Pulmonary Embolism Diagnosed by Contrast-enhanced Virtopsy

To the Editor:

An 83-year-old patient, treated for hypertension, diabetes mellitus, hypothyroidism, atrial fibrillation, and coronary artery disease with a fairly recent aortic bioprosthesis, was transferred to the emergency room because of recent-onset nonfebrile dyspnea. Clinical examination and chest X-rays performed on admission suggested left inferior lobe pneumonia complicated by congestive heart failure. Intravenous antibiotics, heparin, and diuretics were started, and noninvasive ventilation was initiated with a good initial response.

Ten days later, respiratory status had improved, but the patient complained of left leg pain. Lower extremity compression ultrasound disclosed isolated thrombosis of the left superficial femoral vein. During ultrasound examination, asystolic cardiac arrest occurred. External cardiac massage was immediately started, the trachea was intubated and intravenous epinephrine was administered. Despite ongoing effective anticoagulation, pulmonary embolism was considered, and intravenous thrombolysis was administered. After 30 minutes of resuscitation, there was no return to spontaneous cardiac activity, and death was declared.

It was difficult to affirm cardiac arrest related to pulmonary embolism in the absence of direct visualization of a thrombus in the pulmonary arteries, heart cavities, or deep femoral vein. To confirm the hypothesized pulmonary embolism, and after obtaining a relative's informed consent, we performed a postmortem contrast-enhanced computed tomography (CT) scan 15 minutes after the patient's death. A first imaging acquisition was performed without contrast media. Immediately after peripheral intravenous administration of contrast media (2 ml/kg), three rounds of 10 chest compressions were performed to restore partial blood flow, each of which was followed by image acquisition. Progression of contrast media from the right atrium to the right ventricle, and finally to the pulmonary artery circulation, was checked on consecutive imaging sequences. When contrast media reached pulmonary arteries, compression cycles were stopped. After the third cycle of 10 chest compressions, pulmonary embolism was confirmed, associated with left lung pneumonia (Figure 1).

Invasive "body-opening" autopsy is the traditional method of postmortem investigation in humans, but has been performed less and less frequently during the last decades, principally because of difficulties obtaining consent from relatives, resource shortage, and cost (1). Information provided by autopsies is of importance to explain unexpected deaths and improve medical knowledge and practice. Virtual autopsy ("virtopsy"), using imaging, has been developed for several years and seems to be complementary to and even better than conventional autopsy in making some diagnoses such as path of bullet, air embolism, pneumothoraces, or bone fractures (2). Moreover, its noninvasive character may facilitate relatives' acceptance. Nevertheless, virtopsy is generally performed without contrast media owing to the absence of blood flow. In the cohort study reported by Wichmann and coworkers (3), results of virtopsy were sometimes limited, especially when pulmonary embolism was suspected, whereas this disease accounts for up to 15% of diagnoses finally identified during conventional autopsies (4). For postmortem diagnosis of coronary artery disease, several authors proposed to use arterial and/or venous sequences, with contrast media injected through femoral arterial and venous cannulas (5). However, this method is rather cumbersome to implement and not routinely feasible. CT scan with peripherally injected contrast media associated with chest compression could provide vascular opacification in a more simple way.

In the present case, limited chest compression was sufficient to restore blood flow and allowed pulmonary artery imaging. This suggests that postmortem diagnosis of pulmonary embolism is possible using CT scan with peripherally injected contrast media. ■

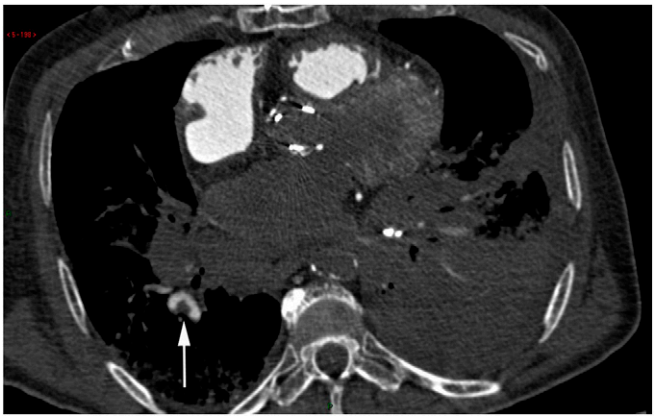

Figure 1. Computed tomographic image of the chest with contrast media injected. *Arrow* indicates the location of pulmonary embolism.

Author Contributions: M.A., N.B., E.M., and L.A. were in charge of the patient; M.A. wrote the report; M.A., N.B., E.M., and L.A. reviewed the final draft.

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The Intrinsic Bias of Generalizations*

To the Editor:

The article by Short and colleagues in the June 15, 2013, issue of the *Journal* demonstrates that propranolol is not effective in treating a subset of individuals with asthma (1). This study and the accompanying editorial from Kazani and Israel (2) express concern about the validity of the hypothesis that certain β-blockers may be useful in chronic asthma therapy. The Editorial concludes: "For now, in the case of β blockers in asthma, what doesn't kill you does not appear to make you stronger" (2). However, both publications treat "β blockers" as a class, or at best recognizing only inverse agonists and antagonists. This simplification does not acknowledge the complexities of β_2-adrenoceptor (β_2AR) signaling (3). Clinical studies exemplified this complexity when only certain β-blockers were shown to be beneficial in the chronic treatment of congestive heart failure (CHF).

The β_2AR signals via at least two distinct pathways: the canonical Gs-cAMP pathway, and signaling via β-arrestin and/or extracellular signal–regulated kinases (ERK) activation (4). The endogenous ligand for the β_2AR, epinephrine, and β_2AR agonists used in asthma therapy like albuterol, salmeterol, and formoterol, activate both pathways (5). However, it is now known some ligands preferentially activate one pathway over the other. These ligands are termed "biased ligands." Further, certain β-blockers can shut down one pathway while activating the alternate one, and β_2AR ligand bias has been shown for β-blockers as well as for β_2AR agonists. Indeed, Lefkowitz and colleagues have proposed that it is carvedilol's ability to activate β-arrestin signaling while shutting down the canonical Gs-cAMP pathway that results in the drug's superior efficacy in the treatment of CHF (6). However, as in CHF, differential β_2AR signaling appears to be important in asthma. Thus, several *in vitro* and *in vivo* studies suggest that β-arrestin/ERK signaling is detrimental in asthma (3, 7). This includes data showing that carvedilol (but not nadolol) increased methacholine sensitivity in the original 2004 murine studies investigating the hypothesis of "chronic use of β-blockers in asthma" (8). Thus the signaling signature produced by carvedilol, the gold standard in the treatment of heart failure, is not likely to be beneficial in asthma.

The data regarding dual β_2AR signaling pathways and biased ligands predicts that nadolol and propranolol would have different effects in asthma treatment. Specifically, various studies have shown that propranolol is a biased ligand similar to carvedilol; it activates β-arrestin and/or ERK signaling while shutting down the canonical pathway (3, 6). These studies also showed that nadolol differs from carvedilol and propranolol in that it shuts down β-arrestin/ERK (3, 6). Thus, one would not expect that studies showing benefit using nadolol would be repeated using propranolol. The article by Short and coworkers, and the Editorial by Kazani and Israel, provide some suggestions for alternate explanations of the study with propranolol, but the implied take-home message (as evidenced by the title and concluding sentence of the Editorial) is that the use of β-blockers in asthma is unlikely to be of benefit. This is unfortunate, because the negative outcome using propranolol is exactly what current receptor knowledge would predict. In a very real sense, the study by Short and colleagues provides some of the best clinical data supporting current hypotheses regarding β_2AR signaling and biased ligands.

The stunning success of carvedilol in CHF might never have been realized if the ineffectiveness of bucindolol had further biased the field against β-blockers by publishing first. There is currently an active multi-center, double-blind, placebo-controlled clinical trial using nadolol in subjects with mild asthma, funded by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (ClinicalTrials.gov Identifier: NCT01804218). Hopefully, like the current report, those results will also add compelling data to support or negate the hypothesis that nadolol, but not propranolol, could be of benefit in asthma therapy. ■

*The title is based on sections from Malcolm Gladwell's book, *What the Dog Saw*, about common, incorrect generalizations, and their consequences.

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