 by Sudoh and colleagues,[3] which

TABLE 2. Common Causes of Brain Natriuretic Peptide Elevation Independent of Heart Failure

Cardiac Related	Non-Cardiac Related
• Acute coronary syndromes • Atrial fibrillation • Cardiac surgery • Cardiac contusion • Cardiomyopathies • Cardioversion • Left ventricular hypertrophy • Myocarditis • Pericardial disease • Valvular heart disease	• Age • Female sex • Critical illness (severe burns, sepsis, transfusion-associated circulatory overload) • Pulmonary (acute pulmonary embolism, chronic obstructive pulmonary disease, obstructive sleep apnea, severe pneumonia, pulmonary hypertension) • Neurological (ischemic and hemorrhagic stroke) • Other (anemia, cancer chemotherapy, cirrhosis of liver, hyperaldosteronism, hypertension, renal insufficiency)

FIGURE 1. Endocrine Heart Response to Burns: Natriuretic Peptide-Releasing Mechanism Following Burn Stress



Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide

was soon followed by the discovery of the largest concentrations in cardiac tissue.[30] Brain natriuretic peptide is localized in the cardiomyocytes of the atrium and stored in atrial granules with ANP; however, in contrast to ANP, it is not found in ventricular granules. The structure of BNP differs among species. The BNP in humans is synthesized as a 134 amino acids pre-prohormone, cleaved into 108 amino acids (pro-BNP cardiomyocytes), which in turn will be cleaved by corin or furin into the biologically active BNP of 32 amino acids and the biologically inactive NT-pro-BNP (76 amino acids). The half-lives of BNP and NT-pro-BNP are approximately 20 minutes and 120 minutes, respectively.[18] The regulation of BNP gene transcription and excretion is based on the myocardial wall stretching resulting from volume overload and/or increased transmural gradient. The main function of the BNP is to control water homeostasis, and it does so through its paracrine function; it promotes diuresis and natriuresis, dilates the arterial system, and antagonizes renin.[19-22,31]

Because BNP has been implicated in many pathologies, such as heart failure and volume overload states, in the year 2000, the US Food and Drug Administration approved a rapid assay for BNP as an adjunct for the diagnosis of heart failure, giving an opportunity to the scientific community to explore its potential usefulness; in recent years, it has become a target of study as a prognostic marker.[32] Lindahl and colleagues conducted a study to determine the relationship between the physiological stress of the body in response to burns by measuring NT-pro-BNP (it has a longer half-life) in adults with burn injuries greater than 10% of total body surface area. The investigators observed a gradual increase in BNP, reaching its peak on the fifth day of hospitalization, concluding that there is a relationship between the NT-pro-BNP and volume overload in burn patients. This volume overload is due to the edema that occurs as a result of capillary leakage and its subsequent increase in preload. They also found that high levels of NT-pro-BNP are related to better outcomes.[33] Elevated BNP levels have also been reported in many other non-heart-related conditions.[27] High levels of BNP have been found in patients with severe burns, indicating the hydration status of the burned patient. It was suggested that elevated BNP was also related to a decrease in capillary leakage and, contrary to the observation in other critically ill patients, to a better outcome[33] (Figure 1).

The role of transforming growth factor β in reducing scar formation has been described,[34] and it has been reported that BNP reduces myocardial scar formation by blocking transforming growth factor β.[35] An in vitro proof-of-principal study revealed the presence of BNP around collagen, epithelial cells, and endothelial cells in human burned skin; in contrast, no BNP was observed in unscarred skin samples, indicating that BNP may be involved in skin wound healing and scarring.[36] Further studies reported the responsiveness of fibroblasts to BNP[37] and the improvement in the gross appearance of scars but without any histologic difference compared with controls in a rat burn model.[38]

EFFECTS OF BETA BLOCKER THERAPY ON CIRCULATING LEVELS OF NATRIURETIC PEPTIDES

Severe burns significantly alter the pharmacodynamics and pharmacokinetics of drugs.[39] Because severely burned patients are usually receiving multiple drug regimens (including analgesia, antiemetic, ulcer prophylaxis), the effects of drug therapy on circulating levels of natriuretic peptides need to be taken into consideration when interpreting such levels.

The hypermetabolic state triggered by burns might become a source of morbidity if left untreated[11,12]; for this reason, many pharmacologic measures have been proposed to attenuate it, with beta blockers becoming first-line agents to reduce these adverse effects.[40,41] However, the studies that have measured natriuretic peptides during beta blocker therapy are contradictory.[42-45] Most of these studies have reported high levels of natriuretic peptides in healthy humans and patients with essential hypertension and coronary artery disease on selective or nonselective beta blocker therapy, probably due to an increase of the synthesis or an inhibition of plasma clearance.[27,42,43] Interestingly, patients with heart failure showed a biphasic response on natriuretic peptides levels. During the first few days and weeks, their levels increased or showed minimal changes; in the long term, however, they markedly decreased. This fluctuation was reported to be in response to hemodynamic changes induced by beta blocker therapy, with the magnitude of this effect shown to be related to the level of natriuretic peptides at baseline.[44-46] Another study showed that, in patients on long-term maintenance hemodialysis with dilated cardiomyopathy, ANP and BNP levels decreased and the left ventricular size and function improved after patients were on metoprolol for 4 months.[47]

CONCLUSIONS

The family of natriuretic peptides has great potential both as therapeutic agents and as biomarkers. They play a key role in water and sodium regulation. With regulation of the blood volume, they also contribute to blood pressure control. Although the greatest source of BNP release comes from the stretching of the myocardial wall, there are other mechanisms that produce its release, such as the inflammatory response triggered by burns. It has been suggested BNP may play a role in the wound-healing process, and it could be of clinical utility to reduce apparent

scar formation; however, increased understanding of the molecular and cellular events that lead to scar formation and the effects of natriuretic peptides are critical to the development of effective therapies to minimize scarring.

REFERENCES

1. Kisch B. Electron microscopy of the atrium of the heart. I. Guinea pig. *Exp Med Surg.* 1956;14(2-3):99-112.
2. Flynn TG, de Bold ML, de Bold AJ. The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. *Biochem Biophys Res Commun.* 1983;117(3):859-865. doi:10.1016/0006-291x(83)91675-3
3. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. *Nature.* 1988;332(6159):78-81. doi:10.1038/332078a0
4. Kangawa K, Matsuo H. Purification and complete amino acid sequence of alpha-human atrial natriuretic polypeptide (alpha-hANP). *Biochem Biophys Res Commun.* 1984;118(1):131-139. doi:10.1016/0006-291x(84)91077-5
5. Dussaule JC, Ledoux S, Pham I. Système endocrinien cardiaque, coeur et vaisseaux. In: *Hormones, Coeur et Vaisseaux.* Les Éditions INSERM; 1998:222-267.
6. Talha S, Piquard F, Geny B. Fonction endocrine du cœur. *EMC Cardiol.* 2015;10:1-8.
7. Dewey CM, Spitler KM, Ponce JM, Hall DD, Grueter CE. Cardiac-secreted factors as peripheral metabolic regulators and potential disease biomarkers. *J Am Heart Assoc.* 2016;5(6). doi:10.1161/JAHA.115.003101
8. Salska A, Chizynski K. Apelin - a potential target in the diagnosis and treatment of the diseases of civilization. *Acta Cardiol.* 2016;71(5):505-517. doi:10.2143/AC.71.5.3167493
9. Chiba A, Watanabe-Takano H, Miyazaki T, Mochizuki N. Cardiomyokines from the heart. *Cell Mol Life Sci.* 2018;75(8):1349-1362. doi:10.1007/s00018-017-2723-6
10. Glembotski CC. Functions for the cardiomyokine, MANF, in cardioprotection, hypertrophy and heart failure. *J Mol Cell Cardiol.* 2011;51(4):512-517. doi:10.1016/j.yjmcc.2010.10.008
11. Santelis SJ, Abali AE, Ozgun G, Ozdemir BH, Tutuncu NB, Haberal M. Impact of severe burns on pancreatic islets: an experimental model in rats. *Burn Care Prevent J.* 2022;2(1):23-28.
12. Santelis SJ. The endocrine response to burn injuries: the role of the hypothalamic-pituitary hormones. *Burn Care Prevent J.* 2022;2(1):3-7.
13. Wen JJ, Cummins C, Radhakrishnan RS. Sildenafil recovers burn-induced cardiomyopathy. *Cells.* 2020;9(6). doi:10.3390/cells9061393
14. Wen JJ, Cummins CB, Radhakrishnan RS. Burn-induced cardiac mitochondrial dysfunction via interruption of the PDE5A-cGMP-PKG pathway. *Int J Mol Sci.* 2020;21(7). doi:10.3390/ijms21072350
15. Xiao R, Lei ZY, Dang YM, Huang YS. Prompt myocardial damage contributes to hepatic, renal, and intestinal injuries soon after a severe burn in rats. *J Trauma.* 2011;71(3):663-671; discussion 672. doi:10.1097/TA.0b013e31822175f6
16. Guillory AN, Clayton RP, Herndon DN, Finnerty CC. Cardiovascular dysfunction following burn injury: what we have learned from rat and mouse models. *Int J Mol Sci.* 2016;17(1). doi:10.3390/ijms17010053
17. Abu-Sittah GS, Sarhane KA, Dibo SA, Ibrahim A. Cardiovascular dysfunction in burns: review of the literature. *Ann Burns Fire Disasters.* 2012;25(1):26-37.
18. Lugnier C, Meyer A, Charloux A, Andres E, Geny B, Talha S. The endocrine function of the heart: physiology and involvements of natriuretic peptides and cyclic nucleotide phosphodiesterases in heart failure. *J Clin Med.* 2019;8(10). doi:10.3390/jcm8101746
19. Schirger JA, Heublein DM, Chen HH, et al. Presence of Dendroaspis natriuretic peptide-like immunoreactivity in human plasma and its increase during human heart failure. *Mayo Clin Proc.* 1999;74(2):126-130. doi:10.4065/74.2.126
20. Chopra S, Cherian D, Verghese PP, Jacob JJ. Physiology and clinical significance of natriuretic hormones. *Indian J Endocrinol Metab.* 2013;17(1):83-90. doi:10.4103/2230-8210.107869
21. Forte M, Madonna M, Schiavon S, et al. Cardiovascular pleiotropic effects of natriuretic peptides. *Int J Mol Sci.* 2019;20(16). doi:10.3390/ijms20163874
22. Bie P. Natriuretic peptides and normal body fluid regulation. *Compr Physiol.* 2018;8(3):1211-1249. doi:10.1002/cphy.c180002
23. Kim M, Platt MJ, Shibasaki T, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med.* 2013;19(5):567-575. doi:10.1038/nm.3128
24. Joffy S, Rosner MH. Natriuretic peptides in ESRD. *Am J Kidney Dis.* 2005;46(1):1-10. doi:10.1053/j.ajkd.2005.04.011
25. Mezzasoma L, Cagini L, Antognelli C, Puma F, Pacifico E, Talesa VN. TNF-alpha regulates natriuretic peptides and aquaporins in human bronchial epithelial cells BEAS-2B. *Mediators Inflamm.* 2013;2013:159349. doi:10.1155/2013/159349
26. Matsukawa T, Miyamoto T. Angiotensin II-stimulated secretion of arginine vasopressin is inhibited by atrial natriuretic peptide in humans. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(3):R624-R629. doi:10.1152/ajpregu.00324.2010
27. Brunner-La Rocca HP, Sanders-van Wijk S. Natriuretic peptides in chronic heart failure. *Card Fail Rev.* 2019;5(1):44-49. doi:10.15420/cfr.2018.26.1
28. Ruskoaho H. Atrial natriuretic peptide: synthesis, release, and metabolism. *Pharmacol Rev.* 1992;44(4):479-602.
29. Onuoha GN, Alpar EK, Gowar J. Plasma levels of atrial natriuretic peptide in severe burn injury. *Burns.* 2000;26(5):449-453. doi:10.1016/s0305-4179(99)00187-4
30. Saito Y, Nakao K, Itoh H, et al. Brain natriuretic peptide is a novel cardiac hormone. *Biochem Biophys Res Commun.* 1989;158(2):360-368. doi:10.1016/s0006-291x(89)80056-7
31. Durocher D, Grepin C, Nemer M. Regulation of gene expression in the endocrine heart. *Recent Prog Horm Res.* 1998;53:7-23; discussion 22-23.
32. Nayer J, Aggarwal P, Galwankar S. Utility of point-of-care testing of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic peptide) in the emergency department. *Int J Crit Illn Inj Sci.* 2014;4(3):209-215. doi:10.4103/2229-5151.141406
33. Lindahl AE, Stridsberg M, Sjoberg F, Ekselius L, Gerdin B. Natriuretic peptide type B in burn intensive care. *J Trauma Acute Care Surg.* 2013;74(3):855-861. doi:10.1097/TA.0b013e31827e154a
34. Shah M, Foreman DM, Ferguson MW. Neutralising antibody to TGF-beta 1,2 reduces cutaneous scarring in adult rodents. *J Cell Sci.* 1994;107 (Pt 5):1137-1157. doi:10.1242/jcs.107.5.1137
35. Kapoun AM, Liang F, O'Young G, et al. B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-beta in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. *Circ Res.* 2004;94(4):453-461. doi:10.1161/01.RES.0000117070.86556.9F
36. Singer AJ, Jurukovski V, Simon M, et al. The presence of B-type natriuretic peptide in burns and the responsiveness of fibroblasts to BNP: proof of principle. *Acad Emerg Med.* 2007;14(6):503-507. doi:10.1197/j.aem.2006.12.018
37. Singer AJ, McClain SA. Development of a porcine incisional wound model and novel scarring scales. *Wound Repair Regen.* 2006;14(4):492-497. doi:10.1111/j.1743-6109.2006.00149.x
38. Taira BR, Singer AJ, McClain SA, Zimmerman T. The effects of brain natriuretic peptide on scar formation in incisional rat wounds. *Acad Emerg Med.* 2008;15(10):945-948. doi:10.1111/j.1553-2712.2008.00243.x

39. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin Pharmacokinet.* 2008;47(10):635-654. doi:10.2165/00003088-200847100-00002
40. Wilmore DW, Long JM, Mason AD, Jr., Skreen RW, Pruitt BA, Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg.* 1974;180(4):653-669. doi:10.1097/00000658-197410000-00031
41. Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. *Ann Surg.* 1988;208(4):484-492. doi:10.1097/00000658-198810000-00010
42. Tanaka M, Ishizaka Y, Ishiyama Y, et al. Chronic effect of beta-adrenoceptor blockade on plasma levels of brain natriuretic peptide during exercise in essential hypertension. *Hypertens Res.* 1996;19(4):239-245. doi:10.1291/hypres.19.239
43. Marie PY, Mertes PM, Hassan-Sebbag N, et al. Exercise release of cardiac natriuretic peptides is markedly enhanced when patients with coronary artery disease are treated medically by beta-blockers. *J Am Coll Cardiol.* 2004;43(3):353-359. doi:10.1016/j.jacc.2003.07.047
44. Sanderson JE, Chan WW, Hung YT, et al. Effect of low dose beta blockers on atrial and ventricular (B type) natriuretic factor in heart failure: a double blind, randomised comparison of metoprolol and a third generation vasodilating beta blocker. *Br Heart J.* 1995;74(5):502-507. doi:10.1136/hrt.74.5.502
45. Hartmann F, Packer M, Coats AJ, et al. NT-proBNP in severe chronic heart failure: rationale, design and preliminary results of the COPERNICUS NT-proBNP substudy. *Eur J Heart Fail.* 2004;6(3):343-350. doi:10.1016/j.ejheart.2004.01.009
46. Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. *Circulation.* 2006;113(7):977-985. doi:10.1161/CIRCULATIONAHA.105.567727
47. Hara Y, Hamada M, Shigematsu Y, Murakami B, Hiwada K. Beneficial effect of beta-adrenergic blockade on left ventricular function in haemodialysis patients. *Clin Sci (Lond).* 2001;101(3):219-225.