

Cardiovascular disease and anaphylaxis

Ulrich R. Mueller

Purpose of review

In severe anaphylaxis, the cardiovascular system is often heavily involved. Preexisting cardiovascular disease may therefore influence the course of anaphylaxis in a negative way.

Recent findings

Systemic mastocytosis and elevated baseline serum tryptase are associated with severe and fatal anaphylaxis to hymenoptera stings. This is due to an increased number of cardiac mast cells resulting in high concentrations of cardiotoxic mast cell mediators in cardiac tissue during anaphylaxis. Severe anaphylaxis in coronary heart disease, in particular, is explained by an increased load of cardiac mast cells together with coronary stenosis favouring myocardial hypoxia. Contraindications for the use of medications for cardiac disease in patients with anaphylaxis, especially β -blockers, have been questioned by epidemiologic studies considering the positive effects of these drugs on much more prevalent cardiac diseases.

Summary

Preexisting cardiovascular disease, mastocytosis and elevated baseline serum tryptase are risk factors for fatal anaphylactic reactions or lasting morbidity due to myocardial or cerebrovascular infarction induced by anaphylaxis. Life-saving cardiac medications like β -blockers may increase the severity of anaphylaxis. Since life-threatening cardiovascular diseases are much more frequent than anaphylaxis, the relative risk of either disease with and without these drugs must be analyzed carefully together with the cardiologist.

Keywords

allergen specific immunotherapy, anaphylaxis, β -blockers, coronary heart disease, mastocytosis

Introduction

It is well known that in severe anaphylaxis the cardiovascular system is frequently involved with symptoms like arterial hypotension, cardiovascular collapse, arrhythmias or chest pain, as documented and discussed in recent publications [1,2]. These symptoms are partly due to vasodilatation and increased vascular permeability leading to hypovolemia, partly also to the direct cardiotoxic effect of mast cell mediators and hypoxemia following bronchospasm and shock. This review will concentrate on preexisting cardiovascular disease (CVD) and its treatment, which may severely aggravate the course of anaphylaxis and make its treatment more difficult.

Case presentation by David Golden MD

A 53-year-old gentleman was referred to me by his internist for evaluation of insect sting anaphylaxis. He had been stung by a yellow jacket (*Vespula* spp.) on the neck and quickly felt woozy, developed nausea and dizziness. He pulled into a gas station, got out of the car, and collapsed on the pavement. We know that he had no hives. Hospital records tell us that he had been found in ventricular fibrillation, was cardioverted four times, intubated and transported to the hospital. No epinephrine was given, because of a presumed acute cardiac event. At hospital entry he had a heavy chest and dyspnea and ST changes were noted on the ECG. He was taken directly to the cardiac catheterization lab but was found to have normal coronary arteries. The background is largely noncontributory. He did have a sting in childhood with no reaction. He has no history of atopy. Noteworthy, however, is that his father died suddenly at age 34 of unknown cause. There is thus a potential family history of sudden cardiac death. He has cardiac risk factors with diabetes and hypertension and is on a number of medications including a β -blocker. The intradermal skin tests 6 weeks after the reaction were negative to all five venoms, but low concentrations of yellow jacket venom-specific immunoglobulin (Ig)-E were detected in the serum. We requested a baseline serum tryptase level because of his presentation of rapid onset vascular collapse after a sting with no hives, which is somewhat classical for mastocytosis. Indeed his serum tryptase level was 30 ng/ml. The bone marrow biopsy showed clusters of abnormal mast cells indicating systemic mastocytosis. Of note, hives are absent in many cases of insect sting allergy with hypotensive shock, especially in this setting of mastocytosis. The cardiologic evaluation focused on the important second issue whether he has familial

Curr Opin Allergy Clin Immunol 7:337–341. © 2007 Lippincott Williams & Wilkins.

Department of Medicine, Zieglerspital, Bern, Switzerland

Correspondence to Prof. Dr Ulrich R. Mueller, Allergiestation Medizinische Klinik, Spital Ziegler Spitalnetz Bern, Morillonstrasse 75-91, CH-3007 Bern, Switzerland
Tel: +41 31 970 7342; e-mail: ulrich.mueller@spitalnetzbern.ch

Current Opinion in Allergy and Clinical Immunology 2007, 7:337–341

Abbreviations

CHD	coronary heart disease
CVD	cardiovascular disease
Ig	immunoglobulin
MI	myocardial infarction
VIT	venom immunotherapy

© 2007 Lippincott Williams & Wilkins
1528-4050

idiopathic ventricular fibrillation. Does he need an implantable cardiac defibrillator? Should he stop the β -blocker? Is venom immunotherapy worthwhile, safe and effective? Dr Mueller has published on this last question, and many other aspects of CVD and anaphylaxis.

Systemic mastocytosis is associated with severe cardiovascular reactions following Hymenoptera stings

The patient of Dr Golden presents the problem of anaphylaxis and cardiac disease in relation to mastocytosis. My group previously described [3] 10 patients with urticaria pigmentosa and systemic Hymenoptera sting reactions. All had severe cardiovascular reactions with shock but only four presented urticaria. Five had no detectable serum IgE to venoms and two also had negative skin tests. Most had elevated baseline tryptase. We put all on venom immunotherapy (VIT), which they tolerated well. Seven were reexposed: six were fully protected, one developed mild urticaria. An association of an elevated baseline tryptase with severe cardiovascular sting reactions has also been described [4–6]. In a recent paper [7], six patients with severe hypotensive reactions to hymenoptera stings and subsequently detected mastocytosis were described. Of special interest is the fact that three of four published cases of fatal sting reactions after stopping VIT occurred in patients with systemic mastocytosis [8,9]. In the fourth mastocytosis was not evaluated [10].

What is the background of association of mastocytosis/elevated baseline tryptase and severe cardiovascular reactions during anaphylaxis? Mast cells are present in cardiac tissue including coronary arteries and their density is increased in patients with coronary heart disease [11]. Mast cell mediators (histamine, leukotrienes) have cardiotoxic effects, including vasoconstriction, negative inotropy and arrhythmogenesis. In mastocytosis, an increased mast cell density is also present in cardiac tissue and is responsible for severe cardiovascular symptoms during anaphylaxis. A further augmentation of mast cell density due to CVD may additionally worsen the course of anaphylaxis.

As a consequence we recommend the following: estimating baseline tryptase in all patients with systemic allergic reactions to Hymenoptera stings; looking for systemic mastocytosis in all those with a baseline tryptase greater than 20 ng/ml; and treating all patients with mastocytosis or baseline tryptase greater than 20 ng/ml by VIT for life. To come back to Dr Golden's patient, we would advise VIT for life, to continue the β -blocker which is preventive for ventricular arrhythmias, and to discuss further measures according to the results of the additional cardiologic exploration.

Preexisting cardiovascular disease may worsen the course of anaphylaxis

In a study on 29 fatalities from Hymenoptera stings [12], we noted that the mean age showed a peak at 60–70 years while it is around 35 in venom patients visiting our clinic. Autopsy in 12 of the fatalities revealed 11 with cardiac disease, 10 had coronary heart disease (CHD) and seven cardiomyopathy. Preexisting CVD thus must be considered as a risk factor for very severe and fatal anaphylactic reactions. In a recent publication on 25 fatalities from anaphylaxis of various causes, at least one significant comorbid disease was identified in 22, and CVD in 16 [13].

In another case report [14], a 67-year-old man suffered from intermittent low back pain for years. In July 2004, he left for a vacation. Due to low back pain he took 50 mg of diclofenac before departing. On the highway soon after, he noted generalized itch, retrosternal pain, and could not see clearly anymore. His wife took over and drove to the next hospital. When he got out of the car he collapsed, lost consciousness and was brought to the ICU. There he was conscious again, his blood pressure was 114/70, pulse 62/min, oxygen saturation 92%. He had generalized urticaria and still complained about chest pain. He was treated with oxygen and got intravenous volume substitution, clemastine and methylprednisolone. Due to the chest pain he received no epinephrine but was given nitroglycerin and soon recovered, with blood pressure rising to 150/80 and chest pain disappearing. The ECG recorded in the acute phase showed anterolateral depression of the ST segment, which on the next day was no longer present. Serum tryptase during the acute reaction was 9.8, 3 weeks later it was 3.8 ng/ml, indicating an acute anaphylactic reaction, most likely provoked by diclofenac. He had definite hyperlipidemia and hypertension persisted during the following weeks. The coronary arteriogram showed pronounced stenosis in the inter-ventricular anterior branch of the left coronary artery. Treatment consisted of angioplasty and introduction of a coronary stent.

In this patient with most likely preexisting hypertension and hyperlipidemia, acute anaphylaxis to diclofenac was accompanied by angina pectoris and thus unmasked CHD. Chest pain during acute anaphylaxis is not rare and may indicate preexisting CHD. In a previous study we observed cardiac complications in 32 of 1463 patients with systemic allergic reactions to Hymenoptera stings (Table 1) [15]. Their mean age was 51 years, definitely higher than that of the whole population and 13 of the 32 had known preexisting CVD. In such patients anaphylaxis may cause cardiac symptoms because of myocardial hypoxemia due to coronary arteriosclerosis or increased local mediator release because of increased mast cell density in the cardiac tissue [11]. Any patient

Table 1 Cardiovascular symptoms in 1463 patients with Hymenoptera sting anaphylaxis

Symptoms	Number of patients (%)	Mean age
Patients with venom anaphylaxis	1463	34.2
Chest pain or tightness	193 (13.2)	
Definite cardiac symptoms	32 (2.2)	51.0
During anaphylaxis		
Typical angina pectoris	12	
Myocardial infarction	2	
Documented arrhythmia	25	
Bradycardia < 50/min	7	
Extrasystolia	8	
Ventricular fibrillation	3	
Asystolia (one fatal)	2	
Preexisting cardiovascular disease documented	13	

Adapted from Müller *et al.* [15].

with severe anaphylaxis should therefore be treated in an ICU and supervised over a prolonged period. Chest pain may be an indication of CHD and requires further cardiologic exploration. Other cases of anaphylaxis inducing acute coronary disease have been described [16].

Treatment of cardiovascular disease may negatively influence the course of anaphylaxis

In 1981, a 61-year-old lady on previously well tolerated immunotherapy for allergic rhinitis was described [17], who developed a severe, protracted and difficult to treat shock reaction to allergen injection after introduction of β -blocker treatment for newly diagnosed hypertension. Many similar case reports followed with the result that β -blockers are generally not recommended in patients with anaphylaxis, those with bronchial asthma and those on allergen immunotherapy. The theoretical explanation is that they interfere with neuro-humoral mechanisms of the cyclooxygenase system and therefore increase synthesis and liberation of mediators from effector cells of anaphylaxis and also block the effect of endogenous or therapeutic epinephrine. This makes anaphylaxis become more severe and its treatment more difficult [18]. The same effects have been reported for angiotensin-converting enzyme inhibitors, which block the inactivation of the anaphylaxis mediator bradykinin [19].

Betablockers and anaphylaxis

The risk of β -blockers in patients with CVD and anaphylaxis was discussed in a recent publication [20]. Anaphylactic reactions are quite rare and are usually unexpected, while CVD is frequent. In CHD, ventricular arrhythmia and cardiac failure β -blockers increase survival very significantly [21,22] and are difficult to replace. In the US, there are an estimated three million patients allergic to peanuts and 150 fatalities from peanut anaphylaxis occur every year, but there are about 13 million patients with CHD and about 1.1 million cases of myocardial infarction or fatal CHD annually. Based on

these data the risk of a fatal reaction in a 58-year-old person after myocardial infarction (MI) or cardiac failure with and without β -blockers was analysed [20]. The risk of death from anaphylaxis was reduced without β -blockers but the risk of dying from CVD in MI and cardiac failure was definitely increased without β -blockers. On the whole, the survival rate was higher with than without β -blockers in both patients with MI and cardiac failure and peanut anaphylaxis.

Betablockers and specific immunotherapy

It is well known that immunotherapy may cause anaphylactic side effects. Therefore, β -blockers are not recommended during immunotherapy. This is rarely a problem in immunotherapy for respiratory allergies, which is usually performed in young patients who are seldom on β -blockers. In insect venom allergy, however, life-threatening and potentially fatal reactions are most often observed in older patients, who are frequently suffering from CVD and therefore are on β -blockers. While there is a good theoretical basis for contraindication of β -blockers during immunotherapy the clinical evidence is modest. There are many anecdotal reports but only one prospective study [23] on more than 3000 patients with about 50 000 injections over 1 year. Sixty-eight patients were on β -blockers. Systemic allergic side effects were observed in 4.5% of those not on β -blockers and in 1.5% (one of 68) of those on β -blockers and all these reactions were rather mild. The frequency of side effects of immunotherapy was thus not increased by β -blockers.

In a recent study [18], we analyzed 1682 patients with venom allergy referred between 2000 and 2003, about half on a first visit and half on a control visit during VIT [18]. All were screened for CVD and for treatment with β -blockers. VIT was recommended in 1389 cases. Of these, 142 (10.2%) suffered from CVD and 44 were on β -blockers, mostly for hypertension, eight for CHD and one for migraine. The mean age for all patients was 34 years, for those with CVD and on β -blockers, 54. In four with CHD or arrhythmia, β -blockers were continued and VIT by ultra-rush was started under close monitoring in the ICU. In another 21 patients, β -blockers were restarted after reaching maintenance dose. Allergic side effects were slightly but not significantly more often observed in patients without β -blockers as previously reported [23]. During VIT, 36 of these patients were reexposed to a sting by the responsible insect and the systemic reaction rate was very similar with and without β -blockers. All reactions were only mild (Table 2).

In one case report [18], a 48-year-old woman was on β -blockers for several years because of severe ventricular arrhythmia and dilative cardiomyopathy. She was also suffering from morbid obesity and hypertension. In the fall of 2001, she developed severe anaphylaxis with

Table 2 Safety and efficacy of β -blockers during venom immunotherapy

	Venom immunotherapy		Total (%)
	With β -blockers (%)	Without β -blockers (%)	
Side effects			
During dose increase	1/4 (25)	16/138 (11.6)	17 (12)
During maintenance	2/25 (8)	10/117 (8.5)	12 (8.5)
Result of reexposure			
Systemic allergic symptoms	1/7 (14.3)	4/29 (13.8)	5 (13.9)

Adapted from Mueller and Haeberli [18].

dyspnea, hypotension, and angioedema after a *Vespula* sting. A milder *Vespula* sting reaction with only urticaria and angioedema had occurred 4 years earlier. She was sent to the allergist and the allergy to *Vespula* venom was documented by skin tests and specific IgE. The allergist recommended immunotherapy and replacement of the β -blocker. The family practitioner did not remember why the patient had received the β -blocker and replaced it with a diuretic 2 weeks before VIT was started. The first injection was well tolerated. Fourteen minutes after the second injection she collapsed, became unconscious and the ECG showed ventricular fibrillation. Cardiac resuscitation started immediately and she was intubated and ventilated. Due to recurrent ventricular fibrillation she was defibrillated 12 times, the following asystolia was treated with a total of 17 intravenous injections of 1 mg epinephrine each. β -blockers were reinstituted. After 30 min the situation stabilized. The patient stayed unconscious on the ventilator and died 3 days later with severe hypoxic brain damage. The analysis of the clinical data showed the absence of any allergy-specific symptoms like urticaria, angioedema, or asthma. Serum tryptase tested 3 h after the start of the reaction and repeatedly thereafter remained in the low to normal range. Venom-specific IgE and IgG antibodies and tryptase did not change significantly compared with the values obtained before starting VIT. Was this anaphylaxis? This patient was definitely allergic and the allergen was applied before. Anaphylaxis can present with only cardiovascular symptoms, may occur at minimal dose and the lack of tryptase increase does not exclude anaphylaxis. Taking all these findings together, however, we think that this was rather a consequence of the withdrawal of the β -blockers shortly before the start of immunotherapy in a patient with severe dilative cardiomyopathy and ventricular arrhythmia.

We have to realize that in venom allergy, the risk of a severe or fatal event due to CVD is most often significantly higher than the risk of a fatal event due to a sting, both in the whole population and in most patients with CVD and venom allergy. A combination of β -blockers and VIT should be discussed with a cardiologist in heavily exposed patients with severe sting reactions and concurrent CHD, cardiac failure or ventricular arrhythmia. The β -blockers can be replaced safely in patients with hypertension, tremor or migraine. In

patients with CVD and a low resting risk, we recommend continuing the β -blockers and withholding VIT but also observing prevention measures carefully [18].

Emergency treatment of anaphylaxis may induce complications in patients with cardiovascular disease

While myocardial infarction and severe arrhythmia including ventricular fibrillation have been described during anaphylaxis before treatment, there are several observations of these symptoms following intravenous epinephrine injections.

In a further case report, a 56-year-old heavy smoker with diabetes was stung by a honeybee in his garden. After 5 min he felt generalized itching, retrosternal pain, then collapsed and lost consciousness. After 30 min at the local hospital he was conscious again, but hypotensive with dyspnea, urticaria and retrosternal pain. Intravenous treatment with volume substitution, epinephrine, anti-histamine and corticosteroids was started and he developed ventricular fibrillation. He was defibrillated five times and given lidocaine intravenously before stabilization. On the ECG acute inferior MI was diagnosed and confirmed by strongly elevated creatinine kinase. Most likely venom anaphylaxis induced myocardial ischemia in this patient with preexisting CHD due to heavy smoking and diabetes. The intravenous epinephrine may have favoured development of the ventricular fibrillation and MI. There are several published reports on patients with documented myocardial ischemia during anaphylaxis. Mean age is above 50 and preexisting CHD was ascertained in more than half. Acute MI occurred in five of the seven; reversible ischemia in two. Only four of seven patients had received epinephrine, three intravenously [15,24–26].

While epinephrine is the first-line medication for treatment of anaphylaxis, boluswise intravenous injection must be avoided because it may induce ventricular fibrillation and vasoconstriction. For emergency treatment it is therefore recommended to give epinephrine intramuscularly in the outside of the thigh [27]. The risk of cardiac side effects is minimized in this way. In the ICU, intravenous infusion with 5–17 μ g/min of epinephrine is recommended [2].

Conclusion

In patients with anaphylaxis, preexisting CVD, mastocytosis and elevated baseline serum tryptase are definite risk factors for severe, sometimes fatal, anaphylactic reactions or long-lasting morbidity due to MI or cerebrovascular infarction. Cardiac medications like β -blockers or angiotensin-converting enzyme inhibitors may increase the severity of anaphylactic reactions and make their treatment more difficult. These drugs are, however, most valuable for the therapy of life-threatening CVD, which is much more frequent than anaphylaxis. Before stopping β -blockers in patients with a history of anaphylaxis, the relative risk of either disease with and without them must be analyzed carefully.

Acknowledgements

Invited presentation to multidisciplinary research conference at Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland, USA, 27 April 2006; with introductory case presentation by David B.K. Golden MD.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 361).

- 1 Helbling A, Hurni T, Mueller UR, *et al.* Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004; 34:285–290.
- 2 Brown SGA. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 2005; 5: 359–364.
- 3 Fricker M, Helbling A, Schwartz L, Mueller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in 10 patients. *J Allergy Clin Immunol* 1997; 100:11–15.
- 4 Schwartz LB, Bradford T, Rouse C, *et al.* Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. *J Clin Immunol* 1994; 14:190–204.
- 5 Ludolph-Hauser D, Rueff F, Fries C, *et al.* Constitutively rised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to hymenoptera stings. *Lancet* 2001; 357:361–362.
- 6 Haeberli G, Brönnimann M, Hunziker T, Mueller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. *Clin Exp Allergy* 2003; 33:1216–1220.
- 7 Sonneck K, Florian S, Mullauer L, *et al.* Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol* 2007; 142:158–164.
- 8 Oude Elberink JN, de Monchy JG, Kors JW, *et al.* Fatal anaphylaxis after a yellow jacket sting, despite immunotherapy, in two patients with mastocytosis. *J Allergy Clin Immunol* 1997; 99:153–154.
- 9 Reimers A, Mueller UR. Fatal outcome of a *Vespa* sting in a patient with mastocytosis after immunotherapy with bee venom. *Allergy Clin Immunol Int* 2005; (Suppl 1):69–70.
- 10 Light WC. Insect sting fatality 9 years after venom treatment. *J Allergy Clin Immunol* 2001; 107:925–926.
- 11 Marone G, Betoraki A, Onorati AM, *et al.* The human heart as a shock organ in anaphylaxis. *Novartis Found Symp* 2004; 257:133–149.
- 12 Sasvary T, Müller U. Fatalities from insect stings in Switzerland 1977 to 1987. *Schweiz Med Wschr* 1994; 124:1887–1894.
- 13 Greenberger PA, Rotschkoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid disease. *Ann Allergy Asthma Immunol* 2007; 98:252–257.
- This analysis of 25 fatalities from anaphylaxis confirms the importance of cardiovascular and other comorbidities in fatal outcome.
- 14 Huber C, Hottinger S, Reimers A, Müller U. Anaphylaxis unmasking coronary heart disease. *Swiss Med Forum* 2005; 5:322–324.
- 15 Müller U, Stettler R, Hottinger S. Cardiac symptoms during anaphylaxis to hymenoptera stings. *J Allergy Clin Immunol* 1989; 83:230.
- 16 Wang CC, Chang SH, Chen CC, *et al.* Severe coronary artery spasm with anaphylactic shock cause by contrast medium: case reports. *Angiology* 2006; 57:225–229.
- 17 Jacobs RL, Rake G, Fournier D, *et al.* Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J Allergy Clin Immunol* 1981; 68:125–127.
- 18 Mueller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol* 2005; 115:606–610.
- 19 Tunon-de-Lara J, Villanueva P, Marcos M, Taytard A. ACE inhibitors and anaphylactic reactions during venom immunotherapy. *Lancet* 1992; 340:908.
- 20 TenBrook JA, Wolf MP, Hoffman SM, *et al.* Should beta-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis. *J Allergy Clin Immunol* 2004; 113:977–982.
- 21 Freemantle N, Cleland J, Young P, *et al.* Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318:1730–1737.
- 22 Foody JM, Farrell MH, Krumholz HM. Beta blocker therapy in heart failure: scientific review. *JAMA* 2002; 287:383–389.
- 23 Hepner MJ, Ownby DR, Anderson JA, *et al.* Risk of systemic reactions in patients taking beta-blockers receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990; 86:407–411.
- 24 Müller U. Cardiovascular disease and insect allergy. *Allergo J* 2005; 569–574.
- 25 Pumphrey RSH. Lessons for the management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144–1150.
- 26 Davidsen JR, Lambrechtsen J, Egstrup K. ST elevation myocardial infarction after therapeutic injection of adrenaline. *Ugeskr Laeger* 2006; 168:1137–1138.
- 27 Simons FER. First aid treatment of anaphylaxis to food: focus on epinephrine. *J Allergy Clin Immunol* 2004; 113:837–844.