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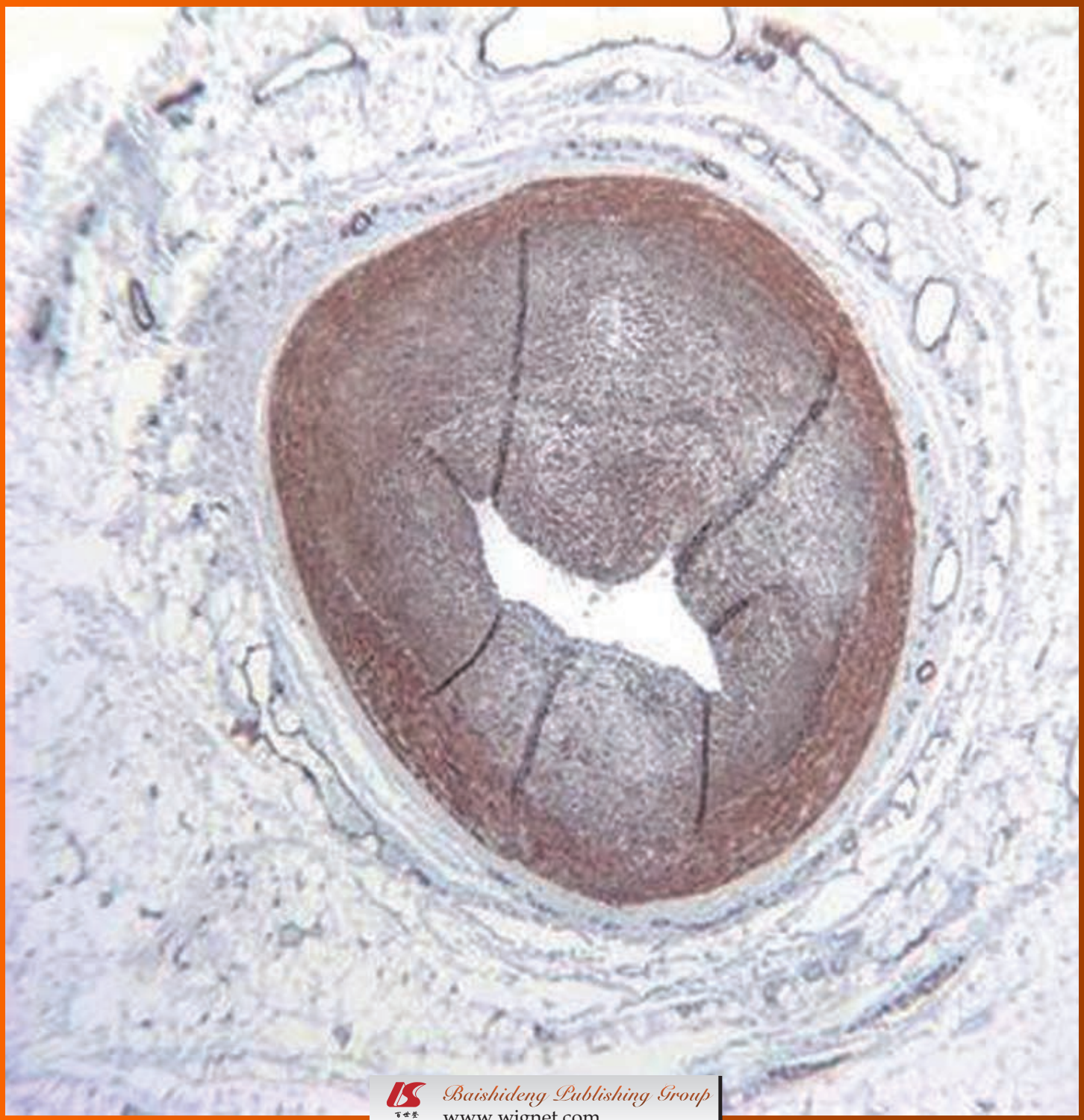

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EDITORIAL

Percutaneous treatment in acute coronary syndromes

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Abstract

Both ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndromes (ACS) are the result of an acute thrombotic lesion obstructing blood flow in the coronary vasculature. Percutaneous treatment has shown to improve clinical outcome in this clinical setting by resolving coronary obstruction with different devices directed to restore coronary blood flow. In comparison with balloon alone angioplasty, implantation of bare metal stents reduced the rate of restenosis and cardiac events, but high rates of restenosis remained, leading to further investigations to develop drug-eluting stents with different pharmacological coatings that reduced restenosis rates and clinical events. In this review, we discuss the current treatment of ACS, reviewing recent randomized clinical trials and advances in medical treatment, including new antiplatelet agents and recent guideline recommendations.

Key words: Coronary revascularization; Acute coronary syndromes; Stent; ST-elevation myocardial infarction; Non-ST-elevation myocardial infarction

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INTRODUCTION

Myocardial revascularization is the key therapy for acute coronary syndromes (ACS). Accordingly, it is in this clinical setting when the expected benefits (increased survival, relief of symptoms, and improvement of quality of life) exceed the potential negative consequences of the procedure[1].

ACS include both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation (NSTE) ACS. However, coronary vasospastic angina (10%-15% presenting with ST-segment elevation) is commonly included in the NSTE-ACS group. Both STEMI and NSTE-ACS are associated with high morbidity and mortality rates. Risk assessment is crucial in contemporary clinical practice and should hinge on developed risk scores[1] to predict mortality, with EuroSCORE for percutaneous and surgical treatment and SYNTAX for percutaneous coronary interventions (PCI).

Recent guidelines[1] have highlighted that patients should take an active role in the decision-making process especially when offered different types of revascularization procedures, so it is necessary to provide clinical information. This strategy has shown to improve outcomes[1]. A multidisciplinary team (Heart Team) should meet and discuss each patient's characteristics and optimize the objective decision-making process, with consideration of

sex, race, availability, technical skills, local results, referral patterns, and patient preference. Coronary artery bypass graft (CABG) surgery may be considered in some patients according to their clinical characteristics, and number and location of coronary lesions.

REVASCULARIZATION IN NSTE ACS

NSTE-ACS is the most frequent manifestation of ACS and represents the largest group of patients with ACS undergoing PCI. Despite continuous advances in medical and interventional treatments, mortality and morbidity remain high and are frequently equivalent to those of patients with STEMI after the initial month[1].

Patients with NSTE-ACS are very heterogeneous with a highly variable prognosis. Therefore, early risk stratification is essential for selection of the best treatment strategy.

Early invasive vs conservative strategy

Randomized clinical trials have shown that an early invasive strategy reduces ischemic endpoints mainly by reducing severe recurrent ischemia and the clinical need for further rehospitalization and revascularization. These trials have also shown a clear reduction in the rate of mortality or myocardial infarction (MI) in the medium term, while the reduction in mortality in the long term has been moderate and MI rates during the initial hospital stay have even been increased (early hazard) (Table 1). The most recent meta-analysis confirms that an early invasive strategy reduces the rate of cardiovascular death or MI at up to 5 years of follow-up[2]. These benefits were more evident in patients at higher risk. Troponin elevation and ST-segment depression at baseline appear to be the most powerful individual predictors of benefit from invasive treatment. Recently published European Society of Cardiology Guidelines on Coronary Revascularization[1] recommend the use of the Global Registry of Acute Coronary Events (GRACE risk score)[3] to guide clinical management[4,5]. Predictors of high thrombotic risk or of high risk for progression to MI, which constitute indications for emergency coronary angiography are[1,6]: (1) ongoing or recurrent ischemia; (2) dynamic spontaneous ST changes (> 0.1 mV depression or transient elevation); (3) deep ST-segment depression in anterior leads V_2-V_4 indicating ongoing posterior transmural ischemia; (4) hemodynamic instability; and (5) major ventricular arrhythmia.

The 2009 American College of Cardiology/American Heart Association Guidelines on coronary revascularization included a new class IIa recommendation to perform coronary angiography within the first 12-24 h after the onset of symptoms for patients with high risk (GRACE score > 140)[7,8]. In lower risk patients, revascularization can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission. Although subgroups of patients, such as women and the elderly, may be at higher risk of bleeding and other complications, they should not be treated differently from other patients included in clinical trials.

Pharmacologic treatment

Aims of pharmacologic treatment in patients with NSTE-ACS undergoing coronary angiography and PCI are: (1) to prevent coronary clot formation or progression; (2) to stabilize atherosclerotic plaques; and (3) to relieve ischemia. Treatment should be decided with consideration of both ischemic (ST-segment changes, elevated troponin, diabetes, GRACE score > 140) and bleeding risk (female sex, age > 75 years, bleeding history, glomerular filtration rate < 30 mL/min and use of femoral access), as they both worsen short- and long-term prognosis.

Angiotensin converting enzyme inhibitors should be initiated as part of the treatment of ACS as they have been shown to reduce left ventricular dilatation and to improve left ventricular ejection fraction. High-dose statin treatment has been shown to improve in-hospital and long-term outcomes in patients presenting with ACS. Up-titration of β-blocker therapy on admission is of critical value for these patients.

Antiplatelet therapy: Dual antiplatelet therapy (DAPT) includes aspirin (ASA) 150-300 mg po or 250-500 mg iv bolus, followed by 75-100 mg daily, and either clopidogrel (600 mg as loading dose, followed by 75 mg daily), or prasugrel (60 mg as loading dose, followed by 10 mg daily), or ticagrelor (180 mg as loading dose, followed by 90 mg twice daily). A higher clopidogrel maintenance dose for 1 or 2 wk immediately following stent implantation has shown some benefit in terms of reduced major adverse cardiac event rates without a significant increase in bleeding[9], but additional studies are necessary in order to confirm preliminary results.

In the TRITON TIMI 38 trial, prasugrel has been tested against a 300 mg loading dose of clopidogrel, with both started in the catheterization laboratory after diagnostic angiography, and proved to be beneficial with respect to a combined thromboembolic-ischemic outcome[10]. Recurrent cardiovascular events were significantly reduced in patients allocated to prasugrel patients. Severe bleeding complications increased with prasugrel, specifically in patients with a history of stroke and transient ischemic attack, in the elderly (≥ 75 years), and in patients with body weight < 60 kg. Bleeding was also increased in prasugrel-treated patients referred for early CABG. Excluding those patients at higher risk of bleeding, prasugrel offers significant benefit over clopidogrel with respect to cardiovascular events without increasing severe bleeding. In diabetic patients presenting with ACS, prasugrel confers a significant advantage over clopidogrel without increased bleeding[11].

Ticagrelor, a non-thienopyridine ADP receptor blocker which reversibly inhibits platelet function, has been compared with clopidogrel. The PLATO study confirmed a significant improvement in combined clinical endpoints,

Table 1 Recommendations for revascularization in non-ST-segment elevation acute coronary syndromes[1]

Situation	Class of recommendation	Level of evidence
An invasive strategy is indicated in patients with: GRACE score > 140 or at least one high-risk criterion Recurrent symptoms Inducible ischemia at stress test	I	A
An early invasive strategy (< 24 h) is indicated in patients with GRACE score > 140 or multiple other high-risk criteria	I	A
A late invasive strategy (within 72 h) is indicated in patients with GRACE score < 140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischemia	I	A
Patients at very high ischemic risk (refractory angina, with associated heart failure, arrhythmias or hemodynamic instability) should be considered for emergent coronary angiography (< 2 h)	IIa	C
An invasive strategy should not be performed in patients: At low overall risk At a particular high-risk for invasive diagnosis or intervention	III	A

GRACE: Global Registry of Acute Coronary Events.

including mortality, in favor of ticagrelor[12]. The rate of severe non-CABG-related bleeding was similar to that of prasugrel in the TRITON-TIMI 38 trial, while CABG-related bleeding was lower than for clopidogrel, most probably a consequence of the faster inactivation of the agent after stopping intake.

The greatest benefit of GP IIb-IIIa inhibitors *vs* placebo was demonstrated in earlier recent clinical trials when ADP receptor blockers were not routinely used[5]. The usefulness of upstream eptifibatide, with or without clopidogrel, was not confirmed in the EARLY-ACS trial. This lack of benefit was associated with a higher bleeding risk[13]. The selective "downstream administration" of abciximab in the catheterization laboratory, in combination with a 600 mg clopidogrel loading dose, has been shown to be effective in troponin-positive NSTE-ACS patients in some studies[14] and may therefore be preferred over upstream use.

Anticoagulation: The golden rule is to avoid crossover especially between unfractionated heparin (UFH) and low molecular weight heparin[5] and to discontinue antithrombinic agents after PCI except in specific individual situations (e.g., thrombotic complications).

Risk stratification in NSTE-ACS patients determines the use of specific agents and doses. Patients at very high ischemic risk (e.g., persistent angina, hemodynamic instability, refractory arrhythmias) should immediately be referred to the catheterization laboratory and receive UFH, combined with DAPT. In patients at high risk of bleeding, bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg per hour) can be used instead of UFH.

In patients at intermediate or high risk (e.g. troponin positive, recurrent angina, dynamic ST changes) for whom an invasive strategy is planned within 24-48 h, options for anticoagulation are: (1) in patients < 75 years, either UFH (60 IU/kg iv bolus, then infusion until PCI, controlled by activated partial thromboplastin time) or enoxaparin (1 mg/kg sc twice daily until PCI) or fondaparinux (2.5 mg daily sc until PCI) or bivalirudin (0.1 mg/kg iv bolus followed by infusion of 0.25 mg/kg per hour until PCI); and (2) in patients ⩾ 75 years, either UFH (60 IU/kg iv bolus, then infusion until PCI) or enoxaparin (0.75 mg/kg sc twice daily until PCI) or fondaparinux (2.5 mg daily sc) or bivalirudin (0.1 mg/kg iv bolus followed by infusion of 0.25 mg/kg per hour until PCI).

Management during catheterization: The initial therapy should be maintained, avoiding switching between different anti-thrombotic drugs (with the exception of adding UFH to fondaparinux). The management during PCI depends on the treatment administered prior to the procedure. (1) Previous treatment with UFH: continue infusion, activated clotting time measurement should be used during PCI with the following target range: 200-250 s with GP IIb-IIIa inhibitors, 250-350 s without GP IIb-IIIa inhibitors; (2) Previous treatment with enoxaparin: In patients with less than 8 h since last sc dose, no additional bolus is needed. In contrast, in patients within 8-12 h of the last sc dose, a 0.30 mg/kg iv bolus should be added, and in those with > 12 h since the last sc dose, a 0.75 mg/kg iv bolus should be administered; (3) Previous treatment with fondaparinux: it is indicated that UFH 50-80 IU/kg be added when PCI is performed. Fondaparinux, an indirect factor Xa inhibitor, has been tested against enoxaparin in the OASIS-5 trial[15]. The combined ischemic event rate was similar, but severe bleeding complications were highly significantly reduced with fondaparinux. This favourable net clinical outcome with fondaparinux included lower long-term mortality and stroke rates. Because of a higher rate of catheter thrombosis when fondaparinux alone was used, UFH should be added for patients referred for angiography and PCI[16]; and (4)Previous treatment with bivalirudin: An additional iv bolus of 0.5 mg/kg should be given and the infusion rate increased to 1.75 mg/kg per hour before PCI. Bivalirudin, a direct antithrombin, alone or in combination with GP IIb-IIIa inhibition, was compared with UFH/enoxaparin + GP IIb-IIIa inhibition. Bivalirudin monotherapy was superior to either regimen with respect to reduced bleeding, without increased ischemic events[17].

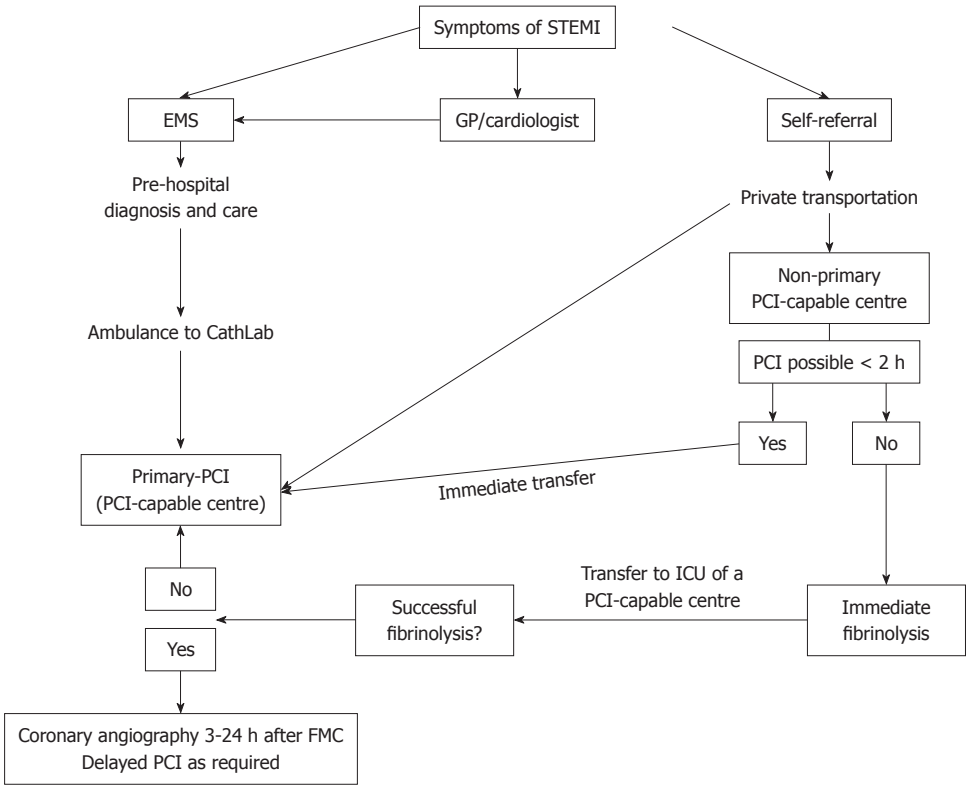

Figure 1 Organization of ST-segment elevation myocardial infarction patient pathway[1]. EMS: Emergency medical service; FMC: First medical contact; GP: General physician; ICU: Intensive care unit; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

REVASCULARIZATION IN ST-SEGMENT ELEVATION ACS

General guidelines

Primary PCI performed within the first 6-12 h after symptom onset has shown to provide more effective restoration of vessel patency, less re-occlusion, improved residual left ventricular function and better clinical outcome compared with fibrinolysis[18-20].

It is essential to minimize all time delays. When the expected delay is > 2 h, patients admitted to a non-PCI centre should receive fibrinolysis and then be transferred to a PCI-capable centre. In cases of persistence of ST-segment elevation after fibrinolysis (more than a half of the maximal initial elevation in the worst ECG lead) and/or persistent ischemic chest pain, rescue PCI should be considered. In the case of successful fibrinolysis, patients may be referred for PCI within 24 h (Figure 1)[7].

In patients presenting > 3 d after the acute event with a fully developed Q-wave MI, revascularization is indicated in those with recurrent angina and/or documented ischemia and viability[1,7].

Cardiogenic shock is the leading cause of in-hospital death for MI patients, even in those treated with primary PCI[21]. Echocardiography should always be performed in the setting of acute heart failure to assess left ventricular function and to rule out life-threatening mechanical complications that may require surgery (mitral regurgitation), ventricular septal defect, free wall rupture or cardiac tamponade[1]. In those patients complete PCI of non-infarcted vessels (i.e. PCI performed in all critically stenosed large epical coronary arteries) should be considered. In the presence of hemodynamic impairment, intra-aortic balloon pumping is recommended[21].

In patients with multivessel disease and STEMI but without cardiogenic shock, early PCI should focus on the coronary artery responsible for the ACS[22,23]. Staged PCI for a complete revascularization is the recommended strategy as it encounters less morbidity and mortality.

PHARMACOLOGIC TREATMENT

Antiplatelet therapy

DAPT consists of ASA 150-300 mg po or 250-500 mg bolus iv, followed by 75-100 mg daily, and either prasugrel (60 mg as loading dose, followed by 10 mg daily), ticagrelor (180 mg as loading dose, followed by 90 mg twice daily), or clopidogrel (600 mg as loading dose, followed by 75 mg daily)[24,25].

Increasing the maintenance dose of clopidogrel to 150 mg/d for 1-2 wk might be effective in STEMI patients, as shown in NSTE-ACS. Prasugrel is superior to clopidogrel (300 mg loading dose, 75 mg maintenance dose) in reducing combined ischemic endpoints and stent thrombosis in STEMI patients without increasing the risk of severe bleeding[24]. A predefined subgroup analysis has demonstrated that STEMI or NSTE-ACS patients referred for PCI significantly benefit from ticagrelor *vs* clopidogrel, with similar bleeding rates[8,26]. Most studies of GP Ⅱb-Ⅲa inhibitors in STEMI have evaluated

abciximab (0.25 mg/kg iv bolus followed by infusion of 0.125 mg/kg per minute up to a maximum of 10 mg/min for 12 h) but more recent trials have also been performed with tirofiban[27]. Findings are mixed regarding the effectiveness of facilitation (early administration) with GP Ⅱb-Ⅲa inhibitors before catheterization. While the only available clinical trial[28] showed no benefit, registries, meta-analyses, and *post hoc* analyses of the APEX-AMI[29] show positive results. The controversial literature data, the negative outcome of the only prospective clinical trial[28], and the beneficial effects of faster acting and more efficacious ADP receptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GP Ⅱb-Ⅲa inhibitors.

Anticoagulation

Options for anticoagulation include mainly UFH (60 IU/kg iv bolus with GP Ⅱb-Ⅲa inhibitor or 100 IU/kg iv bolus without GP Ⅱb-Ⅲa inhibitor under monitoring with ACT), and bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg per hour). Antithrombins can be stopped after PCI for STEMI with few exceptions such as left ventricular aneurysm and/or thrombus, atrial fibrillation, and prolonged bed rest.

A recent study suggested bivalirudin monotherapy as an alternative to UFH plus a GP Ⅱb-Ⅲa inhibitor[30]. Significantly lower severe bleeding rates let to a beneficial net clinical outcome, indicating that bivalirudin may be preferred in STEMI patients at high risk of bleeding. The 1-year outcome of the HORIZONS clinical trial confirmed the beneficial effect of bivalirudin monotherapy *vs* UFH plus a GP Ⅱb-Ⅲa inhibitor. Uncertainty remains in the early phase of primary PCI, when thrombotic complications seem to be higher with bivalirudin monotherapy. Fondaparinux was inferior to UFH in the setting of primary PCI in patients with STEMI (OASIS-6 trial)[31].

DRUG-ELUTING STENTS

Efficacy and safety of drug-eluting stents

Bare metal stents (BMS) were initially designed to treat major dissections, avoid acute vessel closure and prevent restenosis. However, due to a 20%-30% rate of recurrence of angiographic stenosis within 6-9 mo after implantation, restenosis with BMS has often been considered the Achilles' heel of PCI. In native vessels, drug-eluting stents (DES) significantly reduce angiographic restenosis and ischemia-driven target vessel revascularization[32,33]. In recent clinical trials, no significant differences were observed in the long-term rates of death or MI after DES or BMS use for either off-label or on-label indications[33,34]. First-generation DES are safe and efficacious for both on-label and off-label use, when implanted in the native circulation, in spite of a slightly increased propensity for late and very late stent thrombosis[32].

DES with proven efficacy should be considered by default in nearly all clinical conditions and lesion subsets, except if there are concerns or contraindications for prolonged DAPT. Indications for DES in a few specific patient or lesion subsets remain a matter of debate[35]. In selected STEMI patients[36-38], SES and PES were shown to be safe and effective in follow-up extending from 2 to 4 years. Studies based on angiographic endpoints favor the use of DES with strong antiproliferative properties (late lumen loss $\leqslant$ 0.2 mm)[39-42].

CONCLUSION

ACS are a common manifestation of atherosclerotic disease. Continuous advances have reduced morbidity and mortality risks, but there remain elevated rates of complications and mortality. Risk assessment is crucial in the setting of NSTE-ACS. Coronary revascularization is the major treatment of patients presenting with ACS. Optimal medical treatment including dual or triple antiplatelet therapy and anticoagulation are mandatory in this clinical setting. BMS have been used to alleviate coronary stenosis but high rates of restenosis developed. DES are the state-of-the-art treatment for coronary stenosis, excluding patients with elevated bleeding risk with prolonged DAPT. Further investigations will help us determine better pharmacologic regimens to minimize bleeding risk and thrombotic events.

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BRIEF ARTICLE

Assessment of right ventricular afterload by pressure waveform analysis in acute pulmonary hypertension

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Abstract

AIM: To characterize hydraulic right ventricle (RV) afterload by pulmonary arterial pressure waveform analysis in an acute pulmonary hypertension (PH) model.

METHODS: Pulmonary artery (PA) flow and pressure were recorded in six anesthetized sheep. Acute isobaric PH was induced by phenylephrine (active) and PA mechanical constriction (passive). We estimated the amplitude of the forward and reflected pressure waves according to the inflection point. In most cases the inflection pressure was smooth, thus the inflection point was defined as the time at which the first derivative of pulmonary arterial pressure reached its first minimum. We calculated the input and characteristic (Z_c, time-domain Li method) impedances, the capacitance index (stroke volume/pulse pressure), the augmentation index (AI) (reflected pressure/pulse pressure), the fractional pulse pressure (pulse pressure/mean pressure) and the wasted energy generated by the RV due to wave reflection during ejection (E_w).

RESULTS: Pulse pressure, fractional pulse pressure, AI and Z_c increased and capacitance index decreased during passive PH with respect to control ($P < 0.05$). In contrast, Z_c and the capacitance index did not change and E_w and the AI decreased during active PH. Pulse pressure correlated with E_w and Z_c and the AI was correlated with E_w ($r > 0.6$, $P < 0.05$).

CONCLUSION: PA pressure waveform analysis allows the quantification of the dynamic RV afterload. Prospective clinical studies will be necessary to validate this time-domain approach to evaluate the dynamic RV afterload in chronic PH.

Key words: Pulmonary hypertension; Time-domain analysis; Augmentation index; Characteristic impedance; Reflected wave

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INTRODUCTION

Clinical signs of right ventricle (RV) failure are often not clearly related to the progression of pulmonary hypertension (PH), as assessed by pulmonary vascular resistance. Adaptation of the RV to acute and/or chronic PH depends on both the stationary and the pulsatile components of afterload[1,2]. Due to the low resistance and high compliance of the healthy pulmonary vascular tree, it is very important to consider the pulsatile component of hydraulic load. Vascular smooth muscle (VSM) activation improves the buffering function of conduit central vessels, attenuating the pulsatile component of afterload and improving RV-pulmonary artery (PA) coupling in acute PH[3].

The morphology and amplitude of the PA pressure wave (Pp, pulse pressure) results from the interaction between the RV and the PA system. The Pp consists of a forward wave (inflection pressure-diastolic pressure, Pi-Pd) generated by RV ejection, and the arrival of a reflected wave (systolic pressure-Pi, Ps-Pi) from the periphery. Pi is the PA pressure upon the return of the reflected wave (which coincides with maximal pulmonary flow - PF), and the reflected wave/Pp ratio is the augmentation index (AI)[4]. The time to the inflection point (Ti) quantifies the timing of the pressure wave reflection. The forward wave depends on the elastic properties of the main PA and its branches, while the reflected wave depends on those of the entire arterial tree, as well as the pulse wave velocity and the distance from the main reflection sites.

In healthy young individuals, AI is low and weakly contributes to Pp. The reflected pressure wave is rather diffuse and maintains a relatively high central arterial pressure in early diastole, thus reducing pulsatile afterload. Increased proximal arterial stiffness determines the increase and narrowing of the reflected pressure wave, contributing significantly to Pp (high AI value) rather than increasing early diastolic pressure[5]. PA stiffening is also responsible for increasing the characteristic impedance (Zc), thus the forward pressure-wave amplitude increases and also pulse wave velocity is increased, resulting in premature return of the reflected wave during systole and augmentation of central pulse pressure without affecting mean arterial pressure[5].

The capacitance index (Cp), a measure of global pulsatile vascular load, has proved to be an independent predictor of mortality in patients with idiopathic PH[6]. Although both the fractional pulse pressure (Ppf = Pp/mean arterial pressure) and the AI enable a differential diagnosis between idiopathic PH and chronic thromboembolic PH[7], a complete dynamic afterload evaluation in the time domain has not been evaluated in PH.

The aims of the present study were to characterize the stationary (pulmonary vascular resistance, input impedance) and pulsatile (Cp, AI, Zc) components of the hydraulic RV afterload in the time domain (using the PA pressure waveform) in an acute PH ovine model.

MATERIALS AND METHODS

Surgical instrumentation and experimental protocol

Six Merino sheep weighting 25-30 kg were anesthetized with intravenous sodium pentobarbital (35 mg/kg bolus and 3 mg/kg per hour infusion), fentanyl (2 μg/kg bolus and 1 μg/kg per hour infusion) and atracurium (1 mg/kg per hour infusion). The animals underwent tracheostomy and were ventilated using a ventilator (Dräger SIMV Polyred 201, Spain) with a 40% inspired oxygen fraction. Oxygen and carbon dioxide partial pressures were monitored (Radiometer BMS 3 MK2, Copenhagen, Denmark). Both breathing rate and tidal volume were adjusted to maintain arterial pCO_2 between 35 mmHg and 45 mmHg, pH between 7.35 and 7.4 and arterial pO_2 greater than 80 mmHg. Deep periodic inhalations and transitory increases of 5-10 cm H_2O in end-expiratory positive pressure were performed to reduce the occurrence of atelectasis. The right saphenous vein was catheterized to allow administration of saline, anesthetic drugs and phenylephrine. A fluid column catheter was placed from the right femoral artery to the abdominal aorta to monitor systemic arterial pressure and obtain blood samples for gases analysis. A thoracotomy was performed at the 4th left intercostal space. After opening the pericardium, the PA and its main branches were exposed. A transonic perivascular flow probe was placed around the PA (16 mm or 20 mm, Transonic Systems, Ithaca, NY, United States), 2 cm from the pulmonary valve. A solid-state pressure microtransducer (model P7, 1200 Hz, Konigsberg Instruments, Inc., Pasadena, CA, United States), previously calibrated using a mercury manometer, was inserted distal to the flow probe through a small incision in the PA[3,8]. As a result, both the flow and instantaneous pressure signals were recorded simultaneously and in the same location of the PA. An occluder band was placed around each PA branch to induce acute increments in PA pressure. Pulmonary flow was measured using a Doppler flow meter (T-106; Transonic Systems, Ithaca, NY, United States) with a low-pass 100 Hz filter.

Experimental protocol

After surgical instrumentation, 30 min were allowed for stabilization of the recordings. All signals were acquired during three stable hemodynamic states according to the following sequence: (1) control steady state at normal pressure: stable basal state without PA occlusion nor phenylephrine administration; (2) active PH: VSM was activated by iv phenylephrine infusion (5 μg/kg·per min, Sigma, St. Louis, MO, United States), achieving stabilization of pulmonary pressure and flow 15-20 min after infusion; and (3) passive PH: the PA branch occluders were compressed in order to obtain a mechanical high pressure non-active state for 10 min. Pressure levels were established to ensure isobaric pulmonary conditions between this maneuver and phenylephrine.

Between steps 2 and 3, 20 min were allowed to re-

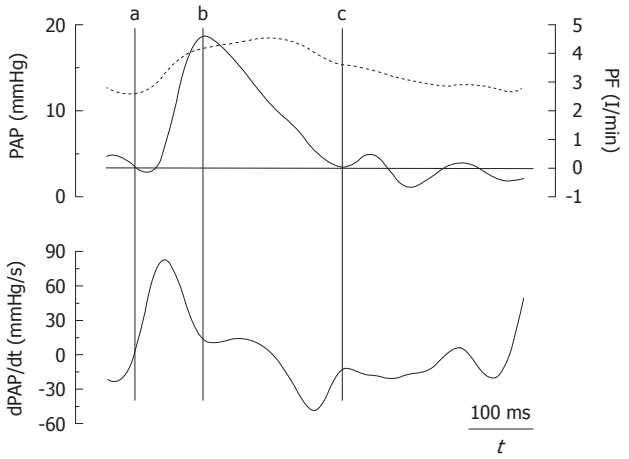

Figure 1 Pulmonary pressure and flow register (top) with the first derivative of the pulmonary arterial pressure (bottom) where the main events are defined as follows. a: Diastolic pressure and beginning of ejection; b: Inflection point (peak pulmonary flow and first minimum of dPAP/dt); c: End of ejection. PAP: Pulmonary artery pressure; dPAP/dt: First derivative of PAP; PF: Pulmonary flow.

establish control state pressure and flow values. The similar level of mean arterial pressure in both PH states enabled an isobaric analysis. Upon completion of the experimental protocol, the animals were sacrificed using a pentobarbital overdose followed by i.v. potassium chloride. The present protocol was approved by the Honorary Commission for Animal Experimentation of the Universidad de la República (Uruguay), in accordance with the principles outlined in the international guides for the care and use of laboratory animals published by the National Institutes of Health (NIH Publication Nº 86-23, revised 1995).

Data acquisition

All invasive signals were monitored in real time and digitized on-line using a 200 Hz A/D converter, and software developed in our laboratory (SAMAY MD16), as previously described[3,8]. Approximately 10-15 consecutive beats were analyzed in each stable hemodynamic state. During data acquisition the ventilator was turned-off. Both direct values and those derived from the signals were processed off-line.

Calculations

The amplitude of the forward (Pi-Pd) and reflected (Ps-Pi) waves were estimated from the inflection point (Pi, Ti). As it was previously reported by Kelly *et al*[9] in the systemic circulation, this point was determined when the first derivative of the arterial pressure reached its first minimum, which coincided with the peak of the local arterial flow (Figure 1). The AI was estimated by Ps-Pi/Pp, and the return time of the reflected wave was estimated by Ti. The energy lost by the RV due to the wave reflected during ejection (extra workload, Ew) was quantified using [(Ts-Ti)(Ps-Pi)π/2], where (Ts-Ti) and (Ps-Pi) correspond to the systolic duration and magnitude of the reflected wave, respectively[4]. Input impedance was estimated by the ratio between mean pulmonary AP and PF. Zc was calculated using the instantaneous quotient of pressure and PF above the diastolic value in the first 60 ms (Li method), assuming a lack of wave reflection in early ejection (Figure 2, shaded area)[10]. Pulmonary Cp was estimated as the ratio between stroke volume and Pp[11,12].

Table 1 Hemodynamic data (mean ± SD, *n* = 6)

	CTL	PPH	APH
Pm (mmHg)	14.8 ± 1.8	21.9 ± 2.7[a]	21.2 ± 2.9[c]
Pp (mmHg)	7.5 ± 2.4	17.8 ± 4.7[a]	11.8 ± 3.5[a,c]
PF (mL/s)	32.7 ± 5.0	36.4 ± 6.0	35.5 ± 5.4
HR (beats/min)	110 ± 23	111 ± 28	105 ± 19
ZO (dyne.s/cm^5)	621 ± 49	961 ± 190[a]	917 ± 180[a]
ZC (dyne.s/cm^5)	82 ± 20	167 ± 60[a]	98 ± 21[c]
Cp (mL/mmHg)	2.63 ± 0.9	1.16 ± 0.36[a]	1.87 ± 0.37[c]

CTL: Control; Cp: Capacitance index; HR: Heart rate; PPH: Passive pulmonary hypertension; APH: Active pulmonary hypertension; Pm and Pp: Mean and pulse pulmonary arterial pressure, respectively; PF: Pulmonary flow; ZO and ZC: Total and characteristic impedances, respectively. [a]$P < 0.05$ *vs* CTL; [c]$P < 0.05$ *vs* PPH.

Statistical analysis

Data were expressed as mean ± SD. Friedman's and Wilcoxon's tests were used, as well as simple linear regression analysis, with P values < 0.05 considered significant.

RESULTS

Hemodynamic data

The grouped values of the three experimental situations are presented in Table 1. Heart rate and PF were similar in all three experimental conditions. During both passive and active PH, mean PA pressure increased in a similar fashion, allowing isobaric analysis. During passive PH, both Pp and Zc increased, whereas Cp decreased with respect to control ($P < 0.05$). While Pp increased during phenylephrine infusion, this increase was significantly lower than in passive PH, with preservation of Zc and Cp.

Time-domain analysis of the PA pressure waveform

Figure 3 shows the recordings of the pressure wave and PF, in addition to the first derivative of the PA pressure during each experimental condition. It shows a good correlation between the time at the first minimum of the derivative of PA pressure and the time at the peak PF. Mean value, and values for each experimental condition, of the various calculated indices are presented in Table 2. Both the forward wave (Pi-Pd) and the reflected wave (Ps-Pi, Ew), Ppf and AI showed a significant increase during passive PH, while phenylephrine caused an isobaric reduction in the magnitude of the reflected wave and the AI ($P < 0.05$). Pi increased significantly during PH. While Ti decreased during PH states, this reduction was signifi-

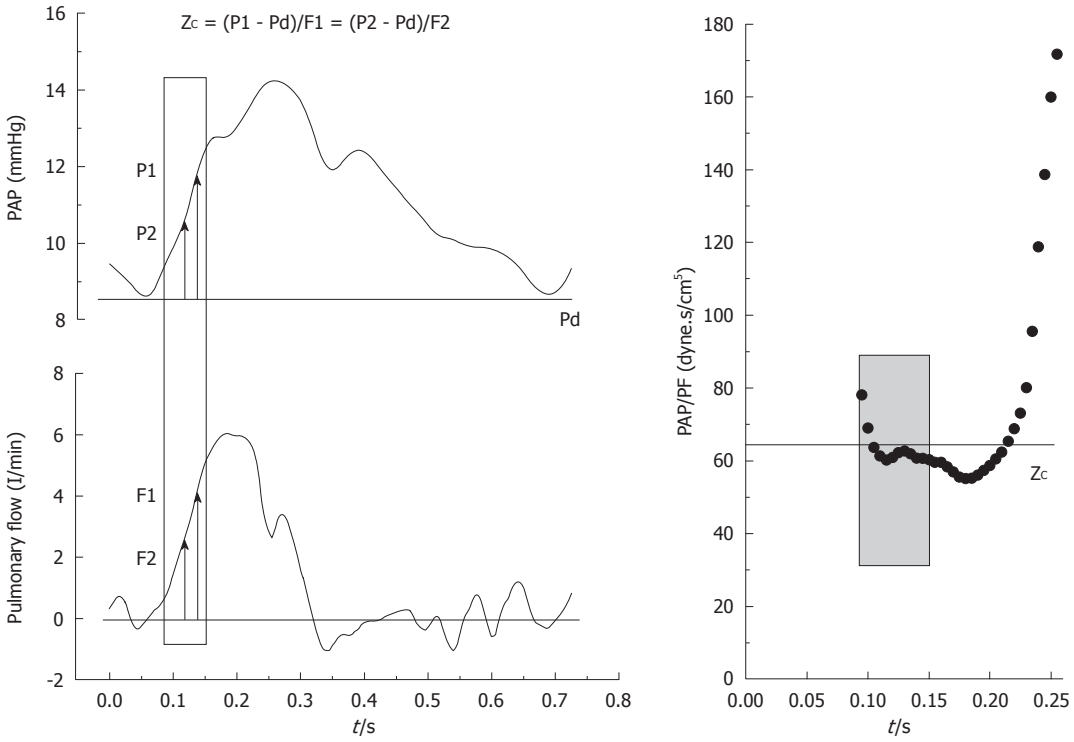

Figure 2 Method for obtaining the characteristic impedance (Z_C) of the pulmonary artery.

Table 2 Indices of dynamic afterload in time domain (mean ± SD, *n* = 6)

	CTL	PPH	APH
Ppf (Pp/Pm)	0.53 ± 0.17	0.83 ± 0.25[a]	0.56 ± 0.17[c]
Pi-Pd (mmHg)	5.9 ± 1.8	9.1 ± 1.9[a]	7.4 ± 2.0[a,c]
Ps-Pi (mmHg)	1.8 ± 0.5	8.7 ± 3.0[a]	4.3 ± 1.7[a,c]
(Ps-Pi)/(Pi-Pd)	0.31 ± 0.08	0.95 ± 0.24[a]	0.6 ± 0.21[a,c]
AI [(Ps-Pi)/Pp]	0.25 ± 0.03	0.48 ± 0.06[a]	0.37 ± 0.08[a,c]
Ti (ms)	104 ± 21	50 ± 13[a]	70 ± 17[a,c]
Pi (mmHg)	16.2 ± 3.3	22.9 ± 4.4[a]	22.1 ± 6.0[a]
EW (mmHg/s)	0.6 ± 0.2	3 ± 1.1[a]	1.6 ± 0.8[a,c]

APH: Active pulmonary hypertension; Ps, Pd, Pi: Systolic, diastolic and inflection pulmonary arterial pressures, respectively; Ppf: fractional pulse pressure; AI: Augmentation index; Ti: Time at the inflection point; EW: Wasted energy generated by the right ventricle due to wave reflection during ejection. [a]$P < 0.05$ *vs* CTL; [c]$P < 0.05$ *vs* PPH.

cantly greater during passive PH. Figure 4 shows the correlations of Pp and AI with pulsatile load (Ew; Z_C) during the 3 experimental conditions. Finally, Z_C was correlated with the forward wave (Pi-Pd) ($r = 0.62$, $P < 0.05$).

DISCUSSION

Although the estimation of arterial impedance (frequency domain) enables a complete description of hydraulic RV afterload, it is complex to obtain and to interpret[12,13]. On the other hand, we have shown here that the analysis of PA pressure wave morphology and amplitude allows both components (stationary and pulsatile) of RV afterload to be quantified, as well as differentiating local PA stiffness (proximal pulsatile load) from the magnitude and return time of the reflected wave (distal pulsatile load). Due to the isobaric condition, it was possible to show that during active PH, the RV pulsatile load was attenuated, by means of preserving proximal PA stiffness and decreasing the magnitude of the reflected wave.

The central PA pressure wave is composed of a forward traveling wave generated by the RV and a later arriving reflected wave returning from the periphery. Adjustments in heart rate and ejection systolic time on the one hand (ventricular factor) and in arterial stiffness (pulse wave velocity) and vasomotor tone (vascular factor) on the other, determine the synchronization between forward and reflected wave, as well as the proportion of the forward wave that is reflected, which in turns enables modulation of ventriculo-arterial coupling[14]. In addition, in order to properly match the pulse wave velocity and pulmonary length, the reflected pressure wave must return to the proximal PA during diastole rather than systole. Proper matching occurs when time required for wave to travel to the periphery and back equals the systolic ejection period. Therefore, correct coupling between pulse wave velocity and the distance from the reflection sites occurs when the time required for the pulse wave to travel to and back from the periphery is similar to systolic time, so the Ti/systolic time quotient should be close to 0.5[15]. Under normal conditions, the Pi was practically similar to the systolic arterial pressure with a Ps-Pi of 1.8 ± 0.5 mmHg and the Ti/systolic time quotient was 0.4 ± 0.09. Thus, the augmentation pressure is low and weakly contributes to Pp.

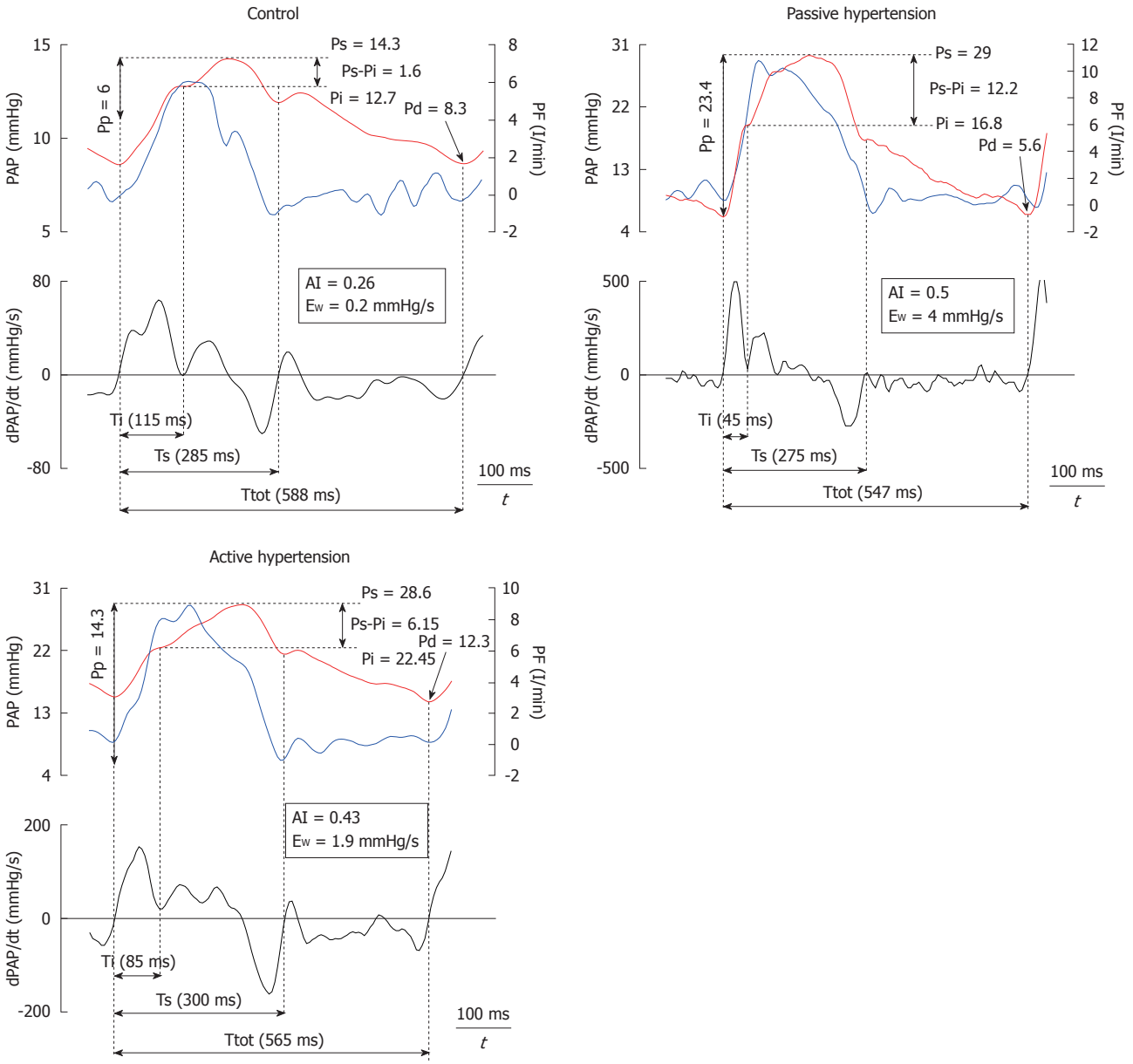

Figure 3 Time-domain analysis of pulmonary pressure and flow of a representative sheep in each of the experimental conditions. Ti, Ts, Ttot: Incident, systolic and total times; Ps, Pi, Pd: Systolic, incident and diastolic pressures.

Though Pp increased significantly during both forms of acute PH, phenylephrine caused a decrease in Pp with respect to passive PH ($P < 0.05$). Whereas mean arterial pressure (stationary component of afterload) depends on cardiac output and peripheral vascular resistance, the determining factors of Pp (ejection volume, arterial stiffness and reflected wave) interact in a complex manner[15]. The passive increase in Pp during PH was due both to an increase in amplitude of the reflected wave (Ps-Pi, Ew) and to an increase in Zc, which was accompanied by a decrease in Cp and an increase in Ppf ($P < 0.05$). During active PH, Zc was unchanged and the increase in the peripheral pulsatile component (due to a lower increase in the reflected wave) was significantly lower than in the passive condition (Ps-Pi, Ew), which explains the preservation of Ppf and Cp. In this respect, our work showed that the reduction in Zc during active PH, despite a reduction in PA diameter secondary to phenylephrine-induced isobaric vasoconstriction, is due to a simultaneous reduction in the parietal elastic index with respect to passive PH, with preservation of the conduit function (to conduct blood) and an improvement in the buffer function (to buffer cardiac pulsatility). This is likely due to the activation of VSM, preventing recruitment of collagen fibers[8].

Figure 4 shows how Pp depends on the peripheral (Ew) and central (Zc) components of pulsatile afterload ($P < 0.05$). Unlike Pp, AI was only correlated with Ew. This concurs with previous studies sustaining that Zc depends on the geometry (radius and thickness) and on the viscoelastic properties of the vascular wall, whereas AI is determined by the amplitude and timing of the reflected wave, in addition to the duration of ventricular ejection[4]. Therefore,

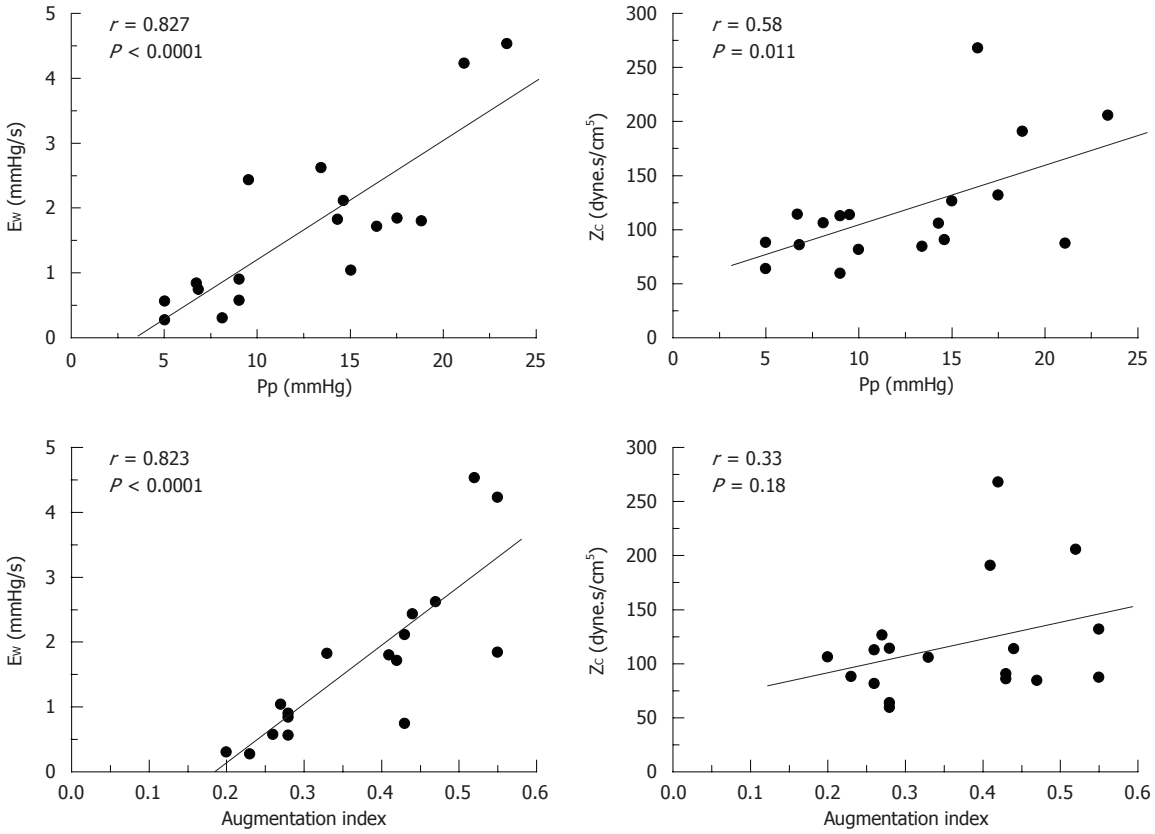

Figure 4 Correlation between pulse pressure (Pp) and augmentation index (AI) with the energy lost by the RV due to the reflected wave during ejection (E_W), and the characteristic impedance (Z_C).

an increase in Pp together with an increase in AI would involve a greater reflected wave (E_W) with or without an increase in Z_C, while an increase in Pp with unchanged AI would mainly involve Z_C (PA stiffness). Although obtaining PF simultaneously enables estimation of Z_C and E_W, Pi could also be determined with the first derivative of PA pressure and the Pi-Pd values correlated with Z_C, allowing it to be applied clinically in hemodynamic studies.

In clinical settings, PH vasculopathy affects either distal resistive and/or proximal elastic vessels, with different dynamic afterload and different RV adaptation. Mitchell *et al*[16] have noninvasively assessed the components of pulsatile hemodynamic load (Z_C, AI and Cp) in compensated patients with chronic heart failure. They emphasized that the increased pulsatile load represents an important therapeutic target in chronic heart failure. Although the current results cannot be extrapolated to chronic pulmonary vascular disease, they provide some facts about the change of pulmonary afterload during passive and active PH and the relation with group 4 (chronic thromboembolic PH, particularly with proximal disease) and group 1 (idiopathic PAH, with diffuse remodeling) of the DanaPoint classification. In agreement with this, Nakayama *et al*[17] have shown that both Ppf, or pulsatility index, and the AI enable a differential diagnosis between idiopathic PH and chronic thromboembolic PH. Also, Castelain *et al*[7], through the comparison of idiopathic PAH and chronic thromboembolic PH patients with similar mean pulmonary pressure and Pp, showed the presence of an early, and greater magnitude reflected wave in patients with chronic thromboembolic PH. We have recently shown that the isobaric steady component analysis differentiated the pulsatile component between idiopathic PAH and proximal operable chronic thromboembolic PH[18]. The higher dynamic RV afterload in chronic thromboembolic PH patients would be related to different vascular wall remodeling.

Instantaneous PA flow velocities can be measured by transthoracic pulsed Doppler echocardiography. Therefore, performing instantaneous PA pressure and flow measurements during a routine right heart catheterization with Doppler echocardiography in patients with PAH would allow estimation of the time-domain parameters[13,16].

A number of limitations of our study need to be emphasized. The experimental model was designed to apply a time domain approach for evaluating the dynamic RV afterload, particularly pulsatile hemodynamics. Although the results of the present study apply to acute PH situations and therefore should not be extrapolated to chronic hypertensive vascular disease, they provide a methodological basis for estimating the whole pulsatile load of RV. Our aim was not to mimic any specific chronic group of the DanaPoint PH classification. However, during phenylephrine infusion both large and small pulmonary vessels contracted, thus, the pressure increase recorded in the main PA was due to increased pulse wave velocity and wave reflection, while during "passive" PH, PA pressure was increased by mechanical obstruction of the proxi-

mal PA, current elements in idiopathic PAH and chronic (proximal) thromboembolic PH.

In conclusion, time-domain analysis of the central PA pressure waveform allows global estimation of the RV dynamic afterload, as well as the analysis of the determining factors in ventriculo-arterial coupling. This may constitute a valid substitute for pulmonary vascular impedance (frequency-domain analysis). Given that RV failure is the chief cause of death in PH patients, this approach may be useful in the diagnosis, follow-up, medical therapeutic effects and prognosis of the various forms of chronic PH. Prospective clinical studies will be necessary to validate this approach to evaluate the dynamic RV afterload in chronic PH.

ACKNOWLEDGMENTS

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COMMENTS

Background

The morphology of the pressure wave contour in any point along the pulmonary arterial vascular tree represents the sum of the forward and reflected waves at that point and depends on three factors: the amplitude and duration of ventricular ejection, the amplitude of the reflected wave, and the pulse wave velocity. These three key parameters are influenced by several important factors including the stiffness (elastic properties and vasomotor tone) of the pulmonary arterial wall, the distance of the wave reflection sites, the heart rate and the pulmonary vascular resistance. Pulmonary artery (PA) stiffening alters right ventricular systolic pressure in two ways: first, by causing a greater rise of pressure at the time of peak pulmonary flow, and second, by increasing pulse wave velocity in the PA and so causing the reflected wave from peripheral sites to return early and boost pressure in late systole. Wave reflection is an integral part of the central pressure waveform that increases right ventricular load by increasing pulmonary arterial pressure in late systole.

Research frontiers

The important focus in the current study was to characterize the hydraulic right ventricular afterload, considering the central pulmonary arterial pressure waveform analysis in an acute pulmonary hypertension (PH) experimental model. This time domain approach should analyze the steady and pulsatile components of the right ventricular afterload by several indexes and has the advantage of assessing the global arterial mechanics concomitantly.

Innovations and breakthroughs

A comprehensive analysis of the central pulmonary arterial pressure waveform has been carried out in an acute PH model, during both passive (pulmonary arterial occlusion) and active (phenylephrine infusion) PH. This may constitute a valid alternative to pulmonary vascular impedance (frequency-domain analysis) in evaluation of dynamic right ventricular afterload in PH.

Applications

Performing simultaneous pulmonary arterial pressure and flow velocity measurements in patients with PH undergoing routine right heart catheterization with Doppler echocardiography, should allow estimation of the different time-domain indexes. We believe that the time-domain study of the central pulmonary arterial pressure waveform and flow in patients with chronic PH may be useful for analyzing direct and long-term effects of specific drugs designed for treatment of pulmonary arterial hypertension.

Peer review

Overall quality of manuscript is good and it is possible to accept for publication with minor revisions.

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BRIEF ARTICLE

Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: A meta-analysis

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Abstract

AIM: To evaluate the association between genetic polymorphisms and angiotensin converting enzyme inhibitor (ACEI)-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

METHODS: We conducted a search in PubMed, EMBASE, Cinahl, and the Cochrane Database without language limitation. A database of 11 studies on ACEI-related cough, with detailed information regarding *ACE I/D* or bradykinin B_2 receptor polymorphisms, was created. Eligible studies were synthesized using meta-analysis methods, including cumulative meta-analysis. A subgroup analysis was also performed using ethnicity.

RESULTS: Six studies were included on *ACE I/D* polymorphism (398 Caucasians, 723 East Asians), and three studies were included on bradykinin B_2 receptor polymorphism (300 East Asians). The distribution of ACE genotypes showed significant differences in the entire population (P = 0.004) and in East Asians (P = 0.005) but not in Caucasians (P = 0.23). Allelic frequencies of ACE showed significant differences in East Asians [odds ratio (OR) = 1.49 (1.11-2.02)]. The meta-analysis with a random effects model showed a significant association between *ACE* allele *I/D* and ACEI-related cough [random effects (RE) OR = 1.49 (1.11-2.02), P = 0.009] in East Asians, but not in Caucasians [RE OR = 0.90 (0.60-1.35)]. The allelic frequencies of the bradykinin B_2 receptor gene were significantly different [OR = 2.25 (1.42-3.57)]. The distributions of the T/C genotypes of the bradykinin B_2 receptor gene were significantly different (χ^2 = 8.366, P = 0.015). The meta-analyses revealed that there was a significant association between the bradykinin B_2 receptor allele and ACEI-related cough in East Asians [RE OR = 2.29 (1.42-3.69), P = 0.001].

CONCLUSION: *ACE I/D* and Bradykinin B_2 receptor polymorphisms contributed to the risk of ACEI-related cough in East Asians, but a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in Caucasians.

Key words: Angiotensin converting enzyme inhibitor; Bradykinin; Cough; Genes; Polymorphism

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INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEI) are widely used for the treatment of hypertension and congestive heart failure. The major adverse effect and the most frequent reason for withdrawal of the ACEI is a persistent, dry (nonproductive) cough[1,2]. The cause of the cough is reported to be intrinsic to the mechanism of action of ACEI, and so change to another ACEI is not recommended because of apparent cross-reactivity[2]. The accumulation of kinins has been suggested to play a major role in ACEI-related cough. This accumulation probably results from inhibition of the degradation of kinins, particularly bradykinin, in the airway, but the precise mechanism is still unknown. It seems reasonable to suspect that a primary, genetically determined characteristic resulting in an alteration of drug action or drug metabolism may be responsible[3].

ACEI-related cough occurs in about 10%-20% of treated patients[4-6]. A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans[7-9], among whom the population prevalence of the *I* allele is high[10]. Some studies showed the relationship between the *ACE I/D* genetic polymorphism and ACEI-related cough[11-13]. Furuya *et al*[11] demonstrated that Japanese patients with *ACE* genotype *II* were most susceptible to cough. However, a significant difference was not observed in two genetic studies in French and British patients[12,13]. Other studies have also implied a genetic predetermination of ACEI-related cough caused by specifically implicated variants of the genes that encode ACE, chymase, and bradykinin B_2 receptors[14-16]. It is controversial whether genetic polymorphisms are associated with ACEI-related cough. There may be a race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy. The aim of this study was to evaluate the association between genetic polymorphisms and ACEI-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

MATERIALS AND METHODS

Selection of trials

We searched Medline, EMBASE, Cinahl, and the Cochrane Database from the earliest available date through September 2010. A search strategy using the Medical Subject Headings and text keywords "angiotensin converting enzyme inhibitor", "cough", "gene", and "polymorphism" were used. The review included genetic association studies fulfilling the following inclusion criteria: (1) providing cases diagnosed with ACEI-related cough; (2) providing information on genotype frequency for *ACE I/D* or bradykinin B_2 receptor -58 T/C polymorphisms; and (3) using validated molecular methods for genotyping. The retrieved studies were manually screened to assess their appropriateness for this study. All references cited in the studies were also reviewed to identify additional published articles not indexed in the database. Case reports, editorials and review articles were excluded. The search was not restricted by language.

Data synthesis

Nineteen meta-analyses were performed to investigate the association between *ACE I/D* and ACEI-related cough for the allele contrast (*D vs I*), the recessive (*DD vs ID/II*), the dominant (*DD/ID vs II*), the additive (*DD vs II*) and the co-dominant (*ID vs DD/II*) models, and the association between bradykinin B_2 receptor -58T/C and ACEI-related cough. We calculated the overall odds ratio (OR) with the corresponding 95% confidence interval (CI) using the random effects (RE; DerSimonian and Laird) models. Statistical heterogeneity across the various studies was tested with the use of the Q-statistic[17]. A P value < 0.10 indicated a significant statistical heterogeneity across studies, allowing for the use of the RE model. A cumulative and recursive cumulative meta-analysis was also carried out[17,18]. Cumulative and recursive cumulative meta-analyses provide a framework for updating a genetic effect from all studies and a measure of how much the genetic effect changes as evidence accumulates. Thus, a cumulative meta-analysis indicates the trend in estimated risk effect and a recursive cumulative meta-analysis indicates the stability in risk effect. In the cumulative meta-analysis, studies were chronologically ordered by publication year, then, the pooled ORs were obtained at the end of each year, i.e. at each information step. In the recursive cumulative meta-analysis, the relative change in pooled OR in each information step (pooled OR in next year/pooled OR in current year) was calculated. In addition to the main (or overall) analysis which included all available data, a subgroup analysis for each "race" was also performed. "Racial" descent was categorized into Caucasian descents and East Asian descents[17].

Statistical analysis

OR and 95% CI for risk factors and significance level for χ^2 are given. Statistical heterogeneity was evaluated *via* the Q statistic. $P < 0.01$ was considered representative of significant statistical heterogeneity.

RESULTS

Eligible studies

Twenty citations identified through the literature search were independently screened by two investigators according to the inclusion criteria. Eleven articles were retrieved and evaluated against the same criteria. Data from 11 studies[11,13,19-26] met the meta-analysis eligibility criteria and were included in the context of the meta-analyses. Figure 1 represents a flow chart of retrieved studies and studies excluded, with specification of reasons. Six studies were included on the *ACE I/D* polymorphism (398 Caucasians, 723 East Asians), and three studies were included on bradykinin B_2 receptor polymorphism (300 East Asians, Table 1). 19 meta-analyses were conducted

Table 1 Distribution of genotypes and allelic frequencies of ACE and bradykinin B_2 receptor polymorphisms in patients with or without cough

	Population	Studies		Genotype			χ^2 test	Studies	Allele		Odds ratio (95% CI)
				I/I	*I/D*	*D/D*			*I*	*D*	
Angiotensin converting enzyme	All	11	Cough (-)	390 (32)	571 (48)	241 (20)	0.004	7	0.51	0.49	1.26
			Cough (+)	338 (39)	381 (44)	142 (17)			0.45	0.55	(0.99-1.61)
	Caucasians	3	Cough (-)	75 (24)	132 (43)	100 (33)	0.230	2	0.53	0.47	0.72
			Cough (+)	23 (19)	51 (41)	50 (40)			0.61	0.39	(0.46-61.4)
	East Asians	8	Cough (-)	315 (35)	439 (49)	141 (16)	0.005	5	0.49	0.51	1.49
			Cough (+)	315 (43)	330 (45)	92 (12)			0.39	0.61	(1.11-12.02)
				T/T	*T/C*	*C/C*			*C*	*T*	
B2 receptor B_2 receptor -58T/C	East Asians	3	Cough (-)	145 (26)	270 (50)	143 (24)	0.015	2	0.56	0.44	2.25
			Cough (+)	139 (30)	244 (52)	85 (18)			0.36	0.64	(1.42-23.57)

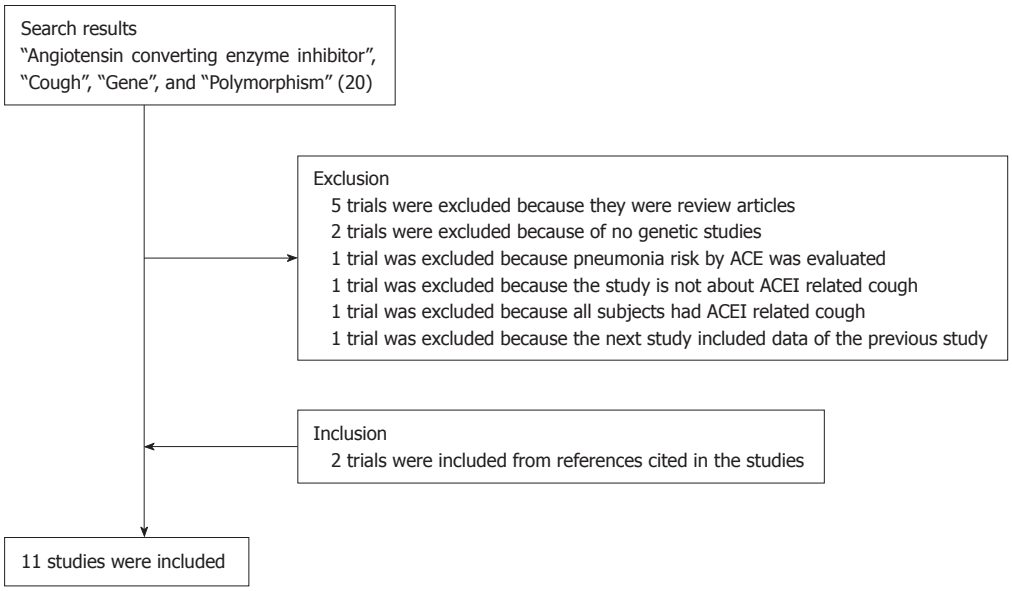

Figure 1 Flow chart of retrieved studies and studies excluded, with specification of reasons.

for these 2 gene polymorphisms of angiotensin-converting enzyme *deletion/insertion* (*ACE D/I*) and bradykinin B_2 receptor -58T/C (Table 2, Figures 2 and 3).

ACE D/I

Table 1 shows the distributions of the genotypes and the allelic frequencies of the polymorphisms of ACE and bradykinin B_2 receptor in subjects with or without cough. In the ACE gene, the distributions of genotypes showed significant differences in the entire population ($P = 0.004$) and in East Asians ($P = 0.005$) but not in Caucasians ($P = 0.23$). Allelic frequencies of ACE showed significant differences in East Asians [OR = 1.49 (1.11-2.02)].

All studies investigating the association between *ACE* allele *I/D* and ACEI-related cough, were included in the meta-analysis. Table 2 shows OR and heterogeneity results for the genetic contrasts of ACE *I/D* and bradykinin B_2 receptor gene polymorphisms. The main analysis revealed no significant heterogeneity (pQ = 0.259), and the random effects pooled OR was not significant [RE OR = 1.15 (0.87-1.52)] in the entire population. In the subgroup analysis by "race", Caucasians showed lack of significant heterogeneity (pQ = 0.799) and non-significant association [RE OR = 0.90 (0.60-1.35)] and East Asians revealed non-significant heterogeneity (pQ = 0.226) and significant association [RE OR = 1.49 (1.11-2.02), $P = 0.009$]. In contrast, there were significant heterogeneities for *DD vs DI* with *II* in the entire population (pQ = 0.005) and in East Asians (pQ = 0.003), and *II vs DD* with *DI* in East Asians (pQ = 0.027), *DD vs II* in the entire population (pQ = 0.008) and in East Asians (pQ = 0.006) in the genetic models.

Racial difference

In Caucasians, the genotype frequencies of ACE were 22.7% for *I/I*, 42.5% for *I/D*, and 34.8% for *D/D*. In East Asians, the genotype frequencies of ACE were 38.6% for *I/I*, 47.1% for *I/D*, and 14.3% for *D/D*. The distributions of genotypes in Caucasians and East Asians with ACEI-related cough differed significantly ($\chi^2 = 103.299$, $P < 0.01$).

Three studies demonstrated differences in the distributions of ACE genotypes by gender. The genotype frequencies of ACE were 44.4% for *I/I*, 46.3% for *I/D*,

Table 2 Odds ratios and heterogeneity results for the genetic contrasts of ACE *I/D* and bradykinin B_2 receptor gene polymorphisms

	Genetic contrast	Population	Studies	Random effects [OR (95% CI)]	*P* value *Q* test	*Z*
Angiotensin converting enzyme	*D vs I*	All	7	1.15 (0.87-1.52)	0.259	0.231
		Caucasians	2	0.90 (0.60-1.35)	0.799	0.612
		East Asians	5	1.49 (1.11-2.02)	0.226	0.009
	DD vs (DI + II)	All	11	0.85 (0.67-1.06)	0.005	0.153
		Caucasians	3	1.14 (0.74-1.76)	0.716	0.563
		East Asians	8	0.76 (0.58-0.99)	0.003	0.042
	(DD + II) vs II	All	11	1.22 (0.91-1.64)	0.052	0.133
		Caucasians	3	0.84 (0.46-1.55)	0.560	0.553
		East Asians	8	1.35 (0.91-2.00)	0.027	0.075
	DD vs II	All	11	0.79 (0.62-1.01)	0.008	0.058
		Caucasians	3	1.12 (0.69-1.83)	0.614	0.626
		East Asians	8	0.70 (0.53-0.93)	0.006	0.013
	ID vs (DD + II)	All	11	0.95 (0.80-1.22)	0.936	0.354
		Caucasians	3	0.97 (0.63-1.50)	0.889	0.900
		East Asians	8	0.94 (0.79-1.13)	0.786	0.342
Bradykinin B_2 receptor -58T/C	*T vs C*	East Asians	2	2.29 (1.42-3.68)	0.298	0.001
	TT vs (TC + CC)	East Asians	3	1.47 (0.56-3.85)	0.002	0.467
	CC vs (TC + TT)	East Asians	3	0.90 (0.66-1.24)	0.661	0.507
	TC vs (TT + CC)	East Asians	3	1.08 (0.87-1.34)	0.947	0.477

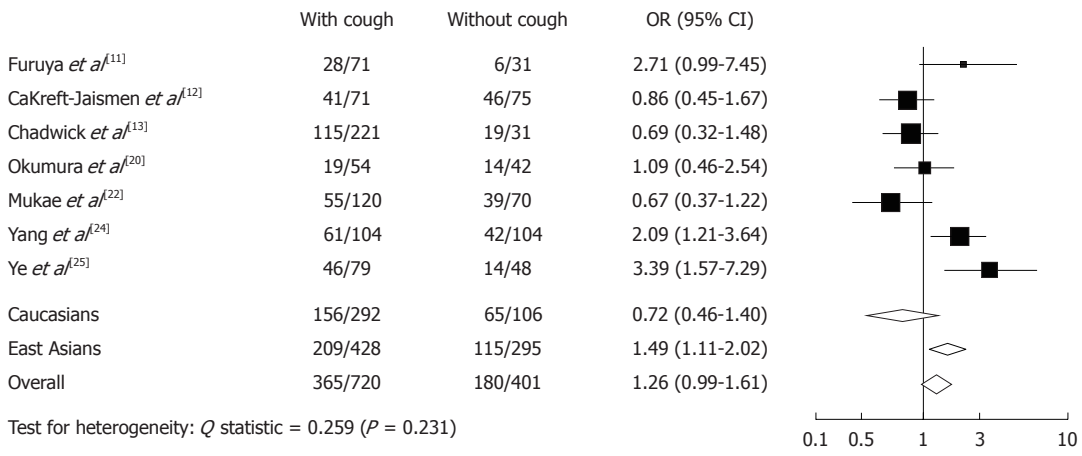

Figure 2 Random effects odds ratio estimates with the corresponding 95% confidence interval of the ACE allele contrast for ACEI-related cough. The odds ratio (OR) estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The confidence intervals of pooled estimates are displayed as a horizontal line through the diamond. The horizontal axis is plotted on a log scale. OR greater than 1 indicates increased risk of ACEI-induced cough.

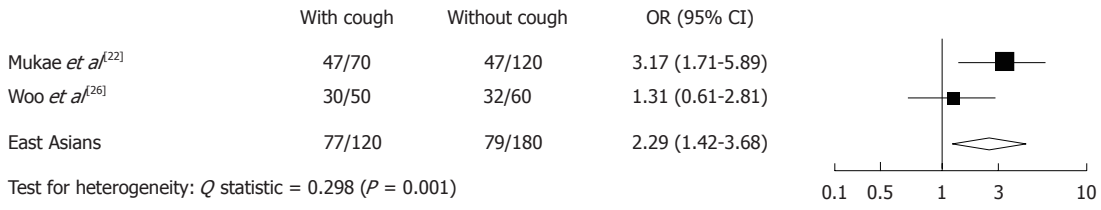

Figure 3 Random effects odds ratio estimates with the corresponding 95% confidence interval of the bradykinin B_2 receptor allele contrast for ACEI-related cough. The odds ratio (OR) estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The confidence intervals of pooled estimates are displayed as a horizontal line through the diamond. The horizontal axis is plotted on a log scale. OR greater than 1 indicates increased risk of ACEI-induced cough.

and 9.3% for *D/D* in male subjects without cough. The genotype frequencies of ACE were 43.3% for *I/I*, 47.2% for *I/D*, and 9.5% for *D/D* in male subjects with cough. These differences were not statistically significant (χ^2 = 0.074, *P* = 0.96). On the other hand, the genotype frequencies of ACE were 44.4% for *I/I*, 46.3% for *I/D*, and 9.3% for *D/D* in female subjects without cough. The genotype frequencies of ACE were 39.5% for *I/I*, 43.7%

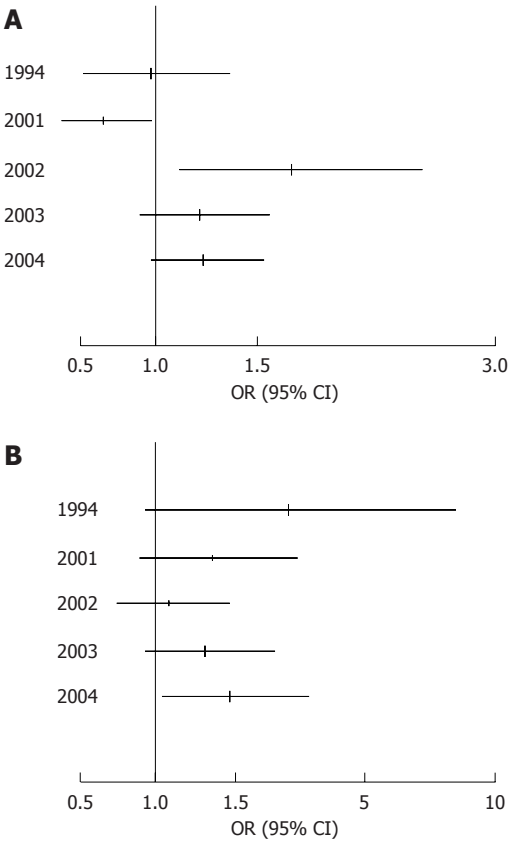

Figure 4 Cumulative meta-analysis of the ACE allele contrast for ACEI-related cough. A: Entire population; B: East Asians. The random effects pooled odds ratio (OR) with the corresponding 95% CI at the end of each year-information step is shown. OR greater than 1 indicates increased risk of ACEI-induced cough.

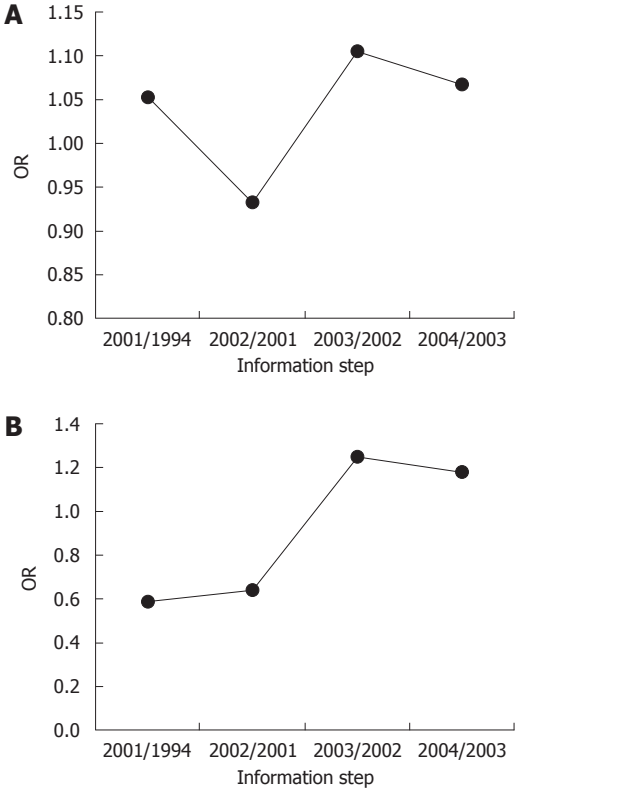

Figure 5 Recursive cumulative meta-analysis of the allele contrast (ACE *D vs I*) for ACEI-related cough. A: Entire population; B: East Asians. The relative change in random effects pooled odds ratio (OR) in each information step (OR in next year/OR in current year) for the allele contrast is shown.

for *I/D*, and 16.7% for *D/D* in female subjects with cough. These differences were statistically significant (χ^2 = 6.026, P = 0.049).

Potential bias

The cumulative meta-analysis of the allelic contrast for ACEI-related cough showed significant association as information accumulates in East Asians (Figure 4B) but not in all population (Figure 4A). In the recursive cumulative meta-analysis, the relative change in RE OR stabilized in a specific OR indicates that there is enough evidence to draw safe conclusions about the modifying effect of *ACE I/D* polymorphism in ACEI-related cough in East Asians (Figure 5B) but not in all population (Figure 5A).

Bradykinin B_2 receptor -58T/C

Bradykinin B_2 receptor -58T/C was investigated only in East Asians. The allelic frequencies of the bradykinin B_2 receptor gene were 0.56 for the C allele and 0.44 for the T allele in subjects without cough, and 0.36 and 0.64 in subjects with cough [OR = 2.25 (1.42-3.57)], respectively. The distributions of the T/C genotypes of the bradykinin B_2 receptor gene were 26% for CC, 50% for TC, and 24% for TT in the subjects without cough, and 30%, 52%, and 18% in the subjects with cough, respectively. The distributions of the T/C genotypes of the bradykinin B_2 receptor gene were significantly different (χ^2 = 8.366, P = 0.015).

In the East Asians subgroup analysis, all studies investigating the association between bradykinin B_2 receptor -58T/C and ACEI-related cough, were included in the meta-analysis. The main analysis revealed no significant heterogeneity (pQ = 0.298), and the random effects pooled OR was significant (RE OR = 2.29 (1.42-3.68)). There was significant heterogeneity for TT *vs* TC with TC (pQ = 0.002). The distributions of the genotypes of the bradykinin B_2 receptor -58T/C polymorphism were 27% for TT, 52% for TC, and 21% for CC in men without cough, and 24% for TT, 53% for TC, and 23% for CC in men with cough. These values were 35% for TT, 46% for TC, and 19% for CC in women without cough, and 25% for TT, 52% for TC, and 23% for CC in women with cough. The distributions of the genotypes of the bradykinin B_2 receptor -58T/C polymorphism showed a trend for a significant difference in women (χ^2 = 5.847, P = 0.054).

Assessment of publication bias

The funnel plot of the *ACE I/D* meta-analysis showed no asymmetry (Figure 6). This result suggested the absence of bias in the present meta-analysis.

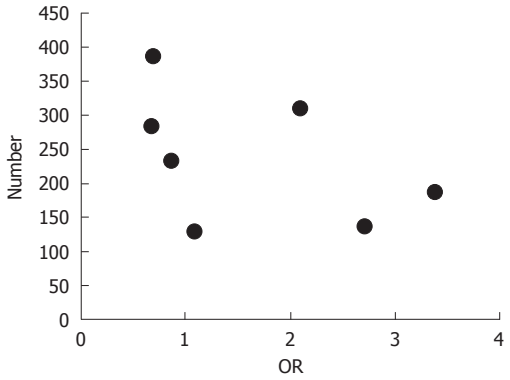

Figure 6 Funnel plot.

DISCUSSION

In these meta-analyses, the studies offered inconclusive and in many cases contradictory results. The most widely investigated genetic polymorphisms were *ACE I/D* and bradykinin B2 receptor T/C polymorphisms. Therefore, it is still controversial as to whether ACE and bradykinin polymorphisms are associated with ACEI-related cough. In our comprehensive meta-analysis, a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in the entire population and positive associations between ACE and bradykinin B2 receptor polymorphisms and ACEI-related cough were observed in East Asians.

The specific mechanism by which ACEIs as a class cause cough is not firmly established. It is likely that increased levels of mediators outside the renin-angiotensin-aldosterone system cascade may be involved in the mechanism of cough. These mediators include kinins such as bradykinin, substance P, a neurotransmitter present in the respiratory tract, C-fibers and two bronchial inflammatory agents derived from arachidonic acid. Cough may be associated with ACE inhibition, not due to blockade of Ang Ⅱ formation, but to inhibition of kinase Ⅱ-related factors[27].

A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans[7-9]. This symptom seems to be more prevalent in females than in males; in larger studies, two thirds of the affected patients were female[28]. Cough is also more common in nonsmokers than in smokers. Lee *et al*[21] showed that ACEI-related cough mainly appeared in female patients with non-insulin dependent diabetes mellitus. Israili *et al*[29] postulated that women have a low cough threshold and may report this adverse effect more often. Because cough is a class effect of ACEIs, and because its occurrence is not predicted by any external factors, it seems reasonable to suspect that a primary, genetically determined characteristic resulting in an alteration of drug action or drug metabolism may be responsible.

ACEI-related cough is thought to result from the interaction of multiple genetic factors. Since the *I/D* polymorphism is an intronic marker, it may be functionally neutral but is in strong linkage disequilibrium with another unobserved functional mutation within the ACE gene. A large majority of previous studies have shown a positive association between the *DD* genotype and an increased risk of myocardial infarction, but results in hypertension, left ventricular hypertension, cardiomyopathy and restenosis after percutaneous coronary intervention remain quite controversial. It was found that the frequency of genotype *II* in patients with cough was increased by 74% compared to patients without cough. It was suggested that a greater *I* allele frequency may increase genetic susceptibility to ACEI-related cough[11]. However, Kreft-Jais *et al*[12] found no significant difference in *ACE* genotype. Chadwick *et al*[13] demonstrated that the distribution of genotypes in British patients with ACEI-related cough and in Japanese patients with ACEI-related cough differed significantly. These results provide one possibility that East Asians experience more cough induced by ACEIs than Caucasians.

The risk of ACEI-related cough was consistent for the allele contrast, although the results showed significant heterogeneity. Heterogeneity may result from differences in sample selection, in genotyping methodology, or may be due to real differences in populations or due to interactions with other unknown risk factors[17]. The results of the meta-analysis were affected by population origin. East Asians showed statistically significant results under the *ACE* allele contrast, whereas Caucasians produced non-significant results. The link between ACEI-related cough and *I/D* polymorphism in the *ACE* gene suggests that ACEI-related cough is related to serum ACE concentration[24,30]. There was a lower frequency of the *DD* genotype in East Asians. Functional analyses of variation in the *ACE* gene have indicated that different loci control ACE levels in particular "racial" groups [31]. The *ACE I/D* polymorphism is associated with serum ACE activity, and patients with the *II* genotype have the lowest serum ACE levels compared with the *ID* and *DD* genotype; therefore the *II* genotype would be associated with an increased risk of developing cough[11]. The present study demonstrated that *ACE I/D* polymorphism showed a significant association with ACEI-related cough in East Asians, but not in the entire population or in Caucasians. The frequency of genotype *II* in patients with cough was significantly increased by 43% compared to patients without cough in East Asians. It is suggested there is a link between the *I* allele and an increased risk for ACEI-related cough in East Asians.

Bradykinins, a family of oligopeptides derived from the enzymatic action of kallikreins on kininogens, can promote all the major signs of inflammation, including hyperemia, leakage of plasma proteins, and pain[32-35]. Kinins act mainly as local hormones by activating specific receptors, known as B1 and B2 receptors, with most of the inflammatory and cardiovascular effects being mediated by the B2 receptor[35,36]. Human bradykinin receptors are cell-surface G-protein-coupled receptors of the 7-transmembrane-domain superfamily[37]. The bradykinin

B_2 receptor gene has been implicated as one of the candidate genes involved in the complex genetic underpinnings of essential hypertension and cardiovascular diseases. Since B_2-bradykinin receptor mediates most of the inflammatory actions of bradykinin and is widely present in most tissues[38,39], a genetic defect of the bradykinin B_2 receptor may lead to altered biological activities of the functional protein.

Single nucleotide polymorphisms (SNPs) located in the coding or regulatory regions of genes are most likely to cause functional differences[40]. Although most SNPs have no effect on gene function, non-synonymous SNPs can serve as valuable markers[41]. Using promoter assay studies of genetic variants of the bradykinin receptor, -58T was found to have a higher transcriptional rate than that of -58C[42,43], and it has been suggested that the transcriptional activity of the promoter might be involved in the appearance of ACEI-related cough[16]. The T/T genotype in the bradykinin B_2 receptor was the most sensitive compared to T/C and C/C, and this tendency was more prevalent among women[16]. The transcriptional activity of the bradykinin B_2 receptor promoter might be involved in the occurrence of ACEI-related cough, and high transcriptional activity of the bradykinin B_2 receptor promoter might induce ACEI-related cough[16]. The present study demonstrated that bradykinin T/C polymorphism showed a significant association with ACEI-related cough in East Asians.

In conclusion, many studies have tried to characterize the effects of *ACE I/D* and bradykinin B_2 receptor polymorphisms on ACEI-related cough. However, the reported results so far are discrepant and inconsistent. The relationship between *ACE* and bradykinin B_2 receptor genetic variation and ACEI-related cough remains an unresolved issue. In view of the available evidence, *ACE I/D* and bradykinin B_2 receptor polymorphisms contributed to the risk of ACEI-related cough in East Asians, but a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in Caucasians.

COMMENTS

Background

Studies in French or in British have not showed the relation between the angiotensin-converting enzyme genetic polymorphism and angiotensin-converting enzyme inhibitors (ACEI) related-cough. The role of genetic polymorphisms in ACEI-related cough remains controversial.

Research frontiers

It is important to perform a worldwide trial in the whole world to evaluate this relation but it is impractical. The research have performed this meta-analysis to evaluate the association with genetic polymorphisms and ACEI-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

Innovations and breakthroughs

This results proved the reason why a high incidence of cough has been reported in the Asians.

Peer review

The current meta-analysis by Nishio et al investigates the relation between ACE I/D and Bradykinin SNP's on the development of cough in different ethnic populations. The subject of the meta-analysis is relevant for daily clinical practice as cough is a major limitation of ACEi usage.

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CASE REPORT

Epicardial coronary artery intimal smooth muscle hyperplasia in a cocaine user

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Abstract

Accelerated epicardial coronary artery atherosclerosis has been well-documented in cocaine users. There are only two reported cases of cocaine-associated diffuse intimal expansion by proliferated smooth muscle cells causing significant coronary luminal compromise. This type of lesion histologically resembled chronic transplant arteriopathy. Here, we report a third such case.

Key words: Cocaine; Coronary artery; Hyperplasia; Smooth muscle

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INTRODUCTION

In cocaine users, thickening of small intramyocardial arteries, coronary artery dissection and accelerated coronary atherosclerosis have been previously reported[1]. Cocaine-associated epicardial coronary artery intimal expansion due to smooth muscle hyperplasia, histologically resembling that seen in chronic transplant vasculopathy, has only been reported twice[2,3]. We now report the third such case.

CASE REPORT

A 22-year-old man was seen collapsing at home after having ingested codeine containing syrup and other unspecified drugs. Emergency medical personnel found pulseless electrical activity, performed successful resuscitation, and brought the patient to the Emergency Department (ED) of an affiliated hospital. History included obesity, sleep apnea, 10 to 15 pack-years of cigarette smoking, and admission for a psychotic episode after having smoked illy (also known as wet or fry). Illy is marijuana treated with embalming fluid (formaldehyde and methanol), usually containing phencyclidine[4]. In addition to the aforementioned drugs, there was a history of alcohol, heroin, and codeine use. In the ED, ventricular fibrillation occurred; defibrillation was successful, but consciousness was never regained during the hospitalization. A urine screen showed cocaine (> 300 ng/mL), opiates (> 2000 ng/mL), and PCP (> 25 ng/mL). The blood alcohol was 8.5 mg/dL. In addition to the loss of consciousness, ventilator-dependent respiratory failure, rhabdomyolysis, acute renal failure, elevated cardiac troponin, bacteremia and brain death

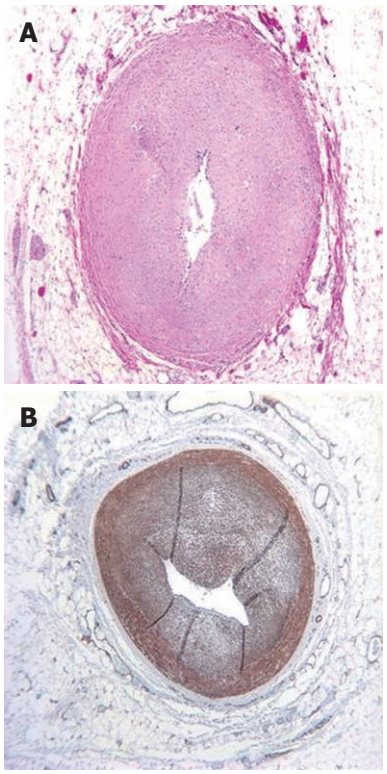

Figure 1 Sections at different segments of the proximal left anterior descending coronary artery. A: Hematoxylin and eosin stain; B: Smooth muscle actin immunohistochemistry (Original magnification, 40 ×). Note intimal expansion and critical luminal compromise in both sections; B shows that most of the intimal expansion is due to smooth muscle cells.

marked the hospital course. With agreement of the family, mechanical ventilation was discontinued on the tenth hospitalization day and death occurred about 10 min later.

Autopsy findings confirmed the clinical history. The heart weighted 500 g. The left anterior descending and a diagonal branch, left circumflex, and right and posterior descending coronary arteries showed diffuse, concentric luminal narrowing almost throughout. The sectioned myocardium showed a focus of pallor involving the base of the heart in the posterior interventricular septum measuring 1.2 cm × 1.3 cm × 3 cm. A small focus of pallor was also present in the left ventricular posterior papillary muscle.

Histologic examination of the coronary arteries showed stenoses of 50% to 90% in different sections from the affected vessels (Figure 1A). Intimal expansion by smooth muscle-actin expressing cells and extracellular matrix caused luminal compromise (Figure 1B). Lipid containing atheromas, recanalized thrombi and calcification were rare. Atherosclerosis was imperceptible in other mid-sized arteries and was only minimal in the large elastic arteries. Histologic sections from the myocardium showed infarcts of varying appearance. The posterior septal sections showed healed infarction. Both left ventricular papillary muscles had foci of necrotic myocytes, minimal fibrosis, and no inflammation. The right ventricle contained a microscopic focus of contraction band necrosis without inflammation.

Other autopsy findings included acute and organizing pneumonia, rhabdomyolysis, acute tubular necrosis, diffuse softening of the brain numerous in the cerebral cortex, hippocampus, brainstem and cerebellum.

DISCUSSION

Direct acute effects of cocaine or PCP on the myocardium, the structural coronary, myocardial lesions described above or any combination of these could have caused death.

Morphologic effects of cocaine on the epicardial coronary arteries have been documented previously and included dissection and atherosclerosis[1].

Cocaine-related non-atherosclerotic intimal smooth-muscle cell proliferation resembling that seen in chronic vasculopathy has been reported in only two cases[2,3]. Our patient, as well as one other patient previously reported[2], used several drugs. Cocaine was considered to be the cause of the coronary lesions, although the possibility that some other agent was involved was not excluded, especially in light of the few reported cases. We have also seen similar lesions in the small mesenteric arterial branches causing bowel infarction in another cocaine user; in this case the coronary arteries were not affected[5].

The mechanism by which cocaine might induce intimal smooth muscle hyperplasia in middle-sized arteries has not been elucidated. Recent findings, however, have suggested that smooth muscle proliferation could be the result of cocaine-induced expression of platelet derived growth factor[6]. Of course, the experimental model, human immunodeficiency virus infected mouse brain endothelial cells differs substantially from the human clinical situation.

In conclusion, we have described the third case of clinically significant non-atherosclerotic intimal smooth muscle hyperplasia in a cocaine user.

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Februrary 25-27
CardioRhythm 2011
Hong Kong, China

March 19-26
Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
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May 20-22
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May 20-22
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May 21-24
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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