Possible Link Between Apical Ballooning Syndrome During Anaphylaxis and Inappropriate Administration of Epinephrine

To the Editor: Manivannan et al[1] published a useful case of apical ballooning syndrome (ABS) after intravenous administration of epinephrine for anaphylaxis. The authors rightly underscored that high doses of intravenous epinephrine may induce ABS. However, specific concerns are warranted regarding some key points. Specifically, ABS occurring after anaphylaxis seems to be related to inappropriate use of epinephrine, including intravenous and intramuscular injections as well as high or low doses.

Five clinical cases have been reported for ABS after epinephrine administration for anaphylaxis (Table).[2-6] Han and Yeon[2] reported the first case, in which 0.2 mg of epinephrine was intravenously injected during moderate anaphylaxis. The authors considered that the midventricular hypokinesis was related to a cardiac manifestation of anaphylaxis. Cabaton et al[3] and Suk et al[5] reported ABS after perioperative anaphylaxis. Cabaton et al[3] showed that epinephrine, even when injected at low intravenous doses, may have been involved in the occurrence of ABS. In this case, the 2 last boluses of epinephrine (0.1 mg × 2) were injected after generalized cutaneous signs appeared (indicating hemodynamic restoration) and were immediately followed by ventricular fibrillation. Suk et al[5] reported ABS after a high dose (1 mg) of intravenous epinephrine associated with a norepinephrine infusion. The authors suggested that excessive catecholamine surges in response to anaphylaxis and/or to the administration of exogenous catecholamines may have played a role in the ABS occurrence. In the case published by Manivannan et al,[1] 2 intravenous doses of 0.5 mg of epinephrine were injected in the absence of cardiovascular disturbances. Hypotension occurring after the first bolus of epinephrine was related to an adverse cardiac response to epinephrine.

Zubrinich et al[4] and Litvinov et al[6] reported ABS after intramuscular injection of epinephrine. The former concluded that, given the mild clinical presentation, epinephrine (0.3 mg) should not have been used.[4] The latter confirmed a direct causal role for suprapharmacologic doses of exogenous epinephrine (5 mg) in the pathophysiology of ABS.[6]

The dangers of epinephrine administration outside the context of severe anaphylaxis have been highlighted by the reports of serious outcomes. Recently, pharmacologic and suprapharmacologic doses of epinephrine have been reported to induce one of the 3 ABS variants.[6] The catechol *O*-methyltransferase genotype and intense psychological stress may also influence predisposition to ABS.[1,6] Finally, all the reported patients[1-6] fulfilled Mayo Clinic criteria for ABS.[1]

TABLE. **Clinical Cases of ABS After Epinephrine Injection During Anaphylaxis**[a,b]

	Manivannan et al[1]	Han & Yeon[2]	Cabaton et al[3]	Zubrinich et al[4]	Suk et al[5]	Litvinov et al[6]
Sex	Female	Male	Female	Female	Female	Female
Age (y)	41	41	54	76	32	24
Allergen	Bee sting	Ioversol	Succinylcholine	Indomethacin	Cefotiam	Tomato
Clinical reaction	Itching, angioedema of the lips and tongue, dyspnea	Pruritus, wheezing, difficulty swallowing, hypotension	Cardiovascular collapse, bronchospasm	Angioedema of the lip, generalized urticaria	Cardiovascular collapse, bronchospasm	Scratchy throat, angioedema of the tongue
Grade of the reaction	2	2	3	1	3	1
Epinephrine dosage (mg)	0.5 + 0.5	0.2	0.1 + 0.1 + 0.1	0.3	1.0	5.0
Administration	IV	IV	IV	IM	IV	IM
Coronary risk factors	NA	NA	Diabetes mellitus	Hypertension	None	None
Electrocardiography	ST-segment elevation in leads I and aVL and ST-segment depression in leads III and aVF	ST-segment elevation in the inferolateral leads and ST-depression in V1-V2 leads	ST-segment elevation in inferior leads	Lateral T-wave inversion	ST-segment elevation in V2-V6 leads	ST-segment depression in V3-V6 and DII, DIII, and aVF
Troponin (peak) (ng/mL)	0.49	2.09	2.69	2.39	0.47	1.06
ABS variant	Inverted	Midventricular	Apical	Apical	Midventricular	Inverted
Coronary angiography	Normal	Normal	Normal	Normal	Normal	Normal
Plasma epinephrine level (pg/mL)	ND	ND	ND	ND	ND	146 (range, 22-110)[c]
Evolution	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable

[a] ABS = apical ballooning syndrome; IM = intramuscular; IV = intravenous; NA = not available; ND = not determined.
[b] SI conversion factors: To convert troponin values to µg/L, multiply by 1; to convert plasma epinephrine values to pmol/L, multiply by 5.459.
[c] Plasma epinephrine level measured 8 h after intramuscular epinephrine injection.

Thus, as suggested during perioperative anaphylaxis, treatment may be initiated according to a 4-step clinical grading scale.[7] Whereas grade 1 involves cutaneous-mucous signs in which epinephrine should never be injected, grade 2 corresponds to mild cutaneous-mucous features that may be associated with cardiovascular and/or respiratory signs for which titrated intravenous boluses (0.01-0.02 mg) of epinephrine may sometimes be necessary. The hallmark of grade 3 is cardiovascular collapse that may be associated with cutaneous-mucous signs and/or bronchospasm; titrated intravenous bolus administration of epinephrine (0.1-0.2 mg) is required and should be renewed if necessary. Finally, grade 4 is cardiac arrest that requires high doses of epinephrine, as warranted during cardiopulmonary resuscitation.

The important issue is not the route of epinephrine administration, but its appropriate use during anaphylaxis. Consequently, these cases emphasize the need for careful patient selection and titration of epinephrine when the clinical situation dictates its use.

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To the Editor: We read with interest the letter by Manivannan et al describing a patient with ABS due to intravenous epinephrine injection given for anaphylactic reaction after a bee sting. We would like to broaden the differential diagnosis in a scenario such as this.

Acute coronary syndrome during an anaphylactic reaction, especially in those who receive epinephrine, can occur for a variety of reasons, including (1) ABS or stress cardiomyopathy, (2) allergic myocardial infarction (ie, Kounis syndrome [KS]), and (3) hypersensitive myocarditis (HM).

Apical ballooning syndrome affects mainly women during emotional stress and is characterized by the presence of normal coronary arteries and reversible apical ventricular dysfunction. In this syndrome, it is thought that myocardial stunning occurs as a result of high levels of circulating (ie, endogenous) catecholamines. Epinephrine triggers a switch in intracellular signal trafficking in ventricular cardiomyocytes from Gs protein to Gi protein signaling via the β_2-adrenoceptor, which in turn protects against the proapoptotic effects of the intense activation of β_1-adrenoceptors. However, this change also causes a negative inotropic effect. Because β-adrenoceptor density is greatest at the apical myocardium, this effect is greatest in that region. Other mechanisms have also been implicated.

It is not surprising that a supratherapeutic dose of intravenous epinephrine could produce a similar phenomenon, as postulated by Manivannan et al. However, this is not the first reported case of ABS due to the administration of epinephrine, as the authors claim. Six cases of stress cardiomyopathy due to epinephrine and 3 due to dobutamine were recently described by Abraham et al.[1] The dose of epinephrine ranged from a minimum of 1 mg to 40 mg. Some recent reports have even linked this syndrome to anaphylactic reaction.[2]

However, other possible etiologies of ABS after a bee sting must also be entertained. The coincidental occurrence of chest pain, electrocardiographic changes, and elevated troponin levels during anaphylactic reaction to bee sting has previously been described as KS by various authors.[3] During hypersensitive reactions, sudden release of histamine and other inflammatory mediators from mast cells, macrophages, and T lymphocytes has been postulated to lead to coronary vasospasm and hence to acute coronary syndrome. A myocardial biopsy will reveal a normal myocardium. However, KS may occur in association with ABS because various cytokines have been implicated in the causation of ABS. In this context, exogenous administration of epinephrine is not required for the development of ABS. A case report of KS with ABS has been published.[4]

Hypersensitive reactions may also involve the heart by causing HM. In patients with HM, the myocardial biopsy will reveal the presence of eosinophils, atypical lymphocytes, and giant cells. Clinically, it is difficult to differentiate HM from KS because both present with signs and symptoms of acute coronary syndrome and for both coronary angiography reveals normal coronary arteries.

The patient described by Manivannan et al had ventricular dysfunction typical of ABS in the presence of an anaphylactic reaction. Hence, we propose that she had KS complicated by ABS due to epinephrine and release of cytokines from the allergic reaction to the bee sting. As such, exogenous epinephrine administration need not be credited as the sole origin of ABS in this patient.

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In reply: We thank Dewachter and Mouton-Faivre for their interest in our letter to the editor regarding ABS after administration of intravenous epinephrine during an anaphylactic reaction. They have raised an interesting observation regarding the association of ABS in anaphylaxis with use of epinephrine irrespective of administration route or dose. We also thank Kumar and Qureshi for their interest in our letter. They have discussed the importance of considering other differential diagnoses, including KS.

We agree with Dewachter and Mouton-Faivre that signs and symptoms are critical in deciding management steps in a patient with anaphylaxis. Of the 6 case reports they cite, only 2 patients had ABS after administration of intramuscular epinephrine. The report by Litvinov et al[1] describes a dose of epinephrine (5 mg) much higher than the recommended intramuscular dose (maximum initial dose in adults, 0.3-0.5 mg of adrenaline) given in a patient who had only mucocutaneous manifestations. Because epinephrine has a narrow therapeutic window, the need for appropriate dosing cannot be overemphasized.[2] In their report of a case of ABS after intramuscular injection of epinephrine, Zubrinich et al[3] concluded that epinephrine (0.3 mg) should not have been administered because the clinical presentation was mild. Epinephrine is not indicated if only the skin and mucosa are involved. However, many severe reactions start as mild reactions followed by rapid deterioration.[2] The benefits of appropriately dosed epinephrine may outweigh the risks in certain situations. Hence, it is essential to use intramuscular epinephrine early, especially if the anaphylactic reaction occurs in a nonmedical setting and is in response to a known allergen.[4]

Much of the controversy surrounding administration of epinephrine in anaphylaxis is due to the lack of universally accepted clinical criteria for the diagnosis of anaphylaxis. Dewachter and Mouton-Faivre have described a 4-step scale[5] to guide therapy. We use the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria.[6] According to these criteria, anaphylaxis is likely when any 2 organ systems are involved after allergen exposure. It could be diagnosed even in the absence of cardiac and respiratory system involvement, and consequently epinephrine may still be indicated.

We agree with Kumar and Qureshi that this patient could have had ABS secondary to the anaphylactic reaction, rather than the intravenous epinephrine. The allergic reaction may have caused coronary artery spasm, as described by Kounis.[7] However, this seems less likely given the sudden onset of cardiovascular symptoms in association with the administration of the intravenous epinephrine. Moreover, coronary artery spasm and plaque rupture, the proposed mechanisms for KS, are not typically seen in ABS.

In conclusion, we concur with Dewachter and Mouton-Faivre that appropriate use of epinephrine in anaphylaxis is of utmost importance. However, we think that intravenous epinephrine should be reserved for patients with hypotension unresponsive to intramuscular epinephrine and fluid resuscitation, cardiovascular collapse, or cardiac arrest. This is primarily based on the recognition of the increased risk of cardiovascular complications with intravenous epinephrine compared with the intramuscular route.[8,9]

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Radiation Therapy for Gynecomastia

To the Editor: We read with interest the excellent review by Johnson and Murad[1] on the pathophysiology, evaluation, and management of gynecomastia. Nevertheless, we want to point out another well-established management technique that was not mentioned in the article: radiation therapy.

Radiation therapy is effective for the prevention and treatment of gynecomastia, particularly caused by androgen abla-

tion for prostate cancer.[2] Radiation therapy is more effective if given prophylactically before administration of hormone therapy. Radiation has been used with some success in managing painful gynecomastia.

In 2003, Widmark et al[3] conducted the largest randomized trial on use of radiation therapy for prevention of gynecomastia (n=253) and found a reduction of gynecomastia rates from 71% to 28% when radiation therapy was given. For the treatment of existing gynecomastia, radiation therapy resulted in improvement or resolution of gynecomastia in 33% of treated patients, with 39% experiencing improvement or resolution of breast pain.[4]

Doses have ranged from 12 Gy in 2 fractions to 20 Gy in 5 fractions,[4] all of which are well tolerated with mild skin erythema being the main adverse effect. It is believed that the potential risk of radiation-induced skin or breast cancer is low, although long-term data are minimal.[5]

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In reply: We appreciate the comments by Luh and Eng regarding the use of radiation therapy for the prevention and treatment of gynecomastia and mastalgia. Our article and most of the literature on gynecomastia do not include radiation therapy in the management of gynecomastia because it is very infrequently used in North America and is only relevant in patients with prostate cancer who are receiving androgen-suppressive therapy, a small subset of the patients with gynecomastia that the review was meant to address.

At Mayo Clinic and at most practices in North America, when androgen-suppressive therapy for prostate cancer is indicated, the primary approach is the use of a luteinizing hormone–releasing hormone antagonist (eg, leuprolide or goserelin). Luteinizing hormone–releasing hormone antagonists do not induce gynecomastia or mastalgia, although weight gain may painlessly increase the volume of adipose tissue in the breast. If a nonsteroidal antiandrogen such as bicalutamide (Casodex) is used, it is generally at the relatively low dose of 50 mg/d and in combination with a luteinizing hormone–releasing hormone antagonist for a 4- to 6-month period. The development of gynecomastia and/or mastalgia correlates with both the dose and the duration of bicalutamide therapy and is less common with this approach. In fact, radiation therapy is used to treat one or fewer men annually at Mayo Clinic in Rochester, MN, for this indication.

In Europe, prostate cancer is increasingly treated with nonsteroidal antiandrogen monotherapy,[1] typically at a high dosage of 150 mg/d. With this high-dose regimen, gynecomastia and/or mastalgia occur with high frequency. Thus, radiation therapy for prevention or treatment of these symptoms is reasonable. Although this approach is sometimes adopted in the United States,[2,3] it is more common in Europe, where the largest randomized trial and much of the literature originate.[4]

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CORRECTIONS

Incorrect heading: In the editorial by Krinsley and Keegan entitled "Hypoglycemia in the Critically Ill: How Low Is Too Low?" that was published in the March 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(3):215-216), the word "Supplement" was added inadvertently underneath the title EDITORIAL. The heading should read as follows: **EDITORIAL**.

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Incorrect words: In the article by Demaerschalk et al entitled "Stroke Telemedicine," which was published in the January 2009 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2009;84(1):53-64), some words were incorrect in Table 1. In Table 1 on page 54, under the column "Specialists On Call[f] (Westlake Village, CA)," 3 uses of the word "No" should have been "Yes." The corrected Table 1 is shown here.

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Incorrect unit: In the article by Sieber et al entitled "Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair," which was published in the January 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(1):18-26), a unit in Table 2 is incorrect. In Table 2 on page 22, under the column "Category," the dose of midazolam should read as follows: Midazolam dose, mean ± SD (**μg**/kg).

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TABLE 1. **Comparison of Telemedicine Systems**

Factor	BF Technologies[a] (San Diego, CA)	Polycom[b] (Pleasanton, CA)	Tandberg[c] (New York, NY)	InTouch Health[d] (Santa Barbara, CA)	Remote Evaluation of Acute Ischemic Stroke Call (REACH)[e] (Augusta, GA)	Specialists On Call[f] (Westlake Village, CA)
Product offering	AccessVideo Telemedicine	VSX/HDX Practitioner Cart System	Tandberg Intern MXP	RP-7 Remote Presence System (integrates robotic platform audiovisual)	Web-based tools that integrate audiovisual communication into clinical practice	Third-party provision of physicians on call 24 h/d, 7 d/wk via video-conference software
Hardware provided	Yes	Yes	Yes	Yes	No	**Yes**
Software	Yes	Yes	Yes	Yes	No	No
Web-based	No	No	No	No	Yes	Yes
Annual cost (US $)	~24,000	~25,000	~25,000	Varies	On the basis of monthly stroke volume	On the basis of monthly stroke volume
Maintenance fee	Yes	Yes	Yes	Yes	No	**Yes**
Technology support 24 h/d, 7 d/wk	Telephone	Telephone and online	Telephone and online	Continuously monitored	Telephone and online	Telephone and online request
Radiology transmission	Yes	Yes	Yes	Yes	No	**Yes**

[a] Web site: http://www.bf-technologies.com/.
[b] Web site: http://www.polycom.com/usa/en/solutions/industry_solutions/healthcare/tele_medicine.html/.
[c] Web site: http://www.tandberg,com/ind_focus/healthcare/hc/_solutions.jsp.
[d] Web site: http://www.intouchhealth.com/products_rp7robot.html.
[e] Web site: http://www.reachcall.com/company.html.
[f] Web site: http://.brainsavingtech.com.