International Journal of Cardiology 202 (2016) 305–310

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Safety of guidewire-based measurement of fractional flow reserve and the index of microvascular resistance using intravenous adenosine in patients with acute or recent myocardial infarction

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ARTICLE INFO

Article history:
Received 19 June 2015
Received in revised form 27 July 2015
Accepted 14 September 2015
Available online 18 September 2015

Keywords:
Adenosine
ST-elevation myocardial infarction (STEMI)
Non ST-elevation myocardial infarction (NSTEMI)
Percutaneous coronary intervention (PCI)
Blood pressure (BP)
Heart rate (HR)

ABSTRACT

Aims: Coronary guidewire-based diagnostic assessments with hyperemia may cause iatrogenic complications. We assessed the safety of guidewire-based measurement of coronary physiology, using intravenous adenosine, in patients with an acute coronary syndrome.

Methods: We prospectively enrolled invasively managed STEMI and NSTEMI patients in two simultaneously conducted studies in 6 centers (NCT01764334; NCT02072850). All of the participants underwent a diagnostic coronary guidewire study using intravenous adenosine (140 μg/kg/min) infusion for 1–2 min. The patients were prospectively assessed for the occurrence of serious adverse events (SAEs) and symptoms and invasively measured hemodynamics were also recorded.

Results: 648 patients (n = 298 STEMI patients in 1 hospital; mean time to reperfusion 253 min; n = 350 NSTEMI in 6 hospitals; median time to angiography from index chest pain episode 3 (2, 5) days) were included between March 2011 and May 2013. Two NSTEMI patients (0.3% overall) experienced a coronary dissection related to the guidewire. No guidewire dissections occurred in the STEMI patients. Chest symptoms were reported in the majority (86%) of patient's symptoms during the adenosine infusion. No serious adverse events occurred during infusion of adenosine and all of the symptoms resolved after the infusion ceased.

Conclusions: In this multicenter analysis, guidewire-based measurement of FFR and IMR using intravenous adenosine was safe in patients following STEMI or NSTEMI. Self-limiting symptoms were common but not associated with serious adverse events. Finally, coronary dissection in STEMI and NSTEMI patients was noted to be a rare phenomenon.

1. Introduction

Coronary guidewire-based sensors can be used in the cardiac catheterization laboratory to provide functional information on coronary artery disease severity and microvascular function. The myocardial fractional flow reserve (FFR) assesses the physiological significance of a coronary stenosis and is expressed as the ratio of maximal blood flow in a stenotic artery to maximal flow if theoretically the artery was unobstructed. FFR-guided management is evidence-based in patients with stable coronary artery disease (DEFER [1], FAME [2], FAME-2 [3]) and has emerging clinical utility for measurement of non-infarct artery disease in patients with recent or acute myocardial infarction (MI) [4,5]. The index of microvascular resistance (IMR) measured in the culprit coronary artery has prognostic importance in patients with acute ST-elevation myocardial infarction (STEMI) [6,7]. However since FFR and IMR measurements involve pharmacological hyperemia and guidewire instrumentation, there are theoretical risks of serious adverse events (SAEs), including ventricular arrhythmias with intravenous adenosine and coronary dissection (both ~0.5% incidence) [8].

Intravenous adenosine induces hyperemia through interactions with A2A receptors. However, due to the ubiquitous expression of adenosine receptors, adenosine is also associated with unwanted off-target side-effects. For example, interaction with bronchial A2B receptors can lead to mast cell degranulation and bronchoconstriction [9]. Furthermore,

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http://dx.doi.org/10.1016/j.ijcard.2015.09.014

activation of cardiac A1 receptors has a myocardial depressant effect with negative chronotropic and dromotropic effects [10]. It is these unwanted effects of adenosine that have motivated researchers to find other drugs for initiation of hyperemia or develop nonhyperemic indices of stenosis assessment in the catheter laboratory [11,12].

Intracoronary adenosine may also be used therapeutically for the treatment of no-reflow in STEMI [13,14], and the role of FFR-guided PCI in STEMI patients with multivessel coronary disease [15] is currently being evaluated in the COMPARE-ACUTE (NCT01399736), COMPLETE (NCT01740479) and PRIMULTI (NCT01960933) clinical trials.

In November 2013 the United States (US) Food and Drug Administration (FDA) issued a safety announcement on the risk of myocardial infarction (MI) and death in patients receiving Adenoscan (adenosine) for stress testing [16] (Supplementary File). This announcement followed from reports in the FDA Adverse Event Reporting System (FAERS) and medical literature of serious adverse events (SAEs) from 1995 to 2013, including 6 cases of MI and 27 cases of death following adenosine administration (typically within 6 h) [16].

We aimed to prospectively assess the safety of guidewire based measurement of coronary physiology using intravenous adenosine amongst patients with acute or recent myocardial infarction (MI). Based on our prior experience with intravenous adenosine in this setting [6,7,17,18], we hypothesized that intravenous adenosine would be safe and well tolerated [19].

2. Methods

2.1. Study population

We simultaneously conducted two prospective studies involving assessments of coronary physiology in patients with acute or recent MI. The first was a study of the natural history of coronary microvascular function in patients with acute STEMI undergoing emergency PCI (the BHF MR-MI study, NCT02072850) [20]. Two hundred and ninety-eight STEMI patients were enrolled acutely and had IMR measured invasively in the culprit coronary artery with a diagnostic coronary guidewire (PressureWire Certus™, St Jude Medical) during primary or rescue PCI. The protocol did not involve FFR or IMR measurements in the non-infarct arteries. The enrolment period was March 2011–November 2012. Patients diagnosed with an acute STEMI [21] and who were undergoing primary or rescue PCI were eligible to participate. In the second study, three hundred and fifty NSTEMI patients were enrolled in the BHF FAMOUS-NSTEMI study (NCT01764334) [4,5]. Six hospitals in the United Kingdom participated (3 academic and 3 non-academic regional hospitals). The patients in this study underwent urgent invasive management and had an FFR measurement in one or more coronary arteries with at least a single coronary stenosis ≥ 30% severity of the reference vessel diameter by visual assessment. The patients with NSTEMI were enrolled during urgent care and the median time to invasive angiography was 3 days (Table 1) [5].

The exclusion criteria for administration of intravenous adenosine included evidence of 2nd or 3rd degree heart block on the ECG, long QT syndrome, cardiogenic shock, or a history of asthma concurrently treated with bronchodilators [22]. The exclusion criteria for both studies are provided in Supplementary Tables 1 and 2. The study was approved by the UK National Research Ethics Service and all participants provided written informed consent.

2.2. Catheter laboratory management

The clinical and catheter laboratory management followed contemporary guidelines for STEMI [21] and NSTEMI [21,23].

2.3. Measurement of FFR and IMR

In patients with STEMI, infarct artery microvascular function (IMR) was measured at the end of the primary or rescue PCI (Fig. 1). Thus we initially opted for a conventional workhorse wire while using a pressure wire at the end of the procedure. In patients with NSTEMI, FFR (and IMR) was measured at the beginning of the diagnostic procedure in all participants. Additionally, the pressure wire was used to perform PCI in most NSTEMI patients. FFR and IMR were measured using a temperature and pressure sensitive guide wire (PressureWire Certus™ St Jude Medical, Uppsala, Sweden). The guidewire was calibrated outside the body, equalized with aortic pressure at the ostium of the guide catheter, and then advanced to the distal third of the culprit artery [6,7,17,18]. Intracoronary nitrate (200 μg) was administered to minimize coronary artery tone and maintain coronary volume. Intravenous adenosine was administered at a rate of 140 μg/kg/min via a large peripheral vein for 1–2 min (Supplementary Table 3).

The patient's response to adenosine administration was a pre-defined safety outcome [20]. Aortic and distal coronary pressures were recorded invasively before and during adenosine administration. In addition, patients' symptoms and heart rate during the adenosine infusion were also prospectively documented using a study proforma. All SAEs in study participants were prospectively documented by clinical and research staff after the patient was enrolled in the study in line with the trial protocol. All adverse events were recorded in the clinical report form (CRF). SAEs were notified to the Sponsor of the studies for pharmacovigilance and assessed, reported, analyzed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) [24].

An SAE was defined as an event that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is otherwise considered medically significant by the investigator.

Major adverse cardiac events (MACE), were defined as the occurrence of death, myocardial infarction, or hospitalization for heart failure [25]. In the STEMI study, source data for all of the SAE and MACE were assessed by a cardiologist (A.M.) who was independent of the research team. This cardiologist was blinded to all of the other clinical data [20]. In the NSTEMI study, source clinical data for all SAEs of suspected cardiovascular origin and all deaths were reviewed by an independent clinical event committee blinded to treatment group assignment (FFR-guided group or angiography guided group) [4,5]. The CEC also assessed the angiograms of SAE attributed to procedure-related complications.

Table 1
Clinical characteristics of the study participants on admission.

Characteristics		STEMI patients n = 298	NSTEMI patients n = 350
Clinical			
Age, years		59.4	62.0
Male sex, n (%)		216 (72)	260 (74)
BMI (kg/m^2)		28.7	29 (5)
History			
Hypertension, n (%)		95 (32)	159 (45)
Current smoking, n (%)		184 (62)	143 (41)
Hypercholesterolemia, n (%)		81 (27)	127 (36)
Diabetes mellitus [‡], n (%)		32 (11)	52 (15)
Previous myocardial infarction, n (%)		20 (7)	46 (13)
Previous PCI, n (%)		16 (5)	38 (11)
Presenting characteristics			
Heart rate, bpm		80 (44)	74 (16)
Systolic blood pressure, mm Hg		135 (25)	141 (27)
Diastolic blood pressure, mm Hg		79 (14)	81 (17)
Time from symptom onset to reperfusion, min		253	–
Time from index episode of myocardial ischemia to invasive angiogram, days		–	3 (2, 5)
Ventricular tachycardia or fibrillation [†], n (%)		20 (7)	0 (0)
Heart failure, Killip class at presentation, n (%)	I	212 (71)	308 (88)
	II	64 (22)	33 (9)
	III	16 (5)	5 (2)
	IV	6 (2)	4 (1)
Coronary angiography			
Reperfusion strategy, n (%)			
Primary PCI		275 (92)	–
Rescue PCI (failed thrombolysis)		23 (8)	–
Adjunctive therapy during PCI			
Aspirin (%)		297 (99)	348 (99)
Clopidogrel (600 mg) (%)		297 (99)	337 (96)
Heparin (%)		298 (100)	333 (95)
Anti-GP IIb/IIIa (%)		273 (92)	79 (26)
Number of diseased arteries, n (%)	0	0 (0)	10 (3)
	1	165 (55)	130 (37)
	2	95 (32)	141 (40)
	3	38 (13)	60 (17)
	4	0 (0)	9 (3)
Culprit artery, n (%)	LMS	0 (0)	2 (1)
	LAD	110 (37)	152 (43)
	LCX	55 (18)	106 (30)
	RCA	133 (45)	90 (26)
TIMI coronary flow grade pre-PCI, n (%)	0/1	214 (72)	–
	2	56 (19)	–
	3	28 (9)	–
TIMI coronary flow grade post-PCI, n (%)	0/1	2 (1)	33 (9)
	2	14 (5)	27 (8)
	3	282 (94)	289 (83)

Abbreviations: body mass index (BMI), percutaneous coronary intervention (PCI), beats per minute (bpm), thrombolysis in myocardial infarction (TIMI), left main stem (LMS), left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA).
[‡] Diabetes mellitus was defined as a history of diet-controlled or treated diabetes.
[†] VF or VT before or during PCI, but prior to adenosine infusion.