J R Coll Physicians Edinb 2019; 49: 204–6 | doi: 10.4997/JRCPE.2019.307 BRIEF RESEARCH PAPER

Incidence of acute bronchospasm during systemic adenosine administration for coronary angiography

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Abstract

Background Adenosine is frequently used during coronary angiography to induce hyperaemia and allow operators to perform quantitative measurements of lesion severity. Acute bronchospasm is a recognised side effect relating to the activation of 'off target' A2B receptors. The true incidence of severe bronchospasm relating to adenosine administration is not known.

Methods Using an electronic patient database, we analysed 100,253 consecutive coronary angiograms over almost 19 years. Fractional flow reserve (FFR) was measured under systemic adenosine in 9,440 cases.

Results Adenosine-related bronchospasm was reported in only five cases (0.05%). One case resulted in a life-threatening respiratory arrest.

Conclusions This study reveals the incidence of acute bronchospasm during FFR testing to be extremely low. Although rare, these reactions can be severe and are not simply limited to patients with brittle airways disease. Physicians should be aware of the utility of bolus intravenous aminophylline providing targeted therapy to reverse and treat adenosine-related bronchospasm.

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Introduction

Cardiologists cannot solely rely on the angiographic appearance of epicardial coronary artery stenosis when evaluating patients with myocardial ischaemia. The emerging field of coronary physiology allows operators to perform quantitative measurements of lesion severity and are evidence based to guide the need for coronary intervention. Pressure-sensitive guidewires may be inserted through a coronary stenosis and ratio of distal coronary pressure (Pd) divided by the aortic pressure (Pa) calculated during hyperaemia. This ratio is known as fractional flow reserve (FFR). The ischaemic threshold of ≤0.80 implies that ≤80% of the maximum achievable flow is available during peak metabolic demand.[1] For practical purposes, maximal hyperaemia is typically induced using systemic administration of adenosine (rather than exercise). Adenosine causes nonselective activation of four different receptors, including A2A-mediated vasodilation of the coronary microcirculation and 'off target' A2B receptor-mediated mast cell degranulation and bronchial constriction.[2] The risk of severe bronchospasm even amongst patients with established airways disease appears to be exceedingly rare, although the true incidence in contemporary daily cardiology practice is not known.

A recent near life-threatening respiratory arrest during intravenous adenosine administration for FFR at our centre prompted a systematic review of over 100,000 invasive coronary angiograms performed over almost two decades. The aim of this study was to identify the incidence and outcomes following severe acute bronchospasm during FFR measurement.

Methods

Using an electronic patient database, we analysed 100,253 consecutive coronary angiograms performed at the Glasgow Royal Infirmary, Western Infirmary Glasgow, Stobhill Hospital and the Golden Jubilee National Hospital over almost 19 years between January 2000 and November 2018. FFR was measured under systemic adenosine in 9,440 cases. Our local protocol administers adenosine at a rate of 0.84 mg/kg/min through a large peripheral

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Table 1 Cases of acute bronchospasm identified from our retrospective review

Case	Age (years)	Indication	Route	Respiratory diagnosis	Bronchospasm severity	Treatment	Intubation required	Outcome
1	78	Angina	IV	Asthma – mild	Mild	Nebulised bronchodilator	No	Procedure aborted Overnight admission
2	60	ACS	IV	COPD – moderate	Moderate	Nebulised bronchodilator	No	Procedure aborted 4-day admission
3	63	Angina	IV	COPD – severe	Severe	Nebulised bronchodilator	No	Procedure aborted Overnight admission
4	51	Angina	IV	COPD – mild	Mild	Nebulised bronchodilator	No	Procedure aborted Overnight admission
5	68	Angina	IV	COPD – moderate	Life-threatening respiratory arrest	IV steroids/ magnesium sulphate (2 g, 8 mmol)/ nebulised bronchodilator	No	Procedure aborted 2-day admission

ACS: acute coronary syndrome; COPD: chronic obstructive pulmonary disease; IV, intravenous

vein. We defined acute severe bronchospasm as acute dyspnoea and wheeze temporally related (within 5 min) to systemic adenosine administration with features of respiratory distress.[3]

Results

Adenosine-related bronchospasm was reported in only five cases (0.05%). These cases are summarised in Table 1.

Discussion

This is a remarkably low number of cases given the high patient volume; however, our results are comparable to other published studies. The largest study to date on the safety profile of adenosine infusion is the Adenoscan Multicenter Trial Registry. It assessed 9,256 consecutive patients given adenosine infusions in the context of radionucleotide imaging. Although dyspnoea was reported in 3,260 (35.2%) cases, only 12 (0.13%) patients were objectively found to have acute bronchospasm.[4] The only large randomised controlled trial to address the incidence of FFR-related bronchospasm within their study has been DEFINE-FLAIR (n = 1,250 in the FFR arm). DEFINE-FLAIR combined procedural ventricular arrhythmia and bronchospasm into a single outcome with eight (0.64%) such episodes reported in the FFR group.[5]

In our study, none of the identified cases of bronchospasm resulted in patient death and no patients required intubation or mechanical ventilation. All five patients were alive at the time of analysis with a mean follow up of 4.91 years.

Interestingly, most bronchospasm cases had a background of chronic obstructive pulmonary disease (COPD) rather than asthma. Bronchospasm was also not limited to those with severe airways disease, which raises the suggestion of an idiosyncratic reaction. Unfortunately, we have no practical method to investigate the COPD/asthma status of our denominator group – it is therefore possible that operators are actively avoiding performing FFR on patients with the most severe airway disease, resulting in a degree of selection bias.

All physicians who administer systemic adenosine should be familiar with the suggested treatment for adenosine-related bronchospasm: aminophylline. It is a competitive, nonselective adenosine receptor antagonist with a fast onset of action in its intravenous formulation. It is routinely used to reverse the adverse effects of adenosine, regadenoson and dipyridamole during nuclear stress imaging. The suggested dose of aminophylline for the reversal of the side effects of adenosine is an intravenous 100 mg bolus given over 30–60 s.[6]

In conclusion, adenosine is a widely used medication in modern cardiology – both for inducing hyperaemia and in the treatment of supraventricular tachycardias. This study of systemic adenosine administration in ~10,000 patients reveals the incidence of acute bronchospasm during FFR testing to be extremely low (0.05%). We hope to provide a reminder that although rare, these reactions can be severe and are not simply limited to patients with brittle airways disease. Physicians should be aware of the utility of bolus intravenous aminophylline providing targeted therapy to reverse and treat adenosine-related bronchospasm. Availability of intravenous aminophylline should be an important consideration for all centres using this drug for induction of hyperaemia.

References

1 Pijls NH, De Bruyne B, Peels K et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; 334: 1703–8.
2 Sheth S, Brito R, Mukherjea D et al. Adenosine receptors: expression, function and regulation. *Int J Mol Sci* 2014; 15: 2024–52.
3 Schatz M, Kazzi AA, Brenner B et al. Introduction. *Proc Am Thorac Soc* 2009; 6: 353–6.
4 Cerqueira MD, Verani MS, Schwaiger M et al. Safety profile of adenosine stress perfusion imaging: results from the adenoscan multicenter trial registry. *J Am Coll Cardiol* 1994; 23: 384–9.
5 Davies JE, Sen S, Dehbi H-M et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017; 376: 1824–34.
6 Doran JA, Sajjad W, Schneider MD et al. Aminophylline and caffeine for reversal of adverse symptoms associated with regadenoson SPECT MPI. *J Nucl Cardiol* 2017; 24: 1062–70.