Commentary

Hypothesis to explain poor outcomes in the ALLHAT and V-HeFT trials: decreased expression of heat shock proteins

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Abstract

An explanation for the higher incidence of cardiovascular disease and heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) with doxazosin and the Vasodilator Heart Failure Trial (V-HeFT) with prazosin might be decreased expression of heat shock proteins. Heat shock proteins help to protect cells from ischemic injury by decreasing oxidation, suppressing cytokine action, refolding damaged proteins, and decreasing apoptosis. I hypothesize that α-adrenergic blockade decreases heat shock protein levels, thus making the heart and vascular system vulnerable to injury from pathologic processes such as ischemia, hypertension, oxidation or inflammation. Similarly, poor cardiovascular outcomes with calcium-channel blockers might be due to decreased expression of heat shock proteins.

Keywords α-adrenergic blockers, calcium-channel blockers, congestive heart failure, doxazosin, heat shock proteins

The expectation that lowering blood pressure with any antihypertensive agent will have a beneficial outcome is now open to question. In particular, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) collaborative research group discontinued doxazosin from that study owing to a doubled incidence of congestive heart failure, as well as a higher rate of angina, and stroke, in patients receiving doxazosin.

ALLHAT is a randomized, double blind, active-controlled trial sponsored by the National Heart, Lung, and Blood Institute that was initiated in 1994. In two arms of the four-arm study, participants were randomly assigned to receive either chlorthalidone (12.5–25 mg/day) or doxazosin (2–8 mg/day) for a planned follow-up of 4–8 years. In January 2000, the decision was made to discontinue doxazosin. However, a mechanism to explain the poor outcome of the study has not been apparent. The ALLHAT collaborators speculated that doxazosin, an α-adrenergic blocker, might increase plasma volume and norepinephrine (noradrenaline) levels, but for the most part they were puzzled by the results of their study [1]. Perhaps not coincidentally, another α-adrenergic blocker, prazosin, has similarly been associated with a higher cardiovascular mortality compared with other after-load reducers, in the Vasodilator Heart Failure Trial (V-HeFT) [2].

The poor outcome of either study was not expected. In fact, α-adrenergic blockers improve patient's metabolic profile by raising high-density lipoprotein levels, lowering triacylglycerol levels and increasing sensitivity to insulin. They also improve fibrinolysis and reduce left ventricular afterload [3].

A hypothesis to explain how α-adrenergic blockers confer harm on the cardiovascular system is that it lowers an important group of cytoprotective proteins, the heat shock proteins (Hsps). Hsps protect cellular elements from injury by refolding proteins, decreasing oxidation, suppressing the production and activity of inflammatory cytokines, and delaying apoptosis (programmed cell death). The Hsp response to stress is one of the most highly conserved

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; V-HeFT = Vasodilator Heart Failure Trial
CVD = cardiovascular disease; Hsp = heat shock protein.

adaptive responses in nature, and Hsps are found in all living cells [4]. Although known to cell biologists for four decades, Hsps have received little clinical attention.

Hsps are modulated by α-adrenergic activity. Prazosin has been shown to block the expression of Hsps in response to cold stress in rats [5]. Additionally, norepinephrine given before inducing ischemia in isolated rat hearts induces Hsp expression and protects against post-ischemic myocardial dysfunction. Pretreatment with prazosin abolishes norepinephrine-induced cardioprotection from ischemia, leaving the heart vulnerable to an ischemic insult [6]. Similarly, the normally reduced infarct size induced by ischemic preconditioning is lost when chloroethylclonodine, an α_{1B}-adrenergic antagonist, is administered prior to inducing the transient ischemia; whereas 5-methylurapidil, an α_{1A}-adrenergic antagonist, does not block it [7]. The stress of a failing heart normally increases the 'protective' expression of myocardial Hsps [8], and yet only when myocardial Hsp levels decrease does the injured heart demonstrate functional deterioration [9].

In contrast, augmentation of Hsp synthesis by a co-inducer of Hsp, bimoclomol, protects myocytes from ischemia [10] and the endothelium from hypertensive damage [11]. Similarly, overexpression of Hsps in transgenic mice reduces apoptosis and infarct size, in both heart and brain ischemic models [12,13]. When Hsp expression is reduced by an α-adrenergic blocker like doxazosin or prazosin, the cardiovascular system might be left unprotected and vulnerable to injury, as was observed in the ALLHAT and the V-HeFT trials.

Is low Hsp expression a cardiovascular risk factor? No prospective study has measured Hsp levels and followed subsequent cardiovascular disease (CVD) outcome. However, lower Hsp responses are observed in conditions associated with CVD such as aging and diabetes, whereas higher Hsp expression is associated with subjects with lower CVD risk – those who regularly exercise or consume modest amounts of alcohol [14].

α-Adrenergic blockers are also used therapeutically to improve prostatic hypertrophy. Apoptosis in the prostate is thought to be a major effect of these agents in their relief of the symptoms of prostatic hypertrophy. A molecular mechanism to explain the ability of α-adrenergic blockers to reduce prostatic hypertrophy is via accelerated apoptosis of stromal and epithelial prostatic tissue [15]. I hypothesize that low Hsp levels induced by α-adrenergic blockers will promote apoptosis which may benefit a person with an enlarging prostate but may be harmful to the heart, resulting in an unfavorable outcome. If the detrimental effects of prazosin and doxazosin are the result of a class effect, then other agents in this class, such as terazosin and tamsulosin, should be studied for adverse outcome. Encouragingly, however, tamsulosin targets α_{1A}-adrenergic receptors in the prostate, not vascular α_{1B}-adrenergic receptors [16], and therefore, theoretically, it should not cause vascular damage.

Are there other classes of drugs that lower blood pressure effectively but produce disappointing outcomes in trials? As a group, calcium-channel blockers have not proved to be beneficial in reducing myocardial infarction or congestive heart failure and yet are efficacious in treating hypertension. In fact, a meta-analysis of nine major hypertension trials suggested that calcium-channel blockers are inferior to other types of antihypertensive drug in reducing the risk of heart disease [17]. Consistent with the previously outlined thesis, a study *in vitro* observed lower Hsp expression in myocytes exposed to calcium-channel blockers [18]. In addition, the higher incidence of gastrointestinal hemorrhage observed with calcium-channel blockers [19] might have been the result of lower levels of Hsps – which normally protect the gastric mucosa from injury [20].

How can we test the hypothesis that α_{1B} blockers put the myocardium at risk through a decrease in Hsp levels? We would start by examining both ischemic and hypertensive animal models of congestive heart failure treated either with a placebo, an α_{1A} blocker, or an α_{1B} blocker, and then study the subsequent cardiac functional outcome with tissue correlations to all of the major Hsps (Hsp 27, 60, 70, and 90). In humans, a trial is needed to study the effect that different adrenergic blockers, used in the therapy of hypertrophy benign prostatic hyperplasia (BPH), have on the cardiovascular risk. Importantly, BPH is itself associated with a two times higher CVD morbidity. Therefore, when studying adverse cardiovascular effects of BPH therapeutic agents in a nonrandomized fashion, it is essential to measure all relevant CVD risk factors in the database and use the information for statistical adjustment [21]. Unfortunately, a simple blood test for Hsps is not currently available.

The need for health outcome studies to guide medical care choices is clearly demonstrated by studies such as the ALLHAT trial. Improvement in cardiovascular risk factors with an α-adrenergic blocker would have predicted a smaller number of cardiovascular events; however, the ALLHAT trial observed the opposite result, prompting early termination of the doxazosin arm of the study. Lower levels of Hsps might explain why α-adrenergic blockers (particularly α_{1B} blockers) and, perhaps, calcium-channel blockers, have a less than ideal effect on cardiovascular health.

Competing interests

None declared.

References

1. ALLHAT Research Group: **Major cardiovascular events in hypertensive patients randomized to doxazosin vs chorthalidone.** *JAMA* 2000, **283**:1967-1975.

2. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb, SR, Shah PM, Saunders R, Fletcher R, Loeb HS, Hughes VC, Baker B: **Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study.** *N Engl J Med* 1986, **314**: 1547-1552.
3. Anderson P, Seljeflot I, Herzog A, Arnesen H, Hjermann I, Holme I: **Effects of doxazosin and atenolol on atherothrombogenic risk profile in hypertensive middle-aged men.** *J Cardiovasc Pharmacol* 1998, **31**:677-683.
4. Benjamin IJ, McMillan DR: **Stress (heat shock) proteins – molecular chaperones in cardiovascular biology and disease.** *Circ Res* 1998, **83**:117-132.
5. Matz JM, La Voi KP, Moen RJ, Blake MJ: **Cold-induced heat shock protein expression in rat aorta and brown adipose tissue.** *Physiol Behav* 1996, **60**:1369-1374.
6. Meng X, Brown JM, Ao L, Banerjee A, Harken AH: **Norepinephrine induces cardiac heat shock protein 70 and delayed cardioprotection in the rat through α_1 adrenoreceptors.** *Cardiovasc Res* 1996, **32**:374-383.
7. Kariya T, Minatoguchi S, Ohno T, Yamashita K, Uno Y, Arai M, Koshiji M, Fujiwara T, Fujiwara H: **Infarct size-reducing effect of ischemic preconditioning is related to α_{1b}-adrenoceptors but not to α_{1a}-adrenoreceptors in rabbits.** *J Cardiovasc Pharmacol* 1997, **30**:437-445.
8. Comini L, Gaia G, Curello S, Ceconi C, Pasini E, Benigno M, Bachetti T, Ferrari R: **Right heart failure chronically stimulates heat shock protein 72 in heart and liver but not in other tissues.** *Cardiovasc Res* 1996, **31**:882-890.
9. Tanonaka K, Furuhama KI, Yoshida H, Kakuta, Miyamoto Y, Toga W Takeo S: **Protective effect of heat shock protein 72 on contractile function of perfused failing heart.** *Am J Physiol Heart Circ Physiol* 2001, **281**:H215-H222.
10. Vigh L, Literati PN, Horvath I, Torok Z, Balogh G, Glatz, Kovacs E, Boros I, Ferdinandy P, Farkas B, Jaszlits L, Jednakovits A, Koranyi Lmaresca B: **Bimoclomol: a nontoxic, hydroxylamine derivative with stress protein-inducing activity and cytoprotective effects.** *Nat Med* 1997, **3**:1150-1154.
11. Jednakovits A, Kurcz I, Nanasi PP: **Effect of subchronic bimoclomol treatment on vascular responsiveness heat shock protein production in spontaneously hypertensive rats**. *Life Sci* 2000, **67**:1791-1797.
12. Rajdev S, Hara K, Kokubo Y, Mestril R, Dillmann W, Weinstein PR, Sharp FR: **Mice overexpressing rat heat shock protein 70 are protected against cerebral infarction.** *Ann Neurol* 2000, **47**: 782-791.
13. Suzuki K, Sawa Y, Kagisaki K, Taketani S, Ichikawa H, Kaneda Y, Matsuda H: **Reduction in myocardial apoptosis associated with overexpression of heat shock protein 70.** *Basic Res Cardiol* 2000, **95**:397-403.
14. Tytell M, Hooper PL: **Heat shock proteins: new keys to the development of cytoprotective therapies.** *Emerging Therapeutic Targets* 2001, **5**:267-287.
15. Chon JK, Borkowski A, Partin AW, Isaacs JT, Jacobs SC, Kyprianou N: **Alpha 1-adrenoceptor antagonists terazosin and doxazosin induce prostate apoptosis without affecting cell proliferation in patients with benign prostatic hyperplasia.** *J Urol* 1999, **161**:2002-2008.
16. Narayan P, Lepor H: **Long-term, open-label, phase III multicenter study of tamsulosin in benign prostatic hyperplasia.** *Urology* 2001, **57**:466-470.
17. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Cavazzini C, Furberg CD: **Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials.** *Lancet* 2000, **356**:1949-1954.
18. Low-Friedrich I, Schoeppe W: **Effects of calcium channel blockers on stress protein synthesis in cardiac myocytes.** *J Cardiovasc Pharmacol* 1991, **17**:800-806.
19. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ: **Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old.** *Lancet* 1996, **347**: 1061-1065.
20. Rokutan K: **Role of heat shock proteins in gastric mucosal protection.** *J Gastroenterol Hepatol* 2000, **15 (suppl)**:D12-D19.
21. Souverein PC, Herings RM, De la Rosette JJ, Man in 't Veld AJ, Farmer RD, Leufkens HG: **Evaluating adverse cardiovascular effects of drug treatment for benign prostatic hyperplasia (BPH): methodological considerations.** *J Clin Epidemiol* 2001, **54**:518-524.