Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2008; 11 (1-4), 8-10

The Funcional Effect of Beta Blockers vs Vasodilators in Hypertension Treatment

Klainman E, Starobin D, Wishnizer R, Yarmolovsky A, Fink G

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

The Functional Effect of Beta Blockers vs Vasodilators in Hypertension Treatment

E. Klainman[1, 2], D. Starobin[2], R. Wishnitzer[2], A. Yarmolovsky[2], G. Fink[2]

Objective: To evaluate and compare retrospectively the physiological effect of beta blockers versus vasodilators in the treatment of hypertensive patients (pts). Methods: 42 diagnosed hypertensive pts (24 male, 18 female) were studied. They were divided into two groups: (1) 16 patients treated with vasodilators only and (2) 26 patients treated only with beta blockers. A cardiopulmonary exercise test (CPET) was performed in all pts while they were taking their medications as usual. The following indices were monitored and measured breath by breath during exercise: heart rate (HR), blood pressure (BP), oxygen consumption (VO_2), oxygen pulse (O_2P), ventilatory anaerobic threshold (VAT) and respiratory exchange ratio (RER). Maximal exercise capacity was considered as RER having reached a value of at least 1.15. Peak values of the CPET indices were compared between the two groups for each index separately by the two-tailed Student T test. P values < 0.05 were considered statistically significant. Results: No significant differences were observed between groups A and B, respectively, as follows: age 58 ± 13 vs 59 ± 10; RER 1.17 ± 0.12 vs 1.17 ± 0.1; and peak O_2P 108 ± 13 vs 102 ± 33. Significant differences between the two groups were observed in: peak HR (% of predicted HR) 90 ± 8 vs 69 ± 12; peak VO_2 (% of predicted VO_2) 96 ± 9 vs 69 ± 11; and VAT (% of max VO_2 predicted) 55 ± 8 vs 43 ± 9 ($p < 0.05$). Conclusions: Beta blockers in the treatment of hypertensive patients demonstrate a significant physiological disadvantage compared to vasodilator treatment. These findings further validate the CPET as an important tool for physiological evaluation of various treatments in hypertensive patients. ***J Clin Basic Cardiol 2008; 11 (online): 8–10.***

Key words: *cardiopulmonary exercise test, hypertension treatment, physiological effect of beta blockers and vasodilators*

The use of beta blockers as first-line therapy for hypertension has been widely conceptual for a long time and they still remain one of the most frequently prescribed drug classes for this purpose. However, in the last few years, debates have been raised about the use of beta blockers as first-line therapy for hypertension. Bangalore et al [1], in a late review of the evidence, noted that no study has shown that beta blocker monotherapy reduces morbidity or mortality in hypertensive patients (pts), even when compared with placebo. Recent data including 13 randomized controlled trials evaluated by a 2005 meta-analysis [2], as well as a large meta-analysis from 1998 [3], demonstrated that beta blockers were ineffective in preventing coronary artery disease, cardiovascular events and all-cause mortality. The results also showed that beta blockers are inferior to other anti-hypertensive drugs with regard to all outcomes including stroke in addition to the above. Another 2006 analysis [4] shows that although beta blockers reduced the risk of stroke compared to placebo, there was only a marginal effect on total cardiovascular events and no effect on all-cause mortality. Moreover, it was reported that pts on beta blockers were more likely to discontinue treatment than those on diuretics or vasodilators. Beta blockers were also shown to be associated with an increased risk for new-onset diabetes mellitus in another large meta-analysis [5], as well as other disadvantages for beta blockers in many other recent reports. The functional effect of these very medications in hypertensive pts, compared to alternative treatment as expressed by cardiopulmonary exercise testing (CPET) is rarely investigated.

The purpose of the present study was to assess the functional-physiological effect of beta blockers on hypertensive pts, compared to vasodilator treatment, by CPET.

Material and Methods

Patients

42 pts diagnosed with mild to moderate hypertension, aged 46–70 years (24 men, 18 women, mean 59 ± 12), were studied retrospectively. They were selected from a pool of 102 pts who underwent a CPET for evaluation of their physiological status under hypertensive treatment. The selected pts were divided into two groups based on their hypertensive treatment: group A contained 16 pts treated with vasodilators only (age 58 ± 13); and group B contained 26 pts treated with beta blockers only (age 59 ± 10).

The criteria for selection were as follows:

- all pts were diagnosed with mild to moderate hypertension before starting any hypertensive treatment;
- all pts demonstrated a well-qualified CPET for collecting relevant data for the study purpose, while taking their anti-hypertensive medications at the test;
- pts with a history of ischemic heart disease (IHD), valvular diseases, CHF, left ventricular dysfunction, atrial fibrillation, pulmonary diseases, peripheral vascular disease or any neuromuscular degeneration were not selected for the study;
- all selected pts were treated for hypertension alone, either using vasodilators only (group A) or with beta blockers only (group B), distribution was as follows:
  Vasodilators
  Ca++ channel blockers:
  – Nifedipine 4 pts, verapamil 2 pts, amlodipine 2 pts, diltiazem 1 pt

Received: July 9, 2008; accepted: August 19, 2008.
From the [1]Gefen – Cardiac Health Center, 1, Korazin st., Givatayim and [2]Exercise Physiology Unit, Pulmonary Institute, Kaplan Medical Center, Rehovot, Israel.
Correspondence to: Prof. Eliezer Klainman, MD, "Gefen" Cardiac Health Center, 1, Korazin St., Givatayim, Z. C. 53583, Israel; e-mail: klainman@zahav.net.il

ACE inhibitors:
– Enalapril 8 pts, ramipril 4 pts, cilazapril 2 pts
Angiotensin-2 receptor blockers (ARBS):
– Losartan 4 pts, candesartan 2 pts, valsartan 2 pts
From the above, 5 pts were treated with both Ca++ blockers and ACE inhibitors or ARBS.
Beta blockers
– Atenolol 19 pts, bisoprolol 4 pts, metoprolol 3 pts

CPET Protocol

An upright symptom-limited test was performed on an electronically braked cycle ergometer (Ergoline-800). After two minutes of free pedaling, exercise was initiated at 20 W, followed by a stepwise increase of 10–20 W every minute until a predefined end point was reached, ie, symptoms, volitional fatigue or attainment of target heart rate or respiratory exchange ratio (RER) of at least 1.15. Only pts who reached an RER value of 1.15 or more at the exercise peak were selected for the study.

Cardiopulmonary data were collected using an online metabolic chart (CPX Medical Graphics, USA). Pts breathed through a low-resistance, two-way valve (Hans-Rudolph, USA) connected to the expiratory limb. The breath-by-breath signals were integrated by a computer yield of 30-second averages of heart rate (HR), minute ventilation (Ve), oxygen uptake (VO_2), carbon-dioxide output (VCO_2) and oxygen pulse (VO_2/HR = O_2P). Ventilatory anaerobic threshold (VAT) was defined as the point at which the ventilatory equivalent of oxygen (Ve/VO_2) increased in absence of a similar increase of the ventilatory equivalent of carbon dioxide (Ve/VCO_2) as described by Beaver et al [6].

Statistical Analysis

The Student two-tailed "t" test was used to compare between the two groups for each index separately. P values < 0.05 were considered statistically significant.

Results

The mean age of all pts (n = 42) was 59 ± 11 years, and breaks down into two groups as follows:
A) 58 ± 13 yrs (n = 16)
B) 59 ± 10 yrs (n = 26)
No statistical differences were found between the two groups.

Table 1 summarized the group data of the CPET as mean ± SD and shows the comparison between the two groups.

Table 1. Group comparison of the CPET indices at peak exercise

	Group A (n = 16)	Group B (n = 26)
Peak-$HR_{(bpm)}$	146 ± 12*	114 ± 16*
% predicted HR	90 ± 8*	69 ± 12*
Peak $VO_{2\ (ml/kg/min)}$	23 ± 4.5*	18 ± 5*
% predicted peak VO_2	96 ± 9*	69 ± 11*
Peak $O_2P_{(ml/beat)}$	14 ± 2.4#	12 ± 3.8#
% predicted peak O_2P	108 ± 13#	102 ± 33#
VAT (ml of VO_2)	1032 ± 170*	817 ± 239*
VAT (% of VO_{2max})	55 ± 8*	43 ± 9*
RER	1.17 ± 0.12#	1.17 ± 0.1#

HR = Heart Rate; VO_2 = Oxygen Consumption; O_2P = Oxygen Pulse; VAT = Ventilatory Anaerobic Threshold; RER = Respiratory Exchange Ratio.
* significant differences between the two values in the same line
# no significant differences between the two values in the same line

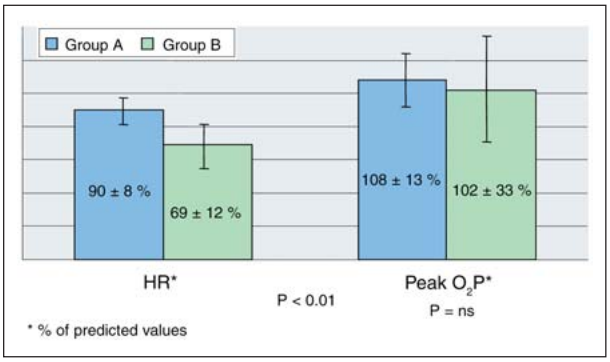

Figure 1. Comparison of peak HR and peak O_2P between the vasodilator group (A) and the beta blocker group (B).

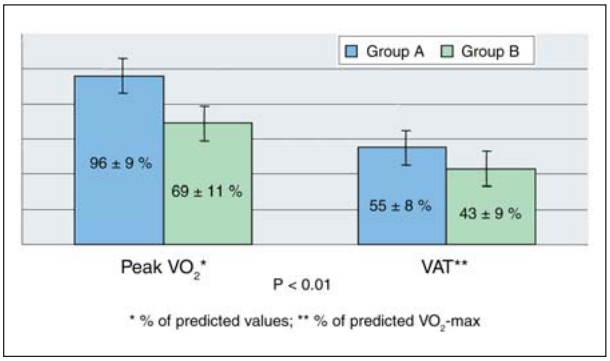

Figure 2. Comparison of the main significant cardiopulmonary indices: peak VO_2 and VAT, both showing significant differences between the two groups.

No significant differences of peak RER and peak O_2P are demonstrated. The mean values of 1.17 for peak RER mean that all pts reached their maximal exercise capacity without significant differences between the two groups. On the other hand, significant differences between the groups are shown in peak HR, peak VO_2 and VAT.

Figure 1 shows that in spite of significant reduction in peak HR in the beta blocker group, no compensation of peak O_2P was demonstrated in the trial to improve cardiac output under the negative chronotropic effect of the beta blockers.

Figure 2 demonstrates the significant differences of the main cardiopulmonary indices – the peak VO_2 and the VAT between the two groups.

Discussion

In the last few years, questions have been raised about the use of beta blockers as first-line therapy for hypertension. Several large studies and meta-analyses have suggested that pts with uncomplicated hypertension under treatment with beta blockers may be at greater risk of stroke and no benefit for all-cause mortality, cardiovascular morbidity and mortality [7].

One recent meta-analysis concludes that in comparison with other antihypertensive drugs, like vasodilators, the effect of beta blockers is less than optimum, with a raised risk of stroke. Hence, the authors believe that beta blockers should not remain first choice in the treatment of primary hypertension [2]. Recent British guidelines mentioned that beta blockers are recommended only as fourth-line hypertensive therapy [8], and an evidence-based medicine review states that beta blockers, especially atenolol, are less effective than other antihypertensive drugs for reducing the risks of stroke and all-cause mortality [9].

In the present study, there is strong functional-physiological support for the disadvantage of beta blockers compared to vasodilators in antihypertensive treatment. It is argued that the use of beta blockers in patients > 60 years is not rational because of physiological changes, including a low cardiac output, low heart rate etc [10]. In our study, pts were significantly younger (59 ± 12; range 46–70), and a significantly poorer functional-physiological performance with beta blockers compared to vasodilators was demonstrated by the CPET.

Another detail mentioned in the present study was the inclusion of several sorts of beta blockers in this very group of pts, although the majority of pts took atenolol. Should it be a limitation, especially with our small sample of pts? Not necessarily. It was already described that no differences in higher risk were shown when comparing all beta blocker treatment with atenolol [2]. Therefore, we assumed that similar physiological effects might be expected with several sorts of beta blockers, not including those with vasodilatory effect like carvedilol.

Replacing beta blockers with vasodilators such as angiotensin-converting enzyme inhibitors has been shown to have positive impact on the quality of life, including improvement of physical activity-related symptoms, as well as equally well-controlled blood pressure even with a lower drug dose [11]. Since the primary hemodynamic hallmark of essential hypertension has been described as elevated systemic vascular resistance it is suggested, therefore, to reduce vascular tone through the use of vasodilators. Angiotensin-converting enzyme inhibitors were preferred in young to middle-aged pts, whereas elderly pts may respond better to calcium channel blockers [12].

The cardiopulmonary exercise test, which may significantly enhance the clinical information available during exercise obtained by concurrent measurement of respiratory gas exchange [13], was performed in all pts for functional evaluation under their anti-hypertensive treatment. Our findings may add some physiological explanations to understand the significant functional differences between the two studied groups. The beta blocker group, compared to the vasodilator group, shows significant reduction of peak HR, peak VO_2 and VAT, and no difference of the peak O_2 pulse between the groups. This means that there is no compensation of stroke volume, expressed by O_2 pulse according to the Fick formula, as demonstrated in the beta blocker group in spite of the significant effect on peak HR reduction as expected by this kind of drugs.

Furthermore, the peak O_2 pulse tends to be lower, even though not statistically significantly, under beta blocker treatment. Since beta blockers might have negative inotropic and chronotropic effects on the heart, our findings are well-explained. As a result, peak VO_2, directly related to cardiac output by the Fick formula and equaling peak O_2 pulse multiplied by peak HR, has to be lower as demonstrated by the present findings. Reduction of cardiac output (expressed by VO_2) might cause elevated systemic vascular resistance which means increased afterload which may cause further reduction of cardiac output. This physiological cascade strongly supports the inferiority of beta blockers compared to vasodilators as anti-hypertensive treatment. As shown in this study (Tab. 1), the cardiopulmonary indices of the vasodilator group are within the normal limits which support strongly the superiority of this very anti-hypertensive treatment. The reduction of the systemic vascular resistance by these medications might explain the physiological advantage as expressed and supported by our findings. On the other hand, Table 1 shows that the treatment of beta blockers does cause, as expected, significant reduction in peak VO_2 and VAT, while demonstrating a similarly adequate effort in both groups (RER = 1.17 ± 0.12 vs 1.17 ± 0.1, respectively; p = ns). These findings might not be in accordance with those of Savolainen et al who report a similar effect of ACE inhibitors (cilazapril) as well as of beta blockers (atenolol) on aortic stiffness in essential hypertension [14]. On the other hand, Kraft et al report that higher peak aerobic capacity in hypertensive pts is not associated with lower aortic stiffness, unlike in healthy normotensive subjects [15]. All this means that the mechanisms and the clinical significance of aerobic capacity as well as of aortic stiffness and correlations between them under anti-hypertensive treatment deserve further studies with larger samples of pts.

No significant difference of peak O_2 pulse between the groups is shown in our study (Tab. 1), which may support some relative compensation of the stroke volume to the overall cardiac output reduction in beta blocker pts, in spite of an expected negative inotropic effect of these very medications.

In conclusion, a CPET might serve as an applicable and effective tool for functional-physiological evaluation of anti-hypertensive treatment. The findings of the present study support physiologically the present trend of preferring other medications than beta blockers for anti-hypertensive treatment.

References:

1. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: A critical review of evidence. J Am Coll Cardiol 2007; 50: 563–72.
2. Lindholm LH, Carlberg B, Samuelsson O. Should beta-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005; 366: 1545–53.
3. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systemic review. JAMA 1998; 279: 1903–7.
4. Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systemic review and meta-analysis. J Hypertens 2006; 24: 2131–41.
5. Bangalore S, Parker S, Grossman E, Messerli FH. A meta-analysis of 94,492 pts with hypertension treated with beta-blockers to determine the risk of new-onset diabetes mellitus. Am J Cardiol 2007; 100: 1254–62.
6. Beaver WL, Wasserman K, Whipp B. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60: 2020–7.
7. Schroeder JS, Block PC. Beta-blockers in hypertension: Should we discard them? Abstract: 22nd Annual Cardiovascular Conference, Hawaii, USA; August 2007.
8. Howard PA. An ongoing debate: Should beta-blockers be used for primary hypertension? Hosp Pharm 2007; 42: 22–6, 86.
9. Rudd P. Review: Beta blockers are less effective than other antihypertensive drugs for reducing risk of stroke in primary hypertension. Evid Based Med 2006; 11: 85.
10. Prisant LM. Should beta-blockers be used in the treatment of hypertension in the elderly? J Clin Hypertens (Greenwich) 2002; 4: 286–94.
11. Paran E, Anson O, Neumann L. The effect of replacing beta-blockers with an angiotensin converting enzyme inhibitor on the quality of life of hypertensive patients. Am J Hypertens 1996; 9: 1206–13.
12. Dzau VJ. Evaluation of the clinical management of hypertension: Emerging role of "specific" vasodilators as initial therapy. Am J Med 1987; 82 (Suppl): 36–43.
13. Milani RV, Lavie CJ, Mehra MR. Cardiopulmonary exercise testing: how do we differentiate the cause of dyspnea? Circulation 2004; 110: e27–e31.
14. Savolainen A, Keto P, Poutanen VP, Hekali P, Standertskjold-Nordenstam CG, Rames A, Kupari M. Effect of angiotensin-converting enzyme inhibition versus beta-adrenergic blockade on aortic stiffness in essential hypertension. J Cardiovasc Pharmacol 1996; 27: 99–104.
15. Kraft KA, Arena R, Arrowood JA, Fei DY. High aerobic capacity does not attenuate aortic stiffness in hypertensive subjects. Am Heart J 2007; 154: 976–82.