

Use of β -blockers during immunotherapy for *Hymenoptera* venom allergy

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Background: β -Blockers may aggravate anaphylactic reactions and interfere with treatment. There is therefore concern about their use in patients who have a history of anaphylaxis or are on allergen immunotherapy. Immunotherapy is the best available treatment for prevention of life-threatening anaphylaxis to *Hymenoptera* stings, which is often observed in elderly patients who have cardiovascular disease and therefore are on β -blocker treatment.

Objective: To analyze the risk of β -blocker treatment during venom immunotherapy.

Methods: We screened all 1682 patients with *Hymenoptera* venom allergy seen during a period of 34 months for immunotherapy, cardiovascular disease, and treatment with β -blockers.

Results: Of the 1389 patients in whom immunotherapy was recommended, 11.2% had cardiovascular disease, and 44 of these were on β -blockers before immunotherapy. In 31 of those, the drug was replaced before starting treatment. In 3 with coronary heart disease and 1 with severe ventricular arrhythmia, the drug was continued throughout immunotherapy. In 9, it was reintroduced after reaching the maintenance dose. In an additional 12 patients, β -blockers were newly started during immunotherapy. Of 25 patients on β -blockers during immunotherapy, 3 (12%) developed allergic side effects, compared with 23 (16.7%) of 117 with cardiovascular disease but without β -blockers. Systemic allergic symptoms after re-exposure by sting challenge or field sting were observed in 1 of 7 (14.3%) with and 4 of 29 (13.8%) without β -blockade. No severe reactions to treatment or sting reexposure were observed in patients with β -blockade.

Conclusion: Combination of β -blockers with venom immunotherapy may be indicated in heavily exposed patients with severe cardiovascular disease. (J Allergy Clin Immunol 2005;115:606-10.)

Key words: Anaphylaxis, β -blockers, *Hymenoptera* venom immunotherapy

Several reports of severe, difficult-to-treat, or even fatal anaphylaxis in patients on β -blocker (BB) treatment¹⁻⁶ have raised concern about the use of these medications in patients with a history of anaphylaxis.^{7,8} Similar obser-

Abbreviations used

AHT:	Arterial hypertension
BB:	β -Blocker
CA:	Cardiac arrhythmia
CHD:	Coronary heart disease
SIT:	Specific allergen immunotherapy
SSE:	Systemic allergic side effect
VIT:	Venom immunotherapy

vations of severe and difficult-to-treat allergic side effects have been published in patients on specific allergen immunotherapy (SIT) and concurrent β -blockade.^{9,10} On the basis of these findings, BBs are generally not recommended in patients with anaphylaxis and during SIT.^{9,11,12}

However, BBs are extremely valuable and hard to replace drugs in the treatment of cardiovascular disease, especially coronary heart disease (CHD), chronic heart failure, and ventricular arrhythmia. Significantly prolonged survival of patients with CHD and cardiac failure under BB has been documented in several large prospective studies.¹³⁻¹⁵ In a recent article,¹⁶ the risk of BB treatment in patients with anaphylaxis to peanuts and concurrent cardiac disease was analyzed on the basis of morbidity and fatality statistics. The authors concluded that the survival is significantly higher in such patients if the BB is maintained.

What about BBs and their contraindication in immunotherapy of allergic disease? *Hymenoptera* venom allergy is one of the 3 leading causes—besides foods and drugs—of fatal anaphylaxis.^{17,18} In contrast with food and drug allergy, allergen specific immunotherapy is very effective in venom allergy.¹⁹ Moreover, fatality studies have shown that especially elderly patients with pre-existing cardiovascular disease die from *Hymenoptera* sting anaphylaxis,²⁰ again in contrast with food allergy, in which mostly younger atopic individuals with bronchial asthma are at risk.²¹ For this reason, unlike for respiratory allergies, immunotherapy with *Hymenoptera* venoms is often recommended in elderly people who are more likely to be on treatment with BB.

This situation together with a recently observed fatal reaction during SIT with *Vespula* venom²² prompted the current study. This fatal reaction occurred in a 40-year-old hypertensive and obese patient who was on BB because of dilative cardiomyopathy and severe ventricular arrhythmia. She was stung by a *Vespula* in 2001, developed anaphylaxis, and was started on immunotherapy with

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Vespula venom after her allergy had been confirmed by skin tests and RAST. The allergist recommended replacement of the BB, and the family practitioner chose indapamid, a thiazide diuretic. Fourteen minutes after the second injection of 40 ng *Vespula* venom, the patient collapsed and fainted because of ventricular fibrillation. Immediate resuscitation was started with repeated defibrillation and intravenous epinephrine injections until her circulation was stabilized. However, she never regained consciousness, had documented severe hypoxic brain damage, and died 3 days later. During the acute reaction, no symptoms specific for an allergic reaction like urticaria, angioedema, or asthma were recorded, and the tryptase serum level did not increase. It is likely that this patient's death resulted from ventricular fibrillation in the frame of her severe cardiac disease, and in relation to the inadequate replacement of the BB by a thiazide diuretic. Neither the absence of allergic symptoms nor the lack of increase of serum tryptase during the acute reaction exclude a contribution of the allergen injection completely.

We therefore decided to analyze a large number of patients allergic to *Hymenoptera* venom with special regard to cardiovascular disease, BB, and venom immunotherapy (VIT).

METHODS

The study included all 1682 patients seen at our clinic for *Hymenoptera* venom allergy during a period of 34 months, between January 2001 and October 2003. A total of 867 were referred for a first examination during this period, and 815 were controlled on VIT started before 2001, usually after 3 to 5 years of treatment.

Examinations included detailed anamnesis, clinical examination, intracutaneous skin tests with *Hymenoptera* venoms,²³ and estimation of *Hymenoptera* venom specific IgE antibodies by CAP (Pharmacia AB, Uppsala, Sweden). On the basis of these data and according to the European guidelines,¹⁹ VIT was recommended in 1389 patients.

Venom immunotherapy was performed according to European guidelines. The dose increase was accomplished by an ultrarush²⁴ with a rapid increase to a total dose of 111.1 µg in 4.5 hours in the intensive care unit, or a conventional protocol with weekly injections until reaching the maintenance dose of 100 µg.¹⁹ Afterward, the usual interval was 4 weeks during the first year and 6 weeks from the 2nd to 5th years. Honeybee and *Vespula* spp (European *Vespula*: *Vespula germanica* and *Vespula vulgaris*) venoms were obtained from ALK-Abello, Horsholm, Denmark. The usual duration of VIT at our clinic is 5 years, but we consider even more prolonged treatment as indicated in beekeepers or patients with mastocytosis or elevated basal serum tryptase.²⁵

The 1389 patients were further screened for the following criteria: age during the first visit; presence of cardiovascular disease, notably CHD, arterial hypertension (AHT), and cardiac arrhythmia (CA); and treatment with BB.

The frequency of side effects in relation to BB use, phase of VIT, and venom used was analyzed by contingency table χ^2 test.

RESULTS

Presence of cardiovascular disease, treatment with BB, and age

Of the 1389 patients in whom VIT had been recommended, 156 (11.2%) had cardiovascular disease or were

on BB treatment. In 142 of the 156 patients, VIT was actually started. Of the 142 in whom VIT was started, 129 (90.8%) had AHT, 18 (12.7%) CHD, 8 (5.6%) CA, and 1 dilative cardiomyopathy. Fifty-six had reacted to honeybee, 62 to *Vespula*, and 6 to both honeybee and *Vespula* stings. In 18, the stinging insect had not been identified, and they had positive diagnostic tests with both venoms. Of the 1389 patients in whom VIT had been recommended, 44 (3.2%) were on BB before their initial visit at our clinic. The indication for BB was arterial hypertension in 38, CHD in 8, and CA in 4. Only one was on BB for a noncardiovascular disease: migraine. All had severe anaphylactic reactions with respiratory and/or cardiovascular symptoms: 16 of grade III according to the classification of Mueller,^{26,27} with predominant respiratory symptoms such as dyspnoe, wheezing, and stridor, and 28 of grade IV with severe cardiovascular symptoms such as arterial hypotension, collapse, and loss of consciousness. Of the 16 patients with grade III reactions, 13 also had cutaneous symptoms such as urticaria, angioedema, or erythema. Of the 28 with grade IV reactions, 22 had cutaneous and 13 respiratory symptoms as well.

The mean age of all 1389 patients in whom VIT was recommended was 34.84 years $\pm$ 17.91 years (range, 2-85 years), whereas the mean age of those with cardiovascular disease was significantly higher, 53.42 years $\pm$ 10.62 years (range, 22-76 years). The same was true for those on BB before VIT, in whom a mean age of 53.96 years $\pm$ 10.09 years (range, 35-73 years) was found.

Decisions in patients on BB before VIT

In 31 patients, the BB was replaced by another drug—in 5 after the last sting reaction by the family practitioner, and in the remaining 26 after our recommendation (Table I). In 9, the BB was replaced during dose increase and then reintroduced during the maintenance phase. In 4 patients, 3 with CHD and 1 with severe ventricular arrhythmia, it was considered too risky to stop the BB. VIT was therefore started with ongoing BB treatment according to an ultrarush protocol over a period of 4.5 hours under close monitoring of electrocardiogram, blood pressure, and respiration in the intensive care unit for 24 hours. BB treatment was continued throughout VIT in these 4 patients.

Tolerance of VIT in patients with cardiovascular disease with or without BB

In 12 of the 815 patients controlled during VIT, we realized that they had been newly started on BB during maintenance treatment because of newly detected AHT in 5, CHD in 4, dilative cardiomyopathy in 1, CA in 1, and migraine in 1 (Table II). A total of 25 patients were thus on BB during VIT, 4 during the whole treatment, and 21 only during the maintenance phase. All 25 patients on BB during VIT previously had severe systemic sting reactions, 12 of grade III and 13 of grade IV. Ten of the 12 with grade III reactions had also cutaneous symptoms. Of the 13 with grade IV reactions, 10 had cutaneous and 7 respiratory symptoms as well. Eleven of the 25 patients

TABLE I. Decision in 44 patients with *Hymenoptera* venom allergy, cardiovascular disease, and BB treatment before starting VIT

Indication for BB	Decision with regard to β -blockade during VIT			Total
	Replacement during whole VIT	Replacement for dose increase	No replacement	
AHT	26	6	—	32
CHD	2	—	2	4
CA	1	—	1	2
AHT and CHD	1	2	1	4
AHT and CA	1	1	—	2
Total	31	9	4	44

were treated with honeybee, 10 with *Vespula* spp, and 4 with both venoms. The mean duration of concurrent VIT and BB use was 37.7 months (range, 3-240 months).

One (25%) of the 4 with BB during the dose increase phase developed systemic allergic side effects (SSEs) consisting of urticaria, heat sensation, and mild dysphagia. Of the 25 on BB during the maintenance phase, 2 (8%) had some SSE: 1 developed sinus tachycardia and chest tightness after the first maintenance injection, which subsided without treatment. The second developed urticaria and angioedema once only, 2 years after the start of VIT. On the whole, 3 of the 25 patients on BB during VIT (12%) developed SSE at least once. All were able to continue VIT on the usual maintenance dose of 100 μ g. One each of the patients on BB with systemic side effects was on VIT with honeybee, *Vespula* spp, or both venoms.

In a total of 138 patients with cardiovascular disease, VIT was started without BB. Fifty-four were treated with honeybee, 62 with *Vespula* spp, and 22 with both venoms. Of the patients without BB, 16 (11.6%) developed SSE during the dose increase phase: 13 presented cutaneous reactions (urticaria, angioedema, pruritus); 2 had respiratory symptoms (dyspnoe, wheezing), 1 of them in combination with cutaneous symptoms; and 3 had cardiovascular symptoms (arterial hypotension, 1; syncope, 1; ventricular tachycardia, 1), 1 of them in combination with cutaneous symptoms. Of the 117 with cardiovascular disease but without BB during the maintenance phase, 10 (8.5%) reported SSE: 9 cutaneous symptoms, 1 of them with dyspnoe; and 1 cardiovascular symptoms (collapse with unconsciousness). The usual maintenance dose of 100 μ g could not be reached in 2. Treatment had to be stopped in 1 patient allergic to *Vespula* venom with repeated SSE over a period of 3 years, preventing a dose increase more than 40 μ g. On the whole, 23 (16.7%) of the 138 patients without BB during either the dose increase or the maintenance phase of VIT developed SSE.

Of these 23 patients with SSE, 15 were on VIT with bee venom, 6 with *Vespula* venom, and 2 with honeybee and *Vespula* venom.

The mean duration of VIT without BB use was 45.2 months (range, 2-138 months).

TABLE II. Tolerance of VIT in patients with cardiovascular disease with and without β -blockade

Phase of VIT	VIT		Total
	With β -blockade	Without β -blockade	
Dose increase n	4	138	142
n with systemic allergic side effects	1 (25%)	16 (11.6%)	17 (12%)
Maintenance dose n	25	117	142
n with systemic allergic side effects	2 (8%)	10 (8.5%)	12 (8.5%)
Total side effects	3 (12%)	23 (16.7%)	26

TABLE III. Results of re-exposure in patients on VIT with cardiovascular disease with and without β -blockade

	Result of re-exposure		Total
	With β -blockade	Without β -blockade	
n re-exposed	7	29	36
n with systemic allergic symptoms	1	4	5
%	14.3%	13.8%	13.9%

On the whole, SSEs were more frequently observed during VIT with honeybee than with *Vespula* venom: 15 of the 56 patients on honeybee venom (26.8%), 6 of the 62 on *Vespula* spp venom (9.7%), and 4 of 24 on both venoms (16.7%) developed SSE. The difference in frequency of SSE during VIT with honey bee and with *Vespula* spp venom is significant ($\chi^2 = 5.887$; $P < .02$). Moreover, respiratory and/or cardiovascular symptoms were observed in 6 patients on honeybee and in 2 on honeybee and *Vespula* spp, but in none on *Vespula* spp venom alone. Although patients on BB were somewhat more often treated with honeybee venom, the frequency of SSE during dose increase, maintenance dose, or both was not significantly different between patients with or without BB ($\chi^2 = 0.39$; $P > .5$).

Results of re-exposure during VIT with and without BB

Of the 142 patients, 36 were re-exposed to a sting by the culprit insect, 18 each by a field sting or a sting provocation test, 20 to a honey bee, 16 to a vespid sting (Table III). Five of the 36 re-exposures (13.9%) were followed by a systemic allergic reaction, 3 to a honeybee and 2 to a *Vespula* sting. One of the 7 re-exposed patients (14.3%) on BB developed a systemic reaction with nausea and dyspnoe after a honey bee field sting on 3 occasions. The symptoms were not documented by a physician in any of these 3 restings. Four of the 29 (13.8%) on VIT without BB developed mostly mild systemic reactions, 2 each after

a honeybee and a vespid sting. The difference between groups is not significant.

DISCUSSION

β -Blockade inhibits the effect of both endogenously released and therapeutically administered epinephrine in case of anaphylaxis and thus enhances generation and release of mediators of anaphylaxis and their effects on end organs.²⁸ If anaphylaxis occurs in a patient on BB, it may therefore be more severe, protracted, and difficult to treat. Although there is ample theoretical and experimental²⁹⁻³¹ and anecdotal clinical evidence¹⁻⁷ for these adverse effects of BB in acute anaphylaxis, this may not justify the strict contraindication in all patients with anaphylaxis, as indicated by the recently published decision analysis in patients with potentially fatal peanut anaphylaxis.¹⁶ In patients with life-threatening *Hymenoptera* venom allergy, there is no valid alternative to the highly effective VIT.

We present here a retrospective analysis of 142 patients with *Hymenoptera* venom allergy and concurrent cardiovascular disease. Of these, 44 were on BB before and 25 during VIT. The limitations of such a retrospective analysis are obvious. However, it was thought that the potential risks for the participants associated with a prospective randomized study design would have been unacceptable. Our results show that more than 10% of the patients with systemic allergic reactions to *Hymenoptera* stings have cardiovascular disease, and about a third of these are treated by BB. Not unexpectedly, the mean age of these patients is considerably—approximately 20 years—higher than in the whole group of patients with *Hymenoptera* venom allergy. On the other hand, we know that most patients who die from sting anaphylaxis are between 50 and 70 years old,^{20,32} and autopsies have revealed pre-existing cardiovascular disease in a high percentage of them.²⁰ In contrast with immunotherapy for inhalatory allergies, VIT is therefore well indicated and often recommended in people older than 50 years and consequently in patients who are likely to have cardiovascular disease and thus often treated by BB. The fact that no fewer than 12 patients were started on BB during ongoing VIT illustrates this situation.

How significant is the risk of a combination of VIT with BB? As in a previous prospective study on a large number of patients on allergen immunotherapy with or without BB observed over a period of 1 year,³³ we did not find an increased but a slightly lower, although not significantly lower, incidence of SSEs to VIT injections, and these were not more severe than in the control group. The shorter mean duration of VIT with BB may explain this small difference. On the other hand, SSEs were somewhat more frequent during the dose increase than the maintenance phase of VIT and significantly more frequent in patients treated with bee than with *Vesputula* venom, as previously reported.^{34,35} Systemic allergic reactions after re-exposure during VIT were neither more frequent nor more severe in

patients on BB. Still, the number of patients on BB during immunotherapy, as in the previous prospective study,³³ was relatively small, and conclusions for the general inconsiderate use of BB during VIT are certainly not justified. Theoretical and clinical evidence for a risk of severe and difficult to treat allergic reactions favored by the use of BB during IT is certainly strong.^{1-12,28-31}

However, when confronted with a patient with a history of severe allergic sting reactions who is on BB, we have to estimate the risk of giving the BB during VIT against the risk of stopping the BB in the presence of cardiovascular disease or even the risk of renouncing VIT and continuing the BB. The significantly prolonged survival of patients with CHD or cardiac failure under BB treatment,¹³⁻¹⁵ the high frequency of deaths caused by cardiovascular disease—in Switzerland every year, more than 25,000 compared, with an average of 3 caused by *Hymenoptera* sting anaphylaxis³⁶—and the exposure of the patient to further stings and the nature of the cardiovascular disease must be considered in this situation, preferably together with the family practitioner and a cardiologist.

A high degree of exposure as in a beekeeper, a farmer, or a gardener, together with a history of severe reactions will make VIT mandatory; if combined with CHD, cardiac failure, or severe ventricular arrhythmia, VIT should be started under BB with special precautions, as in the 4 patients described. On the other hand, if the same patient has arterial hypertension only without overt cardiac disease, the BB may be more easily replaced by a calcium antagonist, a diuretic, or an angiotensin 2-antagonist. Finally if a patient's risk to be restung is only marginal and he has CHD, ventricular arrhythmia, or dilative cardiomyopathy, we may decide to continue the BB and not to put him on VIT, but to confine to prophylactic measures and emergency medications.²⁷

In conclusion, we think that the contraindication for BB use during VIT should not be considered as absolute but as relative, as was already proposed in a recent World Health Organization document on specific allergy vaccination.³⁷ In every patient with *Hymenoptera* venom allergy on BB, the indication for VIT and/or the replacement of the BB must be evaluated very carefully.

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