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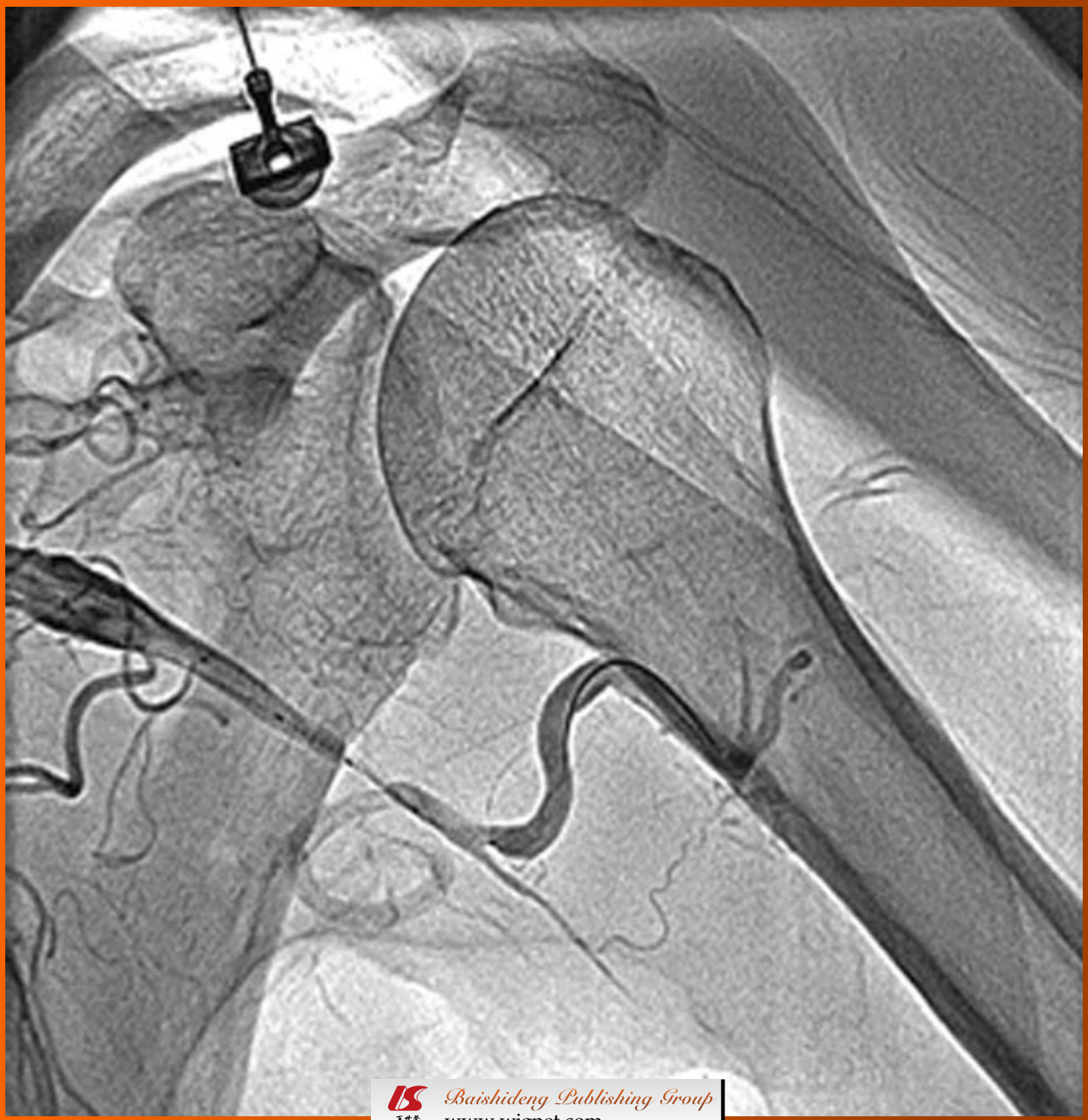

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EDITORIAL

Differential diagnosis of tachycardia with a typical left bundle branch block morphology

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Abstract

The evaluation of wide QRS complex tachycardias (WCT) remains a common dilemma for clinicians. Numerous algorithms exist to aid in arriving at the correct diagnosis. Unfortunately, these algorithms are difficult to remember, and overreliance on them may prevent cardiologists from understanding the mechanisms underlying these arrhythmias. One distinct subcategory of WCTs are those that present with a "typical" or "classic" left bundle branch block pattern. These tachycardias may be supraventricular or ventricular in origin and arise from functional or fixed aberrancy, bystander or participating atriofascicular pre-excitation, and bundle branch reentry. This review will describe these arrhythmias, illustrate their mechanisms, and discuss their clinical features and treatment strategies.

Key words: Typical left bundle branch block; Wide complex tachycardia; Bundle branch reentrant ventricular tachycardia

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INTRODUCTION

The evaluation of wide QRS complex tachycardia (WCT) remains a common clinical dilemma[1]. The process of determining the correct diagnosis can be confusing and cumbersome. Even the presence of hemodynamic stability is not helpful in determining the tachycardia mechanism.

Most physicians understand that the pivotal diagnostic challenge focuses on determining whether the tachyarrhythmia is of supraventricular (with aberrant ventricular conduction) or ventricular origin. While the presence of atrioventricular (AV) dissociation during wide complex tachycardia is highly specific for a ventricular origin, this finding is often not present or is difficult to discern on the surface electrocardiogram (ECG). Complex algorithms have evolved (from 1978 to 2008) to assist the treating physician in making this distinction (Table 1)[2-6]. Many of these algorithms use specific features of the QRS complex, and subcategorize tachycardias into "right bundle branch-like" and "left bundle branch like" morphologies. However, committing these algorithms to memory can be challenging and overreliance on them may impede cardiologists from understanding the underlying tachycardia mechanism.

This review will focus on the subcategory of WCTs that present with a typical (or "classic") left bundle branch block (LBBB) pattern. These tachycardias may be

supraventricular or ventricular in origin and arise from functional or fixed aberrancy, bystander or participating atriofascicular pre-excitation, and bundle branch reentry. We describe the types of tachycardia associated with a typical LBBB morphology, discuss their clinical features and provide diagrams to elucidate their mechanisms.

DEFINITIONS

It is important to understand the distinction between "LBBB-*like*" patterns and a typical LBBB morphology. LBBB is defined as a prolonged QRS duration (≥ 120 ms) with broad monophasic R waves in leads I, V5 and V6 that are usually notched or slurred. There is delayed onset of the intrinsicoid deflection (the beginning of the QRS to the peak of the R wave is > 50 ms) in leads I, V5 and V6. There are secondary ST and T-wave changes in the opposite direction of the major QRS deflection[7]. Most algorithms define LBBB-like morphology as a QRS complex that is predominantly negative in the right precordial leads (specifically, V1) and predominantly positive in the lateral leads (I, aVL, V5, V6)[3]. In typical, or "classic" LBBB, lead V1 will demonstrate either an rS or QS complex, and, more importantly, Q waves will be absent from the left lateral leads. Kindwall and colleagues used the following criteria to distinguish ventricular tachycardia (VT) from supraventricular tachycardia (SVT) with aberrant conduction in patients with LBBB-like morphology: (1) R wave in lead V1 or V2 > 30 ms; (2) any Q wave in V6; (3) a duration of ≥ 60 ms from the onset of the QRS to the nadir of the S wave in V1 or V2; and (4) notching of the downstroke of the S wave in V1 or V2[3].

The ECG appearance of typical LBBB depends on antegrade ventricular activation occurring *via* the right bundle branch. In most instances, activation of the right bundle branch occurs *via* the AV node and His bundle. Atriofascicular accessory pathways bypass the AV node and His bundle and insert directly into (or extremely close to) the right bundle branch. The interventricular septum is depolarized *via* the His-Purkinje system with *subsequent* activation of the left ventricle. Because there is no antegrade conduction *via* the left bundle branch, the electrical impulse must propagate in a cell-to-cell fashion, resulting in delayed conduction to the left ventricle. Q waves will not be seen in the lateral leads on a surface ECG (Figure 1). In contrast, LBBB-like morphologic tachycardias are not confined to the specialized conduction system. They arise from the ventricular myocardium. Electrical impulses travel in a delayed fashion, and may propagate rightward (away from the lateral leads) before exciting the bulk of the left ventricle (Figure 2)[8]. This frequently results in a QRS complex that is wider than a typical LBBB aberrant complex, and explains why Q waves may be recorded in the left-sided ECG leads[9].

The differential diagnosis of a WCT with a typical LBBB morphology is limited to five entities: SVT with fixed LBBB, SVT with functional aberrancy, pre-excited reentrant tachycardias using an atriofascicular accessory pathway as the antegrade limb of the circuit (the retrograde limb is usually the normal ventriculo-atrial conduction system, but may be a second accessory pathway), SVT with a "bystander" atriofascicular pathway and bundle branch reentrant VT (Table 2).

Most of the above-mentioned tachycardias have a reentrant mechanism. Exceptions are limited to physiologic (non-reentrant) sinus tachycardia and automatic atrial tachycardias. Reentrant tachycardias involve continuous propagation of an activation wavefront. Three requirements must be met in order for reentry to occur. First, there must be two anatomically adjacent pathways of myocardial tissue to form a circuit. Differences in the pathways' electrophysiologic properties (refractoriness and conduction velocity) are also a requisite for reentry. Unidirectional conduction block must be present, otherwise the excitation wavefronts travelling down both limbs of the reentrant circuit will collide and extinguish each other. Finally, there must be an area of slow conduction within the circuit in order to allow enough time for previously refractory tissue to regain its excitability before the reentrant wavefront arrives to depolarize it again.

SVT WITH FIXED OR FUNCTIONAL LBBB

Any form of SVT, including sinus tachycardia, that propagates *via* the normal conduction system will demonstrate a typical LBBB morphology in patients with a preexisting (baseline) LBBB. In these patients, a resting ECG in sinus rhythm that demonstrates LBBB will quickly aid in the diagnosis. Such patients often have underlying cardiac disease.

Alternatively, a patient may have a narrow QRS complex during normal sinus rhythm but may develop tachycardia-dependent physiologic (functional) LBBB aberration (intermittent or transient LBBB) (Figure 3)[10]. In this case, the first aberrant complex results from encroachment on the refractory period of the left bundle branch of the previous complex (Figure 4)[11]. Aberration may also result from concealed retrograde penetration (e.g. from a premature ventricular contraction (PVC) originating in the left ventricle) into the left bundle branch rendering it refractory to subsequent beats. Repetitive transseptal retrograde concealed penetration from impulses conducting antegrade *via* the contralateral (right) bundle perpetuates local refractoriness or results in repetitive impulse collision (Figure 5). Other causes of transient BBB such as acceleration-dependent or bradycardia-dependent block result from disease in the His-Purkinje system and should be regarded as abnormal[12].

Abrupt recovery (facilitation) of normal conduction may result when a PVC excites the left bundle early and allows more time for it to recover (peeling back its refractoriness). The refractory period may also shorten because the PVC shortens the cycle length before (and thus the refractory period of) the next spontaneous impulse. In either case, the PVC ends the "linking" sequence created by repetitive concealed transseptal impulses[13].

SVT with fixed or functional aberrancy accounts for approximately 15%-20% of WCTs, and is a significantly

Table 1 Electrocardiographic QRS morphology criteria favoring ventricular tachycardia over supraventricular tachycardia

Authors	Date	Morphology	Criteria favoring ventricular tachycardia
Wellens *et al*[2]	1978	RBBB-like	Monophasic R in V1
			qR, QS, RS in V1
			rS, QS, qR in V6
			R/S < 1 in V6 (S > R or QS in V6)
			Left axis deviation
			QRS width > 140 ms
Kindwall *et al*[3]	1988	LBBB-like	R in V1 or V2 > 30 ms
			Any Q wave in V6
			Onset of QRS to nadir of S ⩾ 60 ms in V1 or V2
			Notching of downstroke of S in V1 or V2
Akhtar *et al*[4]	1988		Positive QRS concordance across the precordium
			Extreme left axis deviation (-90° to ± 180°)
		LBBB-like	Right axis deviation
			QRS > 160 ms
		RBBB-like	QRS > 140 ms
Brugada *et al*[5]	1991		Absence of RS complex in all precordial leads
			R to S interval > 100 ms in ⩾ one precordial lead
			Wellens' morphologic criteria in leads V1 or V6
Vereckei *et al*[6]	2008		Initial R wave in lead aVR
			Initial r or q wave > 40 ms in lead aVR
			Notch on descending limb of negative onset, predominantly negative QRS in lead aVR
			vi/vt ⩽ 1

vi/vt: Ratio of voltage amplitude during initial 40 ms of QRS complex relative to terminal 40 ms in any lead with a bi- or multiphasic QRS complex; LBBB: Left bundle branch block; RBBB: Right bundle branch block.

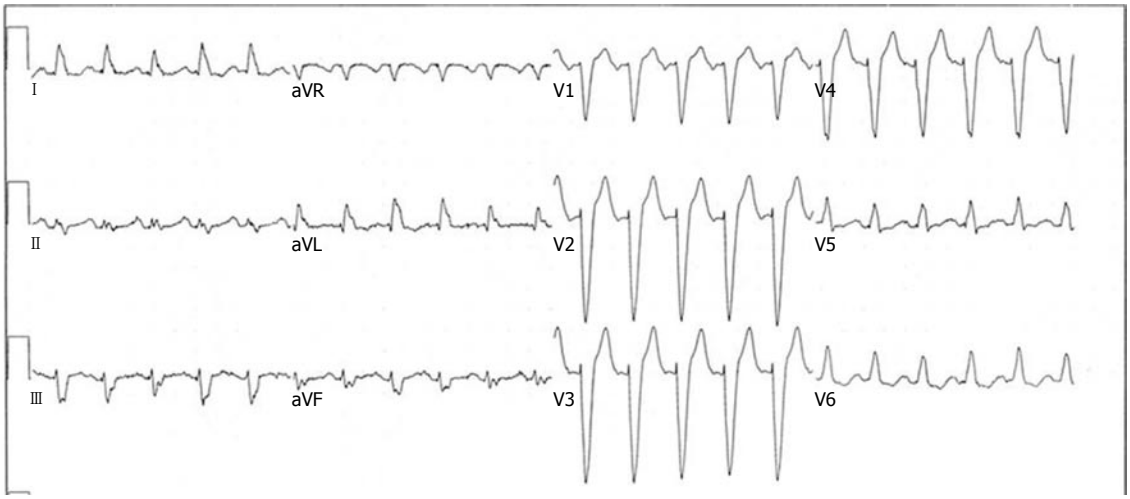

Figure 1 Electrocardiogram example of typical left bundle branch block pattern in a patient with sinus tachycardia. Lead V1 demonstrates an rS complex, while there are monophasic, notched R waves in leads I, aVL, V5 and V6. Q waves are absent in these leads.

more common cause of WCT in patients under the age of 35[14]. Although any SVT may exhibit functional LBBB, it is most commonly seen during orthodromic AV reentry tachycardia with antegrade conduction *via* the AV node and right bundle branch and retrograde conduction *via* a left free wall accessory pathway (Figure 6)[15,16].

ATRIOFASCICULAR ACCESSORY PATHWAY AND SVT WITH A BYSTANDER ATRIOFASCICULAR PATHWAY

Atriofascicular fibers originate in the right atrial free wall and insert into the distal part of the RBB or the adjacent ventricular myocardium. The tissue of these fibers is functionally similar to that of the AV node, and they demonstrate decremental conduction and a Wenckebach-type response to rapid atrial pacing. In addition, they are sensitive to adenosine[17].

Approximately 6% of patients presenting with SVT with a typical LBBB morphology have been found to have an atriofascicular bypass tract[12]. In such cases, antidromic AV reentrant tachycardia (AVRT) results from antegrade conduction down the bypass tract and retrograde propagation *via* the normal conduction system (Figure 7A)[18]. Orthodromic AVRT almost never occurs, because these

Table 2 Differential diagnosis of tachycardia with a typical left bundle branch block QRS morphology

Arrhythmia	ECG and clinical features
SVT with fixed left bundle branch block	LBBB present on baseline ECG QRS during tachycardia usually an identical match
SVT with functional LBBB aberrancy	Most often due to orthodromic AVRT At rapid rates, QRS alternans may be present
Atriofascicular antidromic tachycardia	Preexcitation may be minimal or absent during sinus rhythm Late QRS transition, leftward axis common Frequently coexists with other accessory pathways or AV nodal reentry
SVT with bystander atriofascicular accessory pathway	Accessory pathway does not participate in reentrant circuit of orthodromic AVRT, AVNRT, or atrial tachycardias (including atrial fibrillation and flutter)
Bundle branch reentrant ventricular tachycardia	Associated with acquired structural heart disease (cardiomyopathy, valvular disease) Prolonged PR interval and nonspecific IVCD often present during sinus rhythm

SVT: Supraventricular tachycardia; AVRT: Atrioventricular reentrant tachycardia; IVCD: Intraventricular conduction defect; AVNRT: Atrioventricular nodal reentrant tachycardia.

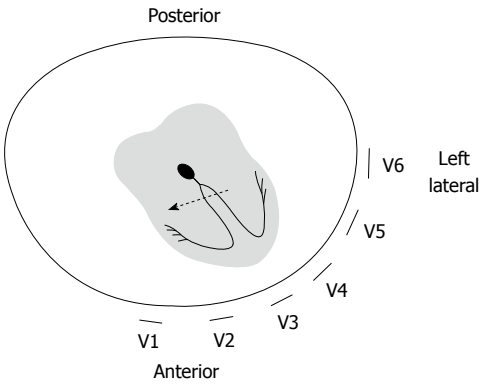

Figure 2 Mechanism of left bundle branch block-*like* electrocardiogram morphology. Electrical activation arises from outside the specialized conduction system and travels rightward before activating the left ventricle. This results in a Q wave in the left lateral electrocardiogram leads. Adapted from[8], with permission.

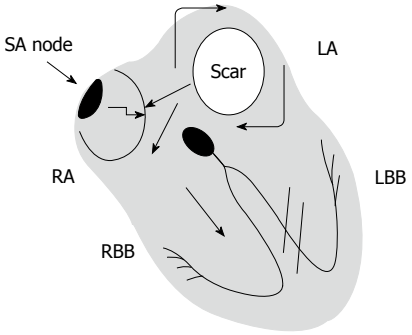

Figure 3 Atrial tachycardia can result in functional left bundle branch block. A reentrant circuit in the left atrium results in tachycardia that rapidly conducts to the ventricle *via* the atrioventricular node. Rate-dependent conduction block occurs in the left bundle branch. Adapted from[10], by permission of Oxford University Press, Inc. LBB: Left bundle branch; RBB: Right bundle branch.

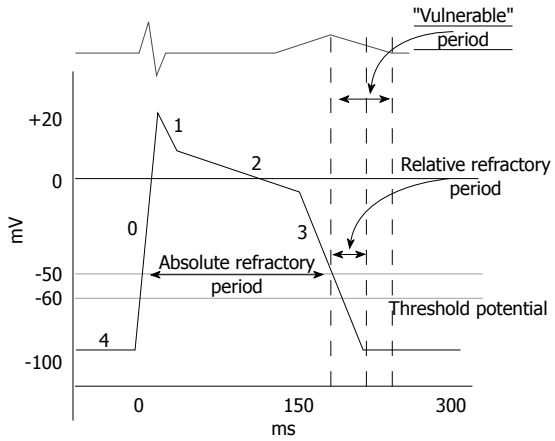

Figure 4 Typical action potential from within the His-Purkinje system. If this potential was from the left bundle branch, impulses that occur (encroach upon) the absolute refractory period will not excite the tissue. A new action potential will not occur and (assuming it is not also refractory) conduction will occur solely through the right bundle branch. Adapted from[11], with permission.

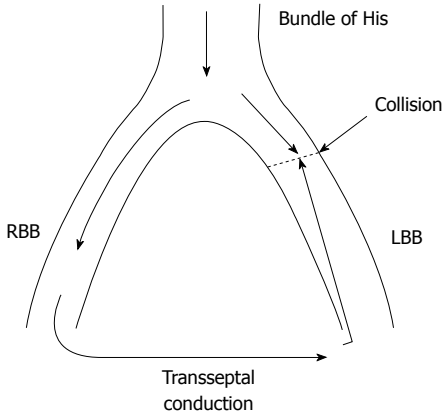

Figure 5 Mechanism of linking in functional left bundle branch block aberrance. Repetitive transseptal retrograde concealed penetration from impulses conducting antegrade *via* the right bundle perpetuates local refractoriness or results in repetitive impulse collision. LBB: Left bundle branch; RBB: Right bundle branch.

bypass tracts generally do not conduct in a retrograde direction. It is not uncommon for atriofascicular fibers to co-exist with other accessory pathways which may serve as the retrograde limb of a pre-excited (typical) LBBB tachycardia or become apparent after ablation of the atriofascicular pathway[19]. Antegrade conduction *via* most right-sided accessory pathways will produce a LBBB-*like* morphology on the ECG. However, since the vast major-

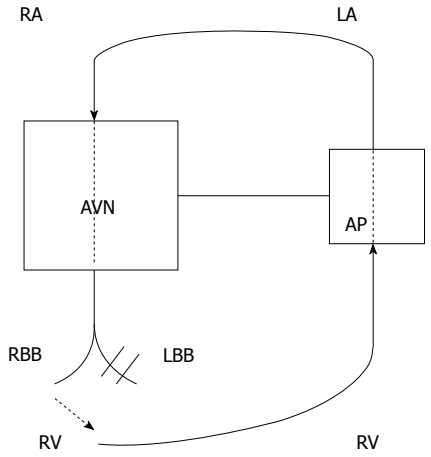

Figure 6 Illustration of orthodromic AV reentry tachycardia resulting in a wide QRS tachycardia with left bundle branch block morphology. A left sided accessory pathway is present. During tachycardia, antegrade conduction is *via* the atrioventricular node and right bundle branch (RBB), and retrograde conduction is *via* the accessory pathway. Adapted from[15], with permission. LBB: Left bundle branch.

ity of these pathways do not insert into the right bundle branch, antidromic conduction during AVRT will not demonstrate the features of typical LBBB.

Atriofascicular bypass tracts may coexist with other SVTs that do not require an AV bypass tract for initiation and maintenance. Therefore, during AV nodal reentrant tachycardia, atrial tachycardia, atrial flutter or atrial fibrillation, atriofascicular pathways may be present and function as a bystander; a conduit to ventricular activation that results in a typical LBBB morphology, but not participating as a requisite component of the tachycardia' s reentrant circuit (Figure 7B)[18].

The site where atriofascicular bypass tracts cross the tricuspid annulus is the preferred target for radiofrequency ablation. Acute success rates have been reported in the range of 90% to 100%[20-22]. Targeting the distal, ventricular insertion site is complicated by its typically broad insertion, with distal arborization. This requires ablation of a large area of the ventricular myocardium in order to be effective, and is commonly associated with development of right BBB.

BUNDLE BRANCH REENTRANT VT

Bundle branch reentrant tachycardia (BBRVT) is a form of VT resulting from macroreentry within the bundle branches. Macroreentry involving the His-Purkinje system was originally described by Akhtar in 1974, in which premature right ventricular stimulation produced ventricular echo beats with a LBBB morphology[23]. Sustained BBRVT as a clinical entity was identified by Caceres *et al*[24] in 1989 and is most commonly seen in patients with acquired structural heart disease. BBRVT has been estimated to be the mechanism of VT in up to 6% of patients with sustained monomorphic VT. BBRVT has also been reported to account for 41%-45% of monomorphic VT in patients with nonischemic dilated cardiomyopathy[25]. However, most electrophysiology laboratories would report percentages that are considerably less than 6% and 41%. BBRVT may also be found in patients with ischemic and valvular heart disease. Patients typically present with presyncope, syncope, or sudden cardiac arrest.

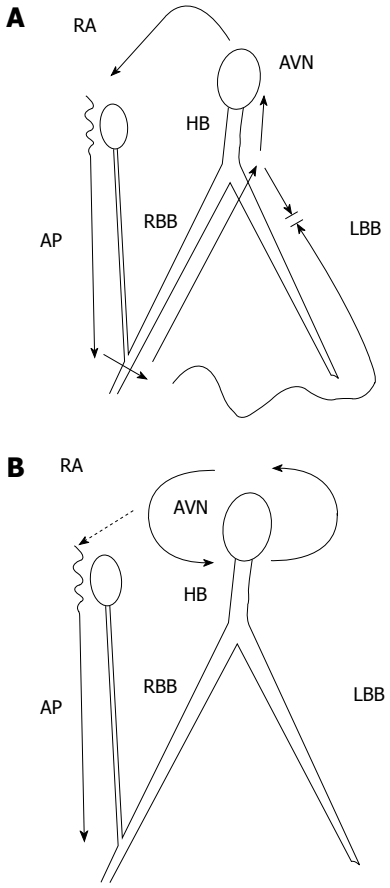

Figure 7 Pre-excitation *via* atriofascicular ("Mahaim") bypass tracts. A: Antidromic AV reentry tachycardia. The tachycardia circuit conducts antegrade down the Mahaim fiber and inserts into the distal right bundle branch (RBB). It propagates retrograde back to the atrium *via* the more proximal portion of the RBB; B: Atrioventricular nodal reentrant tachycardia with a "bystander" Mahaim fiber present. The bypass tract is not part of the tachycardia circuit, but contributes to ventricular activation. A wide QRS complex will be present with a left bundle branch block configuration, but ablation of the bypass tract will not eliminate the tachycardia. Adapted from[18], with permission. LBB: Left bundle branch.

The right bundle branch is responsible for the antegrade limb of the circuit in a majority of cases, with retrograde activation *via* one of the fascicles of the left bundle branch. This results in a typical LBBB pattern on the surface ECG. Tachycardia induction occurs when a paced ventricular beat finds the retrograde right bundle branch refractory. If slow (delayed) retrograde conduction through the left bundle branch occurs, the right bundle branch will recover and be capable of antegrade reactivation resulting in macroreentry (Figure 8). Subsequent retrograde left bundle conduction may perpetuate the sequence resulting in sustained tachycardia. ECGs recorded during sinus rhythm often show evidence of distal conduction system disease, with a prolonged PR interval and a nonspecific "LBBB-like" intraventricular conduction

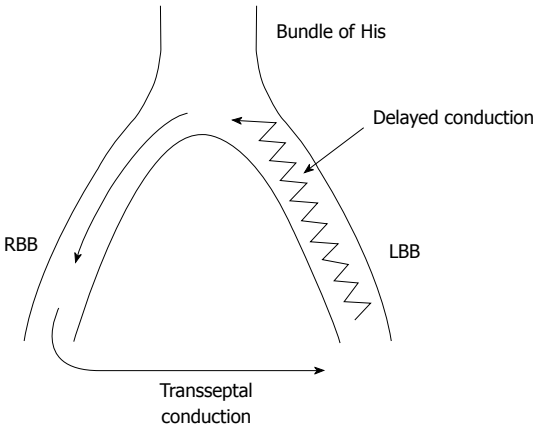

Figure 8 Mechanism of bundle branch reentrant ventricular tachycardia. The right bundle branch (RBB) is the antegrade limb of the circuit, with retrograde conduction *via* the slowly conducting left bundle branch. This allows the RBB to recover and be capable of reactivation, thereby perpetuating the reentrant circuit. LBB: Left bundle branch.

delay (wide QRS complex). Typical LBBB is an uncommon finding on the resting ECG although some patients may have apparent complete antegrade LBBB with intact retrograde left bundle branch conduction[26]. On electrophysiologic testing, conduction through the His-Purkinje system (baseline HV interval) is typically prolonged, averaging 80 ms (normal 35-55 ms) compatible with trifascicular conduction disease. Antiarrhythmic therapy is usually ineffective. Fortunately, radiofrequency ablation of the right bundle branch easily cures this arrhythmia. However, the patient may require permanent pacing if there is baseline antegrade LBBB or the HV interval prolongs to more than 90-100 ms. About 25% of patients have other inducible VTs[27]. These patients are best managed with an adjunctive implantable cardioverter-defibrillator (ICD). Many patients with BBRVT have advanced left ventricular dysfunction, wide QRS complexes and symptoms of heart failure which makes them appropriate candidates for cardiac resynchronization-ICD therapy.

DIAGNOSTIC AND ACUTE THERAPEUTIC MANEUVERS

The patient presenting with a WCT is often a source of anxiety and a diagnostic dilemma for the treating physician. However, when the patient presents with a "typical" or "classic" LBBB, without the presence of Q waves in the lateral precordial leads, the differential diagnosis is limited to the five entities discussed above.

With a more limited differential, the cardiologist can take a number of steps to clarify the underlying mechanism and determine the most appropriate treatment strategy. If a prior ECG is available, it should be reviewed for the possible clues it may provide. LBBB on the resting ECG is highly suggestive of SVT with fixed aberrancy. When LBBB is present on a resting ECG during sinus rhythm the QRS morphology during SVT with fixed aberrancy typically matches precisely[28].

As noted above, the 12-lead ECG during sinus rhythm may help differentiate between VT and SVT as well as provide clues about the tachycardia mechanism. However, a number of circumstances may limit its utility. SVT with fixed LBBB may exhibit electrical alternans (alteration of 0.1 mV or greater of the QRS or T wave) that is absent during sinus rhythm, suggesting the diagnosis of orthodromic AVRT. The presence of QRS alternans is a rate-related phenomenon and does not distinguish SVT from VT[29]. Patients with BBRVT (uncommonly) exhibit LBBB in sinus rhythm (as noted above, a prolonged PR interval and nonspecific intraventricular conduction delay are more common findings) and may have a matching QRS or QRS alternans during tachycardia. Another situation in which the ECG pattern of LBBB during sinus rhythm may not match that seen during SVT may occur with atriofascicular preexcitation. In sinus rhythm, antegrade fusion between AV nodal and accessory pathway conduction contributes to the QRS morphology. During antidromic atriofascicular tachycardia antegrade conduction occurs exclusively *via* the accessory pathway. This may result in a shift in QRS axis and/or duration[30]. Among the features suggestive of atriofascicular preexcitation include a short PR interval (during sinus rhythm) and late (after lead V4) transition of the QRS complex from a negative to a positive deflection[31]. If preexcitation is not visible during sinus rhythm and the LBBB pattern is the result of block in the His-Purkinje system (true anatomically fixed LBBB) the precordial QRS transition may be altered during antidromic atriofascicular tachycardia.

If an LBBB pattern is due to His-Purkinje conduction delay, rather than complete conduction block, it may be subject to rate-related changes[32]. LBBB with right axis deviation (RAD) is uncommon and suggestive of cardiomyopathy[33]. Intermittent RAD has been reported with induced aberration[34]. Hence, the QRS amplitude, duration, precordial transition and axis may all be altered during tachycardia, relative to sinus rhythm with fixed LBBB. It is, however, pivotal to remember that these are all exceptions to a very reliable rule.

If the cardiologist is confident that the WCT has a typical LBBB configuration, and a resting ECG is unavailable, it is reasonable to attempt a vagal maneuver such as carotid sinus massage. In 2009, Marill and associates demonstrated the safety of administering the intravenous AV nodal blocking agent adenosine in hemodynamically stable patients with wide QRS tachycardias[1]. A defibrillator should be present in case of the (unlikely) precipitation of rapid pre-excited atrial fibrillation.

In patients with SVT due to AV nodal reentrant tachycardia or AVRT, blocking AV nodal conduction will effectively terminate the tachycardia and restore sinus rhythm. SVT due to sinus tachycardia, atrial fibrillation or atrial flutter may exhibit transient AV conduction block, allowing for easier diagnosis of the unmasked supraventricular rhythm. This will be followed by subsequent return to an increased ventricular rate. The impact of adenosine on atrial tachycardia is variable (ranging from

no response to transient AV block to tachycardia termination)[35]. Antidromic atriofascicular fiber-mediated tachycardia may also terminate with adenosine if either antegrade accessory pathway or retrograde AV nodal blockade occurs.

BBRVT should be suspected in patients with typical LBBB tachycardia and significant structural heart disease. BBRVT is the only one of these clinical entities that usually exhibits no response to adenosine[36]. Although administration of adenosine may occasionally result in VA dissociation during hemodynamically stable VT, it should be noted that BBRVT is usually rapid and hemodynamically unstable, making DC cardioversion the initial option of choice.

LONG-TERM MANAGEMENT

Long-term management of sinus tachycardia usually requires reversal of its underlying cause. Sinus node reentry tachycardia is uncommon as an isolated entity. When present, it is usually quite amenable to catheter ablation[37]. Catheter ablation is first line therapy for atrial tachycardia and flutter, as well as tachycardias which require participation of an accessory pathway. We believe that catheter ablation is appropriate first-line therapy for AV nodal reentrant tachycardia because of its high cure rate and low complication rate[38,39]. As noted, BBRVT is exquisitely amenable to cure *via* ablation of the right bundle branch. Adjunctive therapy with an ICD is frequently (if not always) indicated. While antiarrhythmic drugs are still first-line treatment for atrial fibrillation, this arrhythmia may be amenable to catheter ablation after a failed trial of drug therapy[40].

CONCLUSION

In 2011**,** it is important for the clinician to be aware of "cutting edge" algorithms and diagnostic/therapeutic maneuvers[1,6]. In addition, respect for traditional electrocardiography is requisite to help physicians distinguish between "typical" LBBB and "LBBB-like" tachycardia morphologies. The clinical features and electrophysiologic characteristics of the five types of tachycardia with a typical LBBB pattern have been outlined above. A clear understanding of their mechanisms should facilitate tachyarrhythmia management. Most are quite amenable to treatment. Administration of adenosine is usually safe in the presence of hemodynamic stability and may aid in making the correct diagnosis. Long-term management strategies usually require referral to an electrophysiologist for catheter ablation.

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REVIEW

Diagnosis and management of pericardial effusion

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Abstract

Pericardial effusion is a common finding in everyday clinical practice. The first challenge to the clinician is to try to establish an etiologic diagnosis. Sometimes, the pericardial effusion can be easily related to a known underlying disease, such as acute myocardial infarction, cardiac surgery, end-stage renal disease or widespread metastatic neoplasm. When no obvious cause is apparent, some clinical findings can be useful to establish a diagnosis of probability. The presence of acute inflammatory signs (chest pain, fever, pericardial friction rub) is predictive for acute idiopathic pericarditis irrespective of the size of the effusion or the presence or absence of tamponade. Severe effusion with absence of inflammatory signs and absence of tamponade is predictive for chronic idiopathic pericardial effusion, and tamponade without inflammatory signs for neoplastic pericardial effusion. Epidemiologic considerations are very important, as in developed countries acute idiopathic pericarditis and idiopathic pericardial effusion are the most common etiologies, but in some underdeveloped geographic areas tuberculous pericarditis is the leading cause of pericardial effusion. The second point is the evaluation of the hemodynamic compromise caused by pericardial fluid. Cardiac tamponade is not an "all or none" phenomenon, but a syndrome with a continuum of severity ranging from an asymptomatic elevation of intrapericardial pressure detectable only through hemodynamic methods to a clinical tamponade recognized by the presence of dyspnea, tachycardia, jugular venous distension, pulsus paradoxus and in the more severe cases arterial hypotension and shock. In the middle, echocardiographic tamponade is recognized by the presence of cardiac chamber collapses and characteristic alterations in respiratory variations of mitral and tricuspid flow. Medical treatment of pericardial effusion is mainly dictated by the presence of inflammatory signs and by the underlying disease if present. Pericardial drainage is mandatory when clinical tamponade is present. In the absence of clinical tamponade, examination of the pericardial fluid is indicated when there is a clinical suspicion of purulent pericarditis and in patients with underlying neoplasia. Patients with chronic massive idiopathic pericardial effusion should also be submitted to pericardial drainage because of the risk of developing unexpected tamponade. The selection of the pericardial drainage procedure depends on the etiology of the effusion. Simple pericardiocentesis is usually sufficient in patients with acute idiopathic or viral pericarditis. Purulent pericarditis should be drained surgically, usually through subxiphoid pericardiotomy. Neoplastic pericardial effusion constitutes a more difficult challenge because reaccumulation of pericardial fluid is a concern. The therapeutic possibilities include extended indwelling pericardial catheter, percutaneous pericardiostomy and intrapericardial instillation of antineoplastic and sclerosing agents. Massive chronic idiopathic pericardial effusions do not respond to medical treatment and tend to recur after pericardiocentesis, so wide anterior pericardiectomy is finally necessary in many cases.

Key words: Pericardial effusion; Etiology; Diagnosis; Therapy

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INTRODUCTION

Pericardial effusion is a relatively common finding in everyday clinical practice. Sometimes the clinical picture of the patient leads directly to the search for pericardial effusion, as occurs in patients with chest pain of pericarditic characteristics or in patients with underlying diseases that can cause pericardial involvement (renal failure, chest irradiation) and thoracic complaints. Other patients, without previous known diseases, seek medical attention because of dyspnea or nonspecific chest discomfort and the thoracic X-ray shows the presence of an enlarged cardiac silhouette with clear lungs. Finally, an unexpected cardiomegaly can be fortuitously found in asymptomatic patients during routine medical control for job or insurance purposes or for unrelated complaints. In any case, the finding of cardiomegaly with clear lungs should raise the suspicion of a pericardial effusion. The echocardiogram is the most available and reliable technique in order to verify the presence and the amount of a pericardial effusion; in addition, the echocardiogram offers valuable data for evaluation of hemodynamic repercussion. Mild pericardial effusion (sum of echo-free spaces in the anterior and posterior pericardial sac of less than 10 mm) is a relatively frequent finding, especially in elderly women[1]. In fact, this finding does not always correspond to true effusion, but to pericardial fat. In these cases, computed tomography (CT) is a reliable method to precisely identify the nature of this echocardiographic finding[2].

Although echocardiography is the standard and most available method for the evaluation of pericardial effusion, CT[2] and magnetic resonance imaging (MRI) can offer some advantages. These imaging techniques allow assessment of the entire chest and detection of associated abnormalities in the mediastinum, lungs and adjacent structures. CT and MRI are also less operator dependent and delineate more precisely the spacial distribution of pericardial effusion in complex pericardial collections. In addition, multidetector CT scanners and MRI may provide valuable information about the function and dynamics of the heart and pericardium. Some of the reported limitations of echocardiography are generally not present with CT, including the possibility of false-positive findings due to adjacent pathologic conditions that may simulate pericardial effusion. Another advantage of CT and MRI is the possibility of identifying hemorrhagic effusions or clots within the pericardium.

The aim of this article is to give a comprehensive review of the etiology, hemodynamic repercussion, and management of moderate (sum of echo-free spaces in anterior and posterior pericardial sac between 10 and 20 mm) and severe (more than 20 mm) pericardial effusion.

CLINICAL APPROACH TO ETIOLOGIC DIAGNOSIS

When a clinician is faced with a patient who presents with a pericardial effusion, the first challenge is to identify its etiology. In some instances, it can be easily related to an associated condition or medical procedure (Table 1). This happens, for example, in patients who develop pericardial effusion in the course of acute myocardial infarction[3,4], in patients with end-stage renal failure, in patients receiving chest radiation, or in patients recently submitted to an invasive cardiac procedure with endocavitary catheters. However, even in these contexts, the possibility of unrelated etiologies should be considered. The finding of a pericardial effusion in patients with underlying malignancy creates a more complex dilemma, as not infrequently pericardial effusion is due to alternative causes and not to direct neoplastic pericardial involvement. In Posner's series[5] malignant pericardial disease was diagnosed in 18 (58%) of 31 patients with underlying cancer and pericarditis, while 32% of the patients had idiopathic pericarditis and 10% had radiation induced pericarditis. Porte *et al*[6] studied 114 patients with recent or remote history of cancer and a pericardial effusion of unknown origin requiring drainage for diagnostic or therapeutic purposes. Pericardioscopy was performed in 112 patients with pericardial fluid analysis and biopsy of abnormal structures or deposits under direct visual control. Malignant pericardial disease was found in 44 (38%) patients, while 70 (61%) patients had non-malignant pericardial effusions (idiopathic in 33 patients, radiation-induced in 20 patients, infectious effusion in 10 patients, and hemopericardium as a result of coagulation disorders in 8 patients). These studies are important since they show that, in more than half of the patients with underlying cancer, a pericardial effusion is due to causes different than direct neoplastic involvement. Therefore, the precise etiology of these effusions needs to be clarified, as obvious prognostic and therapeutic consequences ensue. Pericardioscopy may be helpful in selected cases[7,8]. Imaging techniques such as CT, MRI and positron emission tomography may also be very useful in the investigation of the presence and extension of neoplastic disease.

In many patients the etiology is initially difficult to establish as no apparent cause is present at the time a pericardial effusion is first identified. Although the final diagnosis of the cause of a pericardial effusion should be based on specific data, some simple clinical indicators may be useful in suggesting a likely etiologic category. Agner *et al*[9], in a retrospective series of 133 patients, observed that hemodynamic compromise, cardiomegaly, pleural effusion, and a large pericardial effusion were

Table 1 Causes of pericardial effusion

Secondary to underlying known disease
Acute myocardial infarction
Cardiac surgery
Trauma
Widespread known neoplasia
Chest radiation
End-stage renal failure
Invasive cardiac procedures
Hypothyroidism
Autoimmune diseases
Without underlying known disease
Acute inflammatory pericarditis (infectious, autoimmune)
Previously unknown neoplasia
Idiopathic

more common in patients with tuberculous or malignant pericardial disease than in patients with idiopathic pericarditis. Hemorrhagic pericardial effusion has been associated with neoplasia in some studies[10], but hemorrhagic effusions can also be seen in patients with idiopathic pericarditis. In fact, the predictive value of these different clinical findings for assessing the etiology of pericardial effusions has not been established. We hypothesized that some simple clinical findings such as the presence of underlying disease, development of cardiac tamponade, and presence or absence of inflammatory signs (typical pericarditic chest pain, fever, pericardial friction rub), might be helpful in classifying the patients into a major etiologic diagnostic category. We prospectively studied 322 patients with moderate and severe pericardial effusion[11]. In 60% of these patients a known previous condition that could cause pericardial effusion was present. The pericardial effusion was demonstrated to be related to the underlying disease in all but 7 of these patients. In the patients with no apparent cause of pericardial effusion at the time of diagnosis (40%) we found that the presence of inflammatory signs (characteristic chest pain, pericardial friction rub, fever or typical electrocardiographic changes) was predictive for acute idiopathic pericarditis ($P < 0.001$, likelihood ratio 5.4), irrespective of the size of the effusion and the presence or absence of tamponade. Furthermore, severe effusion with absence of inflammatory signs and absence of tamponade was predictive for chronic idiopathic pericardial effusion ($P < 0.001$, likelihood ratio 20), and tamponade without inflammatory signs for neoplastic pericardial effusion ($P < 0.001$, likelihood ratio 2.9). The search for evidence of previous chronic effusion can be particularly helpful, as it may make it possible to distinguish neoplastic disease from chronic idiopathic pericardial effusion, which sometimes presents with tamponade. Therefore, although the final etiologic diagnosis should certainly be based on specific clinical data in individual patients, we think that the data afforded by this study may be helpful in the initial assessment and in the decision to perform invasive pericardial studies. Tuberculous pericarditis deserves special attention. Most patients with acute pericarditis will be finally diagnosed with idiopathic pericarditis, but a few cases will correspond to tuberculous pericarditis. Identification of these cases is important due to obvious therapeutic implications. The diagnosis can be established through general examination, including the search of tubercle bacilli in sputum or gastric aspirate or by means of pericardial fluid or pericardial tissue examination (indicated in patients with tamponade or with persistent active illness for more than 3 wk).

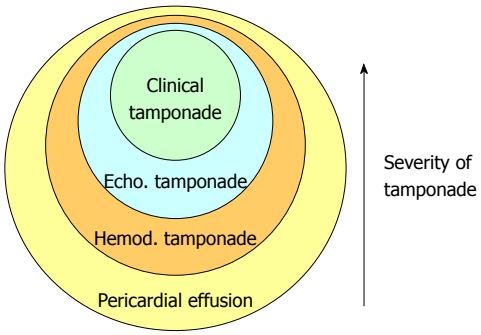

Figure 1 Grading of severity of hemodynamic compromise caused by pericardial effusion. Most pericardial effusions cause abnormalities in hemodynamic parameters as measured in the Cath lab. Some of these patients have echocardiographic findings of tamponade, while only a relative minority of these patients have overt clinical tamponade. Therefore, clinical tamponade represents the highest degree of severity in the spectrum of hemodynamic compromise caused by pericardial effusion. Echo: Echocardiographic; Hemod: Hemodynamic.

EVALUATION OF HEMODYNAMIC COMPROMISE

Clinical tamponade is the most severe manifestation of hemodynamic compromise caused by a tense pericardial effusion (Figure 1). The picture is easily recognized through the presence of the typical findings of dyspnea, tachycardia, jugular venous distension, pulsus paradoxus, and in the more severe cases arterial hypotension and even shock.

Not infrequently the echocardiogram shows findings suggestive of hemodynamic compromise (chamber collapses, characteristic alterations in mitral and tricuspid flows) in patients with moderate and severe pericardial effusion that, on the other hand, do not exhibit any clinical sign of tamponade[12,13]. Cardiologists are puzzled about the clinical relevance of these findings, especially regarding the indication of pericardial drainage. Studies correlating clinical, echocardiographic and catheterization data helped to clarify this problem. For instance, in the study of Mercé *et al*[14], that included 110 patients with moderate or severe pericardial effusion, 34% of 72 patients without clinical tamponade showed collapse of one or more cardiac chambers. In particular right atrial collapse had a low positive predictive value (52%) for clinical cardiac tamponade, while combined right atrial and right ventricular collapse was more specific (positive predictive value of 74%). However, these patients

consistently showed elevation of intrapericardial pressure when submitted to a catheterization study. In the study by Levine *et al*[15], 50 consecutive medical patients with pericardial effusion associated with diastolic right atrial and/or right ventricular collapse, underwent combined right-sided cardiac catheterization and percutaneous pericardiocentesis. Right atrial collapse was present in 92%, and right ventricular collapse in 57% of patients, respectively. Symptoms that led referring physicians to order the echocardiographic study included dyspnea in 44 patients (83%), pleuritic chest pain in 22 (42%), cough in 5 (9%) and hypotension in 2 patients. At physical examination systolic blood pressure was higher than 100 mmHg in 94% of patients, elevation of the jugular venous pressure was suspected in only 74%, hepatomegaly was present in 28%, and pulsus paradoxus was appreciated in only 36% of patients. In fact, clinical suspicion of tamponade was established in only 50% of the patients. At cardiac catheterization the initial pericardial pressure was elevated in all patients (range 3 to 27 mmHg) and was equal to right atrial pressure (therefore, with hemodynamic criteria of tamponade) in 84% of patients. In comparison with the series of Guberman *et al*[16], that included patients in which the decision to proceed to invasive drainage of the pericardial space was made on the basis of clinical findings indicative of hemodynamic compromise, the patients in the series of Levine *et al*[15] had a significantly lower prevalence of hypotension, abnormal pulsus paradoxus, jugular venous pressure elevation and hepatomegaly. All these findings suggest that echocardiography can identify patients with pericardial effusion causing elevation of pericardial pressure before overt hemodynamic embarrassment develops, as the majority of these patients had only mild to moderate clinical tamponade. Even patients with asymptomatic large pericardial effusion without echocardiographic collapses show criteria of hemodynamic tamponade; that is elevation of intrapericardial pressure which equalizes with right atrial pressure and becomes normal after pericardiocentesis together with increase of cardiac output[17]. Experimental[18-21] and clinical studies[22,23] have shown that cardiac tamponade is not an "all-or-none" phenomenon, as previously thought by clinical observation, but a continuum that goes from slight elevations of intrapericardial pressure with subtle hemodynamic repercussion to a situation of severe hemodynamic embarrassment and even death. The concept of continuum was elegantly illustrated by Reddy *et al*[23] based on hemodynamic observations of 77 patients with pericardial effusion submitted to pericardiocentesis. Patients were classified into 3 groups based on the equilibration of intrapericardial, right atrial and pulmonary arterial wedge pressures. They found that even in patients with an intrapericardial pressure lower than the right atrial pressure, pericardiocentesis produced a significant decrease in intrapericardial pressure, right atrial pressure, pulmonary arterial wedge pressure and the inspiratory decrease in arterial systolic pressure. Obviously, these changes were greater in the patients with higher levels of intrapericardial pressure, but, in any case, illustrate the fact that subtle elevations of intrapericardial pressure have hemodynamic consequences. Reddy *et al*[23] concluded that the severity of hemodynamic derangement rather than its presence or absence should be assessed in patients with pericardial effusion.

ETIOLOGIC SPECTRUM OF MODERATE AND LARGE PERICARDIAL EFFUSIONS

A wide variety of conditions may result in pericardial effusion (Table 2). All types of acute pericarditis can be associated with pericardial effusion. In a hospital series[24] pericardial effusion was present in 50% of patients with acute idiopathic or viral pericarditis. Pericarditis secondary to immunologic processes such as systemic lupus erythematosus or rheumatoid arthritis, and pericarditis of physical origin (post-radiation, post-traumatic) are frequently accompanied by pericardial effusion. In addition, pericardial effusion of varying amounts can be seen in other conditions such as neoplasia (with or without direct pericardial involvement), myxoedema, renal failure, pregnancy, aortic or cardiac rupture, chylopericardium, or in the setting of chronic sodium and water retention from many causes, including chronic heart failure, nephrotic syndrome and hepatic cirrhosis. The relative prevalence of these etiologies largely depends on the source of the population studied, the relative size and activity of the different departments in a general hospital (especially the number of patients with neoplastic disease or chronic renal insufficiency who attend each hospital), the study protocol applied, and, of course, on the frequency distribution of the different etiologies of pericardial diseases in each geographic area. For instance, in outpatient populations of the western world the most frequent etiologies are probably idiopathic/viral pericarditis and idiopathic pericardial effusion, while in hospital series neoplastic pericarditis, uremic pericarditis and iatrogenic disease are prominent etiologies of pericardial effusion. In developing countries, especially in Subsaharan Africa, tuberculous pericarditis is the leading cause of pericardial effusion[25].

Four major studies[10,11,26,27] have addressed one of the commonest clinical problems in the setting of pericardial diseases that the cardiologist is faced with: to investigate the etiology of large pericardial effusions of unknown origin. These studies (Table 1) were prospective and were done in general medical centers, but differ in respect to the criteria used to define a pericardial effusion as large, in the number of patients included and, especially, in the study protocol applied to the patients. For instance, Colombo *et al*[10] consider effusions of > 10 mm by M-mode echocardiography as large, and Corey *et al*[26] include as large effusions those > 5 mm, while in the series by Sagristà-Sauleda *et al*[11] moderate effusions were defined as an echo-free space of anterior plus posterior pericardial spaces of 10-20 mm during diastole, and severe effusions as a sum of echo-free

spaces > 20 mm. The series by Colombo *et al*[10] includes 25 male patients all of whom were submitted to an invasive pericardial procedure. Of these patients, 44% presented with cardiac tamponade. The most frequent etiologies of pericardial effusion were: neoplastic (36%), idiopathic (32%), and uremic (20%). Corey *et al*[26] investigated the etiology of pericardial effusion in 57 patients. The prevalence of cardiac tamponade was not reported. Each patient was assessed by a comprehensive preoperative evaluation followed by subxiphoid pericardiotomy. Microscopic examination of the samples of pericardial fluid and tissue was done and they were also cultured for aerobic and anaerobic bacteria, fungi, mycobacteria, mycoplasma, and viruses. An etiologic diagnosis was made in 53 patients (93%). The most common diagnoses were malignancy (23%), viral infection (14%), radiation–induced inflammation (14%), collagen-vascular disease (12%), and uremia (12%). In only 4 patients no diagnosis was made. However, some of the diagnoses consisted of the isolation by culture of pericardial fluid or tissue of unexpected organisms of doubtful clinical relevance, and this series was probably biased toward the inclusion of immunocompromised patients. The study by Sagristà-Sauleda *et al*[11] included 322 patients, 132 with moderate and 190 with severe pericardial effusion. Cardiac tamponade was present in 37%. The patients were studied following our own protocol for the management of pericardial diseases[28], in which invasive pericardial procedures were not systematically performed but were only undertaken under precisely defined indications. In this series, the most common diagnosis was acute idiopathic pericarditis which accounted for 20% of patients. The next most prevalent diagnoses were iatrogenic effusion (16%), neoplastic effusion (13%), and chronic idiopathic pericardial effusion (9%).

The study by Levy *et al*[27], mainly devoted to investigating infectious causes of pericardial effusion, constitutes a paradigmatic example of the possibility of obtaining specific etiologies by using a sophisticated and costly study protocol with systematic use of molecular biology techniques in patients with pericardial effusion accompanying acute pericarditis. These authors investigated 106 pericardial fluid specimens using conventional and molecular methods (PCR) of analysis. A positive etiologic diagnosis of pericardial disease was obtained in 80 of the 106 patients. However, the majority of these diagnoses were obtained with conventional methods commonly used for the assessment of pericardial diseases, either invasive (cytologic examination or culture of effusion) or non-invasive (clinical history, general clinical assessment, serology). In fact, the implementation of the highly complex molecular diagnosis procedure had a net benefit of 4 specific treatments being given in a population of 106 patients.

In addition to the source of the patients and the extension of the study protocol applied, the severity of the hemodynamic repercussion of pericardial effusion has also etiologic implications. In the series of Guberman *et al*[16], that included patients with clinical cardiac tamponade, the most common etiology was metastatic cancer in 18 patients, followed by idiopathic pericarditis in 8 and uremic in five. In the study by Levine *et al*[15], that included 50 patients with echocardiographic tamponade (thus of lower degree of severity than Guberman's series), malignancy was also the most frequent etiology.

MEDICAL TREATMENT

Patients with acute inflammatory signs (fever, chest pain, pericardial friction rub) should receive aspirin or non-steroid anti-inflammatory drugs. In the setting of acute inflammatory pericarditis steroids should be avoided as they increase the possibility of relapses[29,30]. Colchicine is an established indication in patients with relapsing pericarditis[8], and has also been suggested to be useful in the first episode of acute pericarditis in order to avoid the appearance of recurrences[30]. The patients with acute viral or idiopathic pericarditis can be managed on an out-of-hospital basis unless they have clinical predictors of poor prognosis (cardiac tamponade, severe pericardial effusion, immunosuppression, oral anticoagulant therapy or fever > 38℃[31]. The global management of acute pericarditis is shown schematically in Figure 2. When specific etiology is found (bacterial, tuberculous) the treatment should be directed against the causative agent with pericardial drainage if hemodynamic compromise is present. Strict control in the first weeks or months is necessary because of the possibility of evolution to constrictive pericarditis[32,33]. When acute idiopathic or viral pericarditis is accompanied by moderate to severe effusion new echocardiographic controls should be performed (initially every week) until resolution of the disease. The management of neoplastic pericarditis has been excellently reviewed in this Journal recently[34].

INDICATIONS FOR PERICARDIAL DRAINAGE PROCEDURES

Pericardial drainage procedures can be performed for diagnostic or therapeutic purposes (patients with cardiac tamponade). In patients without hemodynamic compromise the diagnostic yield of pericardial fluid or pericardial tissue is very low[24]. In a study by our group[35], which included 71 patients with large pericardial effusion without clinical tamponade, we found that pericardial drainage procedures (performed in 26 patients) had a diagnostic yield of only 7%. On the other hand, no patients developed cardiac tamponade or died as a result of pericardial disease, nor did any new diagnosis become apparent in the 45 patients who did not undergo pericardial drainage initially. Furthermore, moderate or large effusions persisted in only 2 of 45 patients managed conservatively. Even patients with echocardiographic collapses rarely require pericardial drainage for therapeutic purposes during the initial admission. Therefore, pericardial drainage

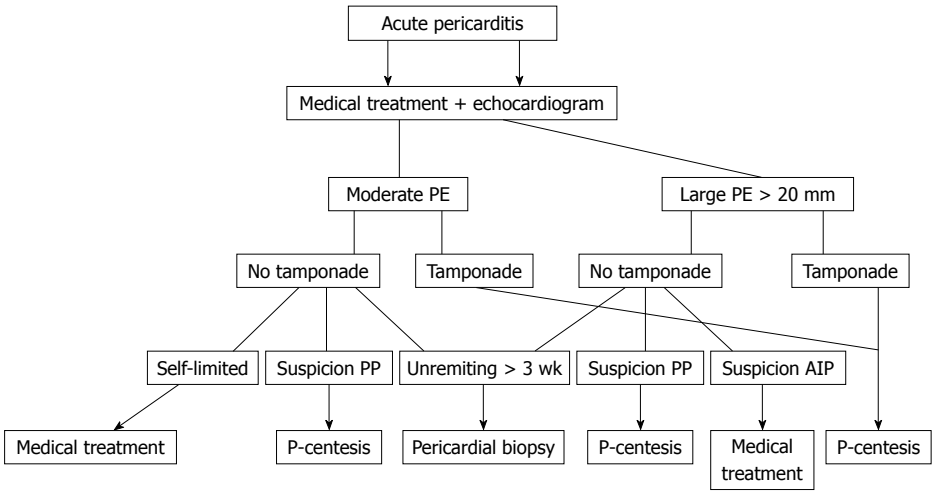

Figure 2 Proposed management strategy for patients with moderate or severe pericardial effusion accompanying acute pericarditis. PE: Pericardial effusion; PP: Purulent pericarditis; AIP: Acute idiopathic pericarditis; P-centesis: Pericardiocentesis.

Table 2 Moderate-large pericardial effusion trials

	Corey *et al*[26]	Colombo *et al*[10]	Sagristà-Sauleda *et al*[11]	Corey *et al*[27]
Effusion	> 5 mm	> 10 mm	> 10 mm	Not reported
n	57	25	322	106
Tamponade (%)	Not reported	44	37	Not reported
Idiopathic (%)	7	32	20[1]	25
Chronic idiopathic effusion (%)	?	?	9	?
Neoplastic (%)	23	36	13	37
Uremia (%)	12	20	6	4
Iatrogenic (%)	0	0	16	0
Post-acute myocardial infarction (%)	0	8	8	0
Viral (%)	14	0	0	7
Collagen vascular disease (%)	12	0	5	5
Tuberculosis (%)	0	0	2	2
Other (%)	9	4	21	20[2]

[1]Acute idiopathic pericarditis; [2]Includes 12 patients with bacterial pericardial effusion; ?: No distinction between acute idiopathic pericarditis and idiopathic chronic pericardial effusion.

procedures are not justified on a routine basis in patients without hemodynamic compromise. Three exceptions to this rule should be noted. Patients with a strong suspicion of purulent or tuberculous pericarditis merit invasive pericardial procedures. On the other hand, in patients with underlying malignancies examination of pericardial fluid is indicated in order to determine whether the effusion is secondary to neoplastic pericardial involvement or is an epiphenomenon (non-malignant effusion) related to the management of the cancer (such as previous thoracic irradiation) or effusions of unknown origin. Lastly, we recommend pericardiocentesis in asymptomatic patients with massive idiopathic chronic pericardial effusion because some of these patients develop unexpected overt tamponade.

SELECTION OF PERICARDIAL DRAINAGE PROCEDURES

A variety of procedures, ranging from simple needle pericardiocentesis to open surgical drainage, are useful for pericardial drainage (Table 3). The selection of a particular procedure largely depends on the etiology of the pericardial effusion. In patients with idiopathic or viral pericarditis simple pericardiocentesis is usually sufficient as the illness is self-limited in days or a few weeks and tamponade rarely relapses. Purulent pericarditis should be drained surgically, usually through subxiphoid pericardiotomy.

The management of cardiac tamponade in patients with neoplastic pericardial involvement merits a special comment. The goals of the treatment are relief of tamponade and prevention of reaccumulation of fluid, which is frequent in these patients. As a rule, less invasive procedures should be preferred, especially in patients with advanced disease and poor general condition. Simple pericardiocentesis alleviates symptoms in most cases but pericardial effusion relapses in as many as 40%-50% of patients[36]. Therefore, pericardiocentesis is the procedure of choice in terminal patients, when recurrence of effusion is not a real issue. In patients with a longer expected survival the treatment has to contemplate possible fluid reaccumulation. Indwelling pericardial catheters have a success rate (defined as alleviation of tamponade and no need of further procedures) of 75% approximately. The catheter should be maintained as long as the amount of drainage is greater than 25 mL/d. In different series[37-40] the duration of catheter drainage averaged 4.8 d. Catheter infection is a potential complication but in our experience we have not observed any case with such a complication. The aims of a prolonged indwelling pericardial catheter are to achieve a complete pericardial drainage and to provoke adherence between the two layers of the pericardium in order to prevent recurrence of pericardial effusion. This goal can be favoured by intrapericardial

Table 3 Procedures of pericardial drainage

Pericardiocentesis only
Indwelling pericardial catheter
Percutaneous ballon pericardiotomy
Subxiphoid pericardiotomy
Pleuropericardial window
Partial pericardiectomy
Wide anterior pericardiectomy

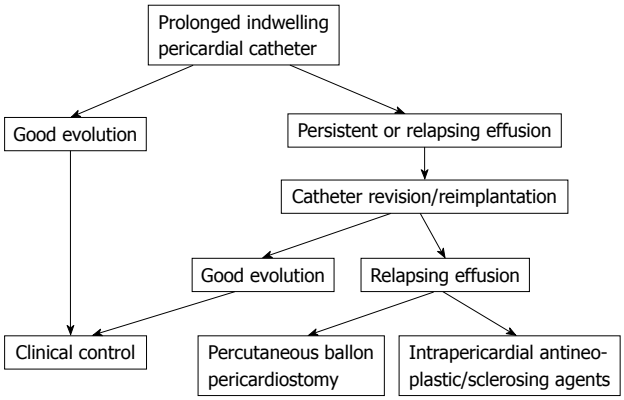

Figure 3 Proposed management strategy for patients with neoplastic pericardial effusion.

sclerosis with tetracycline or other agents. However, some authors[41] have observed no additional advantages over indwelling pericardial catheters and sclerosing agents can provoke "excessive" sclerosis with evolution to constrictive pericarditis with clinical repercussion. Therefore, we think that instillation of sclerosing agents should be avoided in patients with relatively good life expectancy. Balloon pericardiotomy is an alternative to surgical creation of a pericardial window. Access to the pericardial space is gained *via* a conventional subxiphoid pericardiocentesis. A guide wire is advanced into the pericardium, and a balloon catheter is straddled across the pericardium and inflated to create a window[42]. The fluid drains into the pleura or the peritoneal spaces. This technique has been especially adopted for patients with malignancy and reduced life expectancy, and it is successful in more than 80% of cases[42-45]. Reported complications include fever, pneumothorax, left pleural effusion and bleeding from pericardial blood vessels[44,45].

Surgical drainage procedures should be considered in some patients. Some confusion exists about the precise surgical technique of the different procedures (complete pericardiectomy, partial pericardiectomy, subxiphoid pericardiotomy, anterior transthoracic window, pleuropericardial window) but probably all these procedures have a similar efficacy in relieving pericardial effusion (80%-90%). However, inherent perioperative risks, especially if performed under general anesthesia, are a concern. In fact, the overall 30 d mortality for surgical drainage of malignant pericardial effusion has been reported to be 19.4%[46]. In general, the more complex the procedure, the higher the mortality rate.

Our personal attitude in patients with neoplastic pericardial effusion is to begin with an indwelling pericardial catheter. This procedure can be repeated in cases of relapse. The second option would be a subxiphoid percutaneous pericardiotomy or instillation of sclerosing agents. In our experience, surgical drainage techniques are rarely required. The global management strategy is shown schematically in Figure 3.

Some patients show persistence of clinical findings of systemic venous hypertension after effective drainage of the pericardial effusion. In these cases, a possible component of additional constriction physiology should be suspected ("effusive-constrictive pericarditis")[47].

IDIOPATHIC CHRONIC PERICARDIAL EFFUSION

Most patients with a large (more than 20 mm), chronic (longer than 3 mo), idiopathic pericardial effusion are asymptomatic and may remain clinically stable for many years. However, this condition may entail a less than good prognosis, as unexpected overt tamponade can develop in up to 29% of such patients[17]. The trigger of tamponade is unknown, but hypovolemia, paroxysmal tachyarrhythmias, and intercurrent acute pericarditis may precipitate tamponade; accordingly, these events should be vigorously managed. Medical therapy, particularly corticosteroids, colchicine or antituberculous therapy, is not useful.

Pericardiocentesis is the first option in patients with overt tamponade. We think that elective pericardial drainage has to be performed as well in asymptomatic patients as a prophylactic measure to prevent unexpected tamponade. In these patients pericardiocentesis should drain as much pericardial fluid as possible. In cases with relapsing effusion, a second pericardiocentesis is warranted. This sequence may result in definitive disappearance of chronic pericardial effusion as was the case in 8 of 19 patients with effusions present for at least 4 years[17]. When a large pericardial effusion relapses after two pericardiocenteses we recommend surgical drainage with wide anterior pericardiectomy even in asymptomatic patients. In our experience this procedure is safe (no mortality has been observed) and is very effective in the long-term[17,48].

PROGNOSIS

The prognosis of pericardial effusion depends on the underlying etiology[10,11,15,16] being especially poor in patients with neoplastic pericardial effusion secondary to lung cancer and positive cytologic study (presence of malignant cells) in pericardial fluid. Prognosis is very good in idiopathic/viral pericarditis. In patients with tuberculous or purulent pericarditis the prognosis depends on the precocity of the diagnosis and adequate treatment, but purulent pericarditis frequently occurs in patients with underlying debilitating disease (diabetes mellitus, liver cirrhosis, widespread infections). The prognosis is good in chronic idiopathic pericardial effusion but tamponade can occur.

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PPARγ activator, rosiglitazone: Is it beneficial or harmful to the cardiovascular system?

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Abstract

Rosiglitazone is a synthetic agonist of peroxisome proliferator-activated receptor γ which is used to improve insulin resistance in patients with type Ⅱ diabetes. Rosiglitazone exerts its glucose-lowering effects by improving insulin sensitivity. Data from various studies in the past decade suggest that the therapeutic effects of rosiglitazone reach far beyond its use as an insulin sensitizer since it also has other benefits on the cardiovascular system such as improvement of contractile dysfunction, inhibition of the inflammatory response by reducing neutrophil and macrophage accumulation, and the protection of myocardial injury during ischemic/reperfusion in different animal models. Previous clinical studies in type Ⅱ diabetes patients demonstrated that rosiglitazone played an important role in protecting against arteriosclerosis by normalizing the metabolic disorders and reducing chronic inflammation of the vascular system. Despite these benefits, inconsistent findings have been reported, and growing evidence has demonstrated adverse effects of rosiglitazone on the cardiovascular system, including increased risk of acute myocardial infarction, heart failure and chronic heart failure. As a result, rosiglitazone has been recently withdrawn from EU countries. Nevertheless, the effect of rosiglitazone on ischemic heart disease has not yet been firmly established. Future prospective clinical trials designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone would be the best way to resolve the uncertainties regarding the safety of rosiglitazone in patients with heart disease.

Key words: Rosiglitazone; Ischemic reperfusion injury; Heart disease; Type Ⅱ diabetic; Thiazolidinediones

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INTRODUCTION

Type Ⅱ diabetes mellitus (T2DM) is a disease whose incidence is dramatically increasing and requires continuing medical management in many countries[1,2]. T2DM is characterized by insulin resistance and impaired glucose tolerance[3]. The development of T2DM involves 3 metabolic defects that include insulin resistance, alterations in hepatic glucose production and β-cell deficiency[4]. The

earliest defect seen in the development of T2DM is insulin resistance[4]. In this state, the β-cells produce large amounts of insulin reaching a supraphysiologic level as a compensatory response to peripheral tissue insulin resistance. If insulin resistance is left untreated, the β-cells begin to fail to produce insulin, resulting in a state of relative insulin deficiency[4]. T2DM is known to develop after this phase. T2DM patients have a 2- to 4-fold increased risk of developing coronary artery disease, unstable angina and myocardial infarction (MI)[5,6]. Furthermore, T2DM patients have been shown to have a worse prognosis than non-diabetic patients after a cardiovascular event[7,8].

Thiazolidinediones (TZDs) are an oral medication developed to reduce insulin resistance in T2DM patients and have been used since 1997[9]. TZDs exert their properties by stimulating a nuclear hormone receptor, the peroxisome proliferator-activated receptor γ (PPARγ)[10]. Troglitazone was the first drug developed but was withdrawn from the market due to liver toxicity[9]. Currently, pioglitazone and rosiglitazone are the only compounds that are available for clinical use[9]. However, the effects of rosiglitazone have been controversial regarding cardiovascular effects in both animal and clinical studies[11-59]. On the positive side, rosiglitazone has been shown to exert its potent insulin sensitization by improving insulin resistance in T2DM[10,60]. Various studies demonstrated that the therapeutic effects of rosiglitazone could reach far beyond its action as an insulin sensitizer because it has other therapeutic effects on many organs especially in the cardiovascular system in both animal models and humans[11-59]. Nevertheless, in the past decade growing evidence from both basic and clinical studies indicates that rosiglitazone could be harmful to the heart[11-25]. Because of its serious undesired effects, rosiglitazone has been recently withdrawn from the EU market[61], and is under close monitoring by the US Food and Drug Administration[62,63].

In this review, we aim to summarize and discuss the overall benefits as well as the adverse effects of rosiglitazone on the heart from both pre-clinical and clinical reports. Understanding the inconsistent findings as well as the limitations found in each study using rosiglitazone should allow investigators to carefully design future studies that hopefully can clarify previous inconsistent findings, and to indicate whether rosiglitazone should be used in patients.

BENEFICIAL EFFECTS OF ROSIGLITAZONE ON THE CARDIOVASCULAR SYSTEM

Previous studies reported that rosiglitazone had beneficial effects on the cardiovascular system in *in vitro*, *in vivo* and clinical studies. These beneficial effects of rosiglitazone are summarized in Table 1. In rat models of ischemic/reperfusion (I/R) injury, pretreatment with rosiglitazone reduced the infarct size and improved ischemia/reperfusion-induced myocardial contractile dysfunction[26,46,48]. Rosiglitazone treatment also improved left ventricular (LV) systolic pressure and positive and negative maximal values of the first derivative of LV pressure (dP/dt) during I/R injury[32,46]. In addition, in both obese and normal rats rosiglitazone could decrease systolic blood pressure, improve contractile function and normalize the insulin level[31,44,45]. These findings suggested that rosiglitazone could prevent the development of hypertension associated with insulin resistance. This notion was supported by the finding that rosiglitazone treatment could enhance nitric oxide (NO)-mediated arteriolar dilation[28]. Furthermore the accumulation of neutrophils and macrophages and expression of monocyte chemoattractant factor (MCP)-1 in the ischemic heart was diminished by rosiglitazone[46]. Likewise, rosiglitazone treatment in diabetic rat and mouse models reduced the blood levels of glucose, triglycerides, and free fatty acids, and enhanced cardiac glucose oxidation in the ischemic myocardium[26,50]. Rosiglitazone treatment also reduced myocardial apoptosis and infarction size post I/R injury by restoring the balance between the pro-apoptotic and anti-apoptotic mitogen-activated protein kinase (MAPK) signaling pathway, increasing phosphatidylinositol-3-kinase-Akt phosphorylation, and inhibiting p42/44 MAPK[26,35,38,41,59].

In *in vitro* studies, incubation of a rat cardiomyoblast cell line with rosiglitazone demonstrated cardioprotective effects against oxidative stress, and the antioxidant enzyme heme oxygenase 1 was upregulated in these cells after rosiglitazone treatment[40]. Furthermore, rosiglitazone could inhibit cardiac fibroblast proliferation, increase connective tissue growth factor expression and decrease NO production induced by advanced glycation endproducts in cultured neonatal rat cardiac fibroblasts[37]. In addition, rosiglitazone could prevent cardiac hypertrophy by inhibiting angiotensin Ⅱ[27,32,54].

Many clinical studies reported that the beneficial effects of rosiglitazone on the cardiovascular system were similar to those from animal studies. Rosiglitazone therapy has been shown to reduce cardiovascular complications associated with T2DM[47,49,58]. Data from preliminary studies in patients who underwent coronary angioplasty and stent implantation demonstrated that rosiglitazone treatment for 6 mo led to a lower occurrence of restenosis and a lower degree of stenosis of the luminal diameter after angioplasty[64]. Furthermore, a study in patients with T2DM demonstrated that treatment with 4 mg/d of rosiglitazone for 12 wk decreased not only insulin resistance but also pulse wave velocity, which is a direct parameter of arterial stiffness in patients with diabetes and coronary arteries disease (CAD)[58]. Rosiglitazone has been shown to reduce plasma levels of C-reactive protein[5,51,56,58], matrix metalloproteinase-9 and MCP-1[58] in T2DM patients, suggesting that rosiglitazone plays an important role in protecting against arteriosclerosis by normalizing metabolic disorders and reducing chronic inflammation of the vascular system. Rosiglitazone treat-

Table 1 Reports of the beneficial effects of rosiglitazone on the cardiovascular system in pre-clinical and clinical studies

Models	Dose of rosiglitazone	Major findings	Interpretation	Ref.
Cultured neonatal rat cardiomyocytes	5 μmol/L; pretreated for 30 min before stimulation with Ang Ⅱ (1 μmol/L) for 48 h	Inhibited Ang Ⅱ-induced upregulation of skeletal α-actin and ANP genes, and prevent an increase in cell surface area	Rosiglitazone involved in the inhibition of cardiac hypertrophy	[27]
Isolated and cultured neonatal rat ventricular myocytes	1, 5, 10 μmol/L; pretreated for 48 h	Accelerated Ca^{2+} transient decay rates Increased SERCA2 mRNA levels Upregulation of IL-6 secretion Enhanced TNF-α- and lipopolysaccharide-induced NF-κB-dependent transcription	Cardioprotective effects of rosiglitazone may be mediated *via* NF-κB	[43]
Isolated and cultured adult rat ventricular myocytes	10^{-8}-10^{-5} mol; pretreated for 24 h	Did not increase protein synthesis Did not attenuate hypertrophic response to noradrenaline, phorbol-12-myristate13-acetate and endothelin-1	Rosiglitazone did not directly induce cardiomyocyte hypertrophy in cardiomyocytes	[30]
Cultured neonatal rat ventricular myocytes	10 μmol/L; pretreated for 24 h	Inhibited the endothelin-1-induced increase in protein synthesis, surface area, calcineurin enzymatic activity, and protein expression Inhibited the nuclear translocation of NFATc4 Enhanced the association between PPARγ and calcineurin/nuclear factor of activated T-cells	Rosiglitazone inhibited endothelin-1-induced cardiac hypertrophy *via* calcineurin/nuclear factor of activated T-cells pathway	[29]
Cultured rat cardiomyoblast cell line H9c2(2-1)	100 μmol/L; pretreated for 24 h	Increased expression of heme oxygenase 1 Increased cell viability under oxidative stress induced by H_2O_2	Rosiglitazone had cardioprotective effects against oxidative stress	[40]
Cultured neonatal rat cardiac fibroblasts	0.1, 1, 10 μmol/L pretreated for 48 h	Inhibited cardiac fibroblast proliferation Increased connective tissue growth factor expression Decreased nitric oxide production induced by advanced glycation endproducts	Rosiglitazone could prevent myocardial fibrosis	[37]
Cultured neonatal rat ventricular myocytes	1 μmol/L; pretreated for 30 min prior to H_2O_2 treatment	Decrease cell apoptosis Increase Bcl-2 protein content	Rosiglitazone protected cells from oxidative stress through upregulating Bcl-2 expression	[42]
Cultured neonatal rat cardiac myocytes	0.1, 1, 3, 10, 30 μmol/L; pretreated for 30 min before hypoxia	Decreased cytoplasmic accumulation of histone-associated DNA fragments Increased reoxygenation-induced rephosphorylation of Akt Did not alter phosphorylation of the MAP kinases ERK1/2 and c-Jun N-terminal kinase	Rosiglitazone protected cardiac myocytes against I/R injury by facilitating Akt rephosphorylation	[35]
Fatty Zucker rats	7-7.5 μmol/L per kilogram po; 9-12 wk	Decreased systolic blood pressure Decreased fasting hyperinsulinemia Improved mesenteric arteries contraction and relaxation	Rosiglitazone prevented the development of HT and endothelial dysfunction associated with insulin resistance	[45]
Rats with I/R injury	3 mg/kg per day po; pretreated for 7 d; 1 and 3 mg/kg iv given during I/R	Improved left ventricular systolic pressure, dP/dt_{max} and dP/dt_{min} Reduced neutrophils and macrophages accumulation Reduced the infarct size Downregulation of CD11b/CD18 Upregulation of L-selectin on neutrophils and monocytes	Rosiglitazone decreased infarct size and improved contractile dysfunction during I/R possibly *via* inhibition of the inflammatory response	[46]
Fatty Zucker rats with I/R injury (*Ex vivo* model)	3 mg/kg po; 7 or 14 d prior to isolated perfuse heart study	Normalized the insulin resistance Restored GLUT4 protein levels Improved contractile function Prevented greater loss of ATP	Rosiglitazone protected obese rat heart from I/R injury	[44]
I/R injury in isolated perfused normal and STZ- induced diabetic rat hearts (*Ex vivo* model)	1 μmol/L given prior to ischemia; 10 μmol/kg per day po after STZ injection for 4 wk	Inhibited activating protein-1 DNA-binding activity Inhibited of Jun NH_2-terminal kinase phosphorylation Reduced lactate levels and lactate dehydrogenase activity	Rosiglitazone attenuated postischemic myocardial injury in isolated rat heart	[34]
Sprague-Dawley rats	5 mg/kg per day po; 7 d	Reduced systolic blood pressure reduced vascular DNA synthesis, expression of cyclin D1 and cdk4, AT_1 receptors, vascular cell adhesion molecule-1, and platelet and endothelial cell adhesion molecule, and NF-κB activity	Rosiglitazone prevented the development of hypertension and endothelial dysfunction	[31]
T2DM mice	3 mg/kg per day po; 7 d	Did not affect serum glucose and insulin Increased serum 8-isoprostane and dihydroethydine-detectable superoxide production Enhanced catalase and reduced NAD(P)H oxidase activity Did not affect SOD activity	Rosiglitazone enhanced nitric oxide mediation of coronary arteriolar dilations *via* attenuating oxidative stress in T2DM mice	[28]

Hypercholesterolemic New Zealand rabbits with I/R injury	3 mg/kg per day po; 5 wk prior to I/R	Attenuated postischemic myocardial nitrative stress Restored a beneficial balance between pro- and anti-apoptotic MAPK signaling Reduced postischemic myocardial apoptosis Improved cardiac functional recovery	Rosiglitazone attenuated arteriosclerosis and prevented I/R-induced myocardial apoptosis	[38]
Zucker diabetic fatty rats with I/R injury	3 mg/kg per day po; 8 d prior to I/R	Reduced blood glucose, triglycerides, and free fatty acids levels Enhanced cardiac glucose oxidation Increased Akt phosphorylation (Akt-pS473) and its downstream targets (glycogen synthase kinase-3β and FKHR-pS256) (forkhead transcription factor) Reduced apoptotic cardiomyocytes and myocardial infarct size	Rosiglitazone protected heart against I/R injury	[26]
Sprague-Dawley rats with I/R injury	3 mg/kg per day po; 7 d prior to I/R	Reduced infarct size Decreased myocardial expression of AT_1 receptors Increased AT_2 mRNA and protein expression Inhibited p42/44 MAPK Did not alter Akt1 expression	Rosiglitazone attenuated myocardial I/R injury possibly *via* increase expression of AT_2 and inhibition of p42/44 MAPK	[41]
Sprague-Dawley rats with I/R injury	3 mg/kg per day po for 8 wk prior to I/R	Improved left ventricular dP/dt_{max} and dP/dt_{min} Inhibited myocardial angiotensin Ⅱ and aldosterone No significant effects on myocardial AT_1 and AT_2 mRNA	Rosiglitazone had a beneficial effect on post-infarct ventricular remodeling, but had a neutral effect on mortality	[32]
WT and eNOS knockout mice with I/R injury	3 mg/kg ip; pretreated for 45 min prior to I/R	WT mice: increased the recovery of left ventricular function and coronary flow following ischemia eNOS knockout mice: suppressed the recovery of myocardial function following ischemia	Rosiglitazone protected the heart against I/R injury *via* nitric oxide by phosphorylation of eNOS	[48]
Isolated perfused hearts from T2DM mice	23 mg/kg per day po; pretreated for 5 wk	Normalized plasma glucose and lipid concentrations Restored rates of cardiac glucose and fatty acid oxidation Improved cardiac efficiency due to decrease in unloaded myocardial oxygen consumption Improved functional recovery after low-flow ischemia	Rosiglitazone improved cardiac efficiency and ventricular function	[50]
WT and APN knockdown/knockout mice with myocardial infarction	20 mg/kg per day po; pretreated 72 h prior to MI and continuously treated until 7 and 14 d	Improved the postischemic survival rate of WT mice at 14 d of treatment Increased adipocyte APN expression Elevated plasma APN levels Reduced infarct size Decreased apoptosis and oxidative stress Improved cardiac function	APN was crucial for cardioprotective effects of rosiglitazone in myocardial infarction	[57]
Hypercholesterolemic rats	4 mg/kg per day po; pretreated for 5 mo	Reduced Ang Ⅱ level Upregulated AT_2 Improved lipid metabolism	Rosiglitazone protected the heart against cardiac hypertrophy *via* improved lipid profile, reduced Ang-Ⅱ and increase AT_2 expression	[54]
Mice with I/R injury	3 mg/kg per day po; pretreated for 14 d prior to I/R	Reduced ratio of infarct size to ischemic area (area at risk) Reduced the occurrence ventricular fibrillation Attenuated cardiac apoptosis Increased levels of p-Akt and p-GSK-3α	Cardioprotective effects of rosiglitazone against I/R injury were mediated *via* a PI3K/Akt/GSK-3α-dependent pathway	[59]
T2DM patients (n = 21)	4 mg/d; 6 mo	Weight loss (first 12 wk) Decreased waist circumference Decreased systolic and diastolic blood pressure Reduced HbA1c	Rosiglitazone amplified some of the positive benefits of lifestyle intervention	[55]
Randomized, double-blind, placebo-controlled study in T2DM (n = 357)	4 or 8 mg/d; 26 wk	Reduced C-reactive protein, matrix metalloproteinase-9 and white blood cell levels Did not alter interleukin-6 level	Rosiglitazone had beneficial effects on overall cardiovascular risk	[49]
Randomized, double-blind in CAD patients without diabetes (n = 40, control = 44)	4 mg/d for 8 wk followed by 8 mg/d for 4 wk	Reduced E-selectin Reduced von Willebrand Reduced C-reactive protein & fibrinogen Reduced homeostasis model of insulin resistance index Elevation of LDL and triglyceride level	Rosiglitazone reduces markers of endothelial cell activation and levels of acute-phase reactants in CAD patients without DM	[56]
Randomized, double-blind, placebo-controlled study in T2DM with CAD patients (n = 54)	4-8 mg/d; 16 wk	Improved glycemic control and whole-body insulin sensitivity Increased myocardial glucose uptake in both ischemic and non-ischemic regions	Rosiglitazone facilitated myocardial glucose storage and utilization in T2DM with CAD patients	[36]
Randomized controlled trial in patients with impaired glucose tolerance (n = 2365, control = 2634)	8 mg/d; 3 yr	Facilitated normoglycemic Did not alter cardiovascular event	Rosiglitazone reduced incidence of T2DM and increased normoglycemia	[47]

Randomized, double-blind, placebo-controlled trial in patients with T2DM (n = 70, control =16)	8 mg/d; 6 mo	Decreased plasma glucose and HbA1c with a trend to decrease HOMA index Decreased C-peptide and fasting insulin Reduced C-reactive protein Improved endothelium-dependent dilation	Rosiglitazone improved endothelial function and C-reactive protein in patients with T2DM	[51]
Randomized, controlled trial in patient with T2DM with CAD (Rosiglitazone; n = 25)	4 mg/d; 12 wk	Decreased insulin resistance Decreased pulse wave velocity Reduced plasma levels of C-reactive protein and monocyte chemoattractant protein 1	Rosiglitazone prevented arteriosclerosis by normalizing metabolic disorders and reducing chronic inflammation of the vascular system	[58]
Prospective and cross-sectional study in T2DM (Rosiglitazone; n = 22, metformin/ rosiglitazone; n = 100)	Treated with rosiglitazone 6 mo	Decreased endotoxin Increased adiponectin levels	Lower endotoxin and higher adiponectin in the groups treated with rosiglitazone may be responsible for the improved insulin sensitivity	[39]
Comprehensive meta-analysis of randomized clinical trials (n = 42922, control = 45483)	Results of 164 trials with duration > 4 wk	The OR for all-cause and cardiovascular mortality with rosiglitazone was 0.93 and 0.94, respectively The OR for nonfatal MI and heart failure with rosiglitazone was 1.14 (0.9-1.45) and 1.69 (1.21-2.36), respectively The risk of heart failure was higher when rosiglitazone was administered as add-on therapy to insulin	Rosiglitazone did not increase risk of MI or cardiovascular mortality	[52]

Ang: Angiotensin; ANP: Atrial natriuretic peptide; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; Hb: Hemoglobin; HOMA: Homeostatic Model of Insulin Resistance; CAD: Coronary artery disease; WT: Wild-type; APN: Adiponectin; eNOS: Endothelial nitric oxide synthase; GSK: Glycogen synthase kinase; LDL: Low density lipoprotein; AT: Angiotensin receptor type; SOD: Superoxide dismutase; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidyl inositol-3-kinase; STZ: Streptozotocin; I/R: Ischemia/reperfusion; TNF: Tumor necrosis factor; IL: Interleukin; NF: Nuclear factor; SERCA: sarcoendoplasmic reticulum calcium ATPase; HT: Hypertension; NFAT: nuclear factor of activated T cells; ERK: Extracellular signal-regulated kinase; PPAR: Peroxisome proliferator-activated receptor; MI: Myocardial infarction.

ment in patients with T2DM with/without CAD has also been shown to improve myocardial glucose uptake and utilization[36,47]. Rosiglitazone decreased both systolic and diastolic pressure[53,55], suggesting that this drug could improve systolic and diastolic function. All of these findings indicate that in addition to improving insulin resistance in T2DM patients, rosiglitazone also has the beneficial effects on overall cardiovascular risk.

ADVERSE EFFECTS OF ROSIGLITAZONE ON THE CARDIOVASCULAR SYSTEM

Despite these previously mentioned beneficial effects of rosiglitazone on the cardiovascular system, growing evidence indicates other adverse cardiovascular outcomes. The effect of rosiglitazone in increasing mortality in post-MI rats was first reported by Lygate *et al*[21] in 2003. Later, more studies, including clinical trials, demonstrated undesirable effects of rosiglitazone on the cardiovascular system. These findings suggested that rosiglitazone treatment may be harmful and should be used with caution in cardiovascular patients. A summary of reports on the adverse effects of rosiglitazone in various models as well as clinical studies are shown in Table 2.

Rosiglitazone treatment has been shown to induce apoptotic cell death in cultured vascular smooth muscle cell by increasing caspase 3 activity and the cytoplasmic histone-associated DNA fragmentation *via* the proapoptotic extracellular signal-regulated kinase 1/2-independent pathway[17]. Likewise, in an *in vivo* I/R injury model, it has been demonstrated that rosiglitazone therapy for 8 wk in non-diabetic rats with MI did not reduce either LV infarct size or LV hypertrophy, and increased mortality rate after I/R injury[21]. These findings suggested that rosiglitazone did not have cardioprotective effects in myocardial I/R injury. Furthermore, rosiglitazone treatment has been shown to increase cardiac phosphorylation of the p38MAPK signaling pathway[15], suggesting that rosiglitazone could facilitate cardiomyocyte apoptosis. In addition, rosiglitazone has been shown to be associated with an increased incidence of cardiac hypertrophy due to the increased expression of atrial natriuretic peptide, B-type natriuretic peptide, collagen I and Ⅲ and fibronectin[16], leading to cardiac hypertrophy. The deterioration in cardiac function was also found in mice and rats when treated with rosiglitazone[12,24].

In a large animal model, which is more similar to a human, a recent study in swine has demonstrated that intravenous administration of rosiglitazone at clinically relevant doses attenuated epicardial monophasic action potential shortening during ischemia, possibly *via* blockade of cardiac ATP-sensitive potassium channels, and increased the propensity for ventricular fibrillation[20].

Growing evidence from recent clinical trials suggest that rosiglitazone could have serious harmful effects on the cardiovascular system[11,13,14,18,19,22,23,65]. The meta-analysis by Nissen *et al*[11] was the first report raising concerns about the cardiovascular safety profile of rosiglitazone. In a meta-analysis, Nissen *et al*[11] demonstrated that T2DM patients who received rosiglitazone treatment had a significantly increased risk of MI, heart failure and cardiovascular mortality. Although the method and statistical analysis used in this study have been criticized[14,52,66], the subsequent meta-analyses showed similar concerns

Table 2 Reports of the adverse effects of rosiglitazone on the cardiovascular system in pre-clinical and clinical studies

Model	Dose of rosiglitazone	Major findings	Interpretation	Ref.
Isolated and cultured vascular smooth muscle cells	1-10 μmol/L; incubated for 24 h	Induced cell death in a concentration-dependent manner Increased caspase 3 activity and the cytoplasmic histone-associated DNA fragmentation PD98059 (MAPKK inhibitor) did not abolish rosiglitazone induced ERK1/2 activation (proapoptotic effects)	Rosiglitazone induced apoptotic cell death through an ERK1/2-independent pathway	[17]
Rats with I/R injury	3 mg/kg per day po; pretreated for 14 d prior to I/R	Did not reduce left ventricular infarct size or hypertrophy Increased mortality rate Improved ejection fraction and prevented an increase left ventricular end diastolic pressure	Rosiglitazone did not prevent left ventricular remodeling, but was associated with increased mortality after myocardial infarction	[21]
Swine with I/R injury	3 mg/kg per day po; pretreated for 8 d prior to I/R	Increased expression of PPARγ Had no effect on myocardial contractile function Did not alter substrate uptake and proinflammatory cytokines expression	Rosiglitazone had no cardioprotective effects in a swine model of myocardial I/R injury	[25]
PPARγ-knockout (CM-PGKO) mouse	10 mg/kg per day po; 4 wk	Increased phosphorylation of p38 mitogen-activated protein kinase Induced phosphorylation of extracellular signal-related kinase 1/2 Did not affect phosphorylation of c-Jun N-terminal kinases Induced cardiac hypertrophy	Rosiglitazone caused cardiac hypertrophy at least partially independent of PPARγ in cardiomyocytes	[15]
Wild type and PPARγ overexpression mice	10 mg/kg per day po; 15 d	Increased lipid accumulation Increased size of the heart Decreased fractional shortening Increased CD36 expression	Rosiglitazone and PPARγ overexpression could be harmful to cardiac function	[24]
Swine with I/R injury	0.1, 1.0 10 mg/kg iv; pretreated for 60 min	Attenuated MAP shortening during ischemia by blocking cardiac KATP channels Increased propensity for ventricular fibrillation during myocardial ischemia	Rosiglitazone promoted onset of ventricular fibrillation during cardiac ischemia	[20]
Sprague-Dawley rats	15 mg/kg per day po; 21 d	Induced eccentric heart hypertrophy associated with increased expression of ANP, BNP, collagen Ⅰ and Ⅲ and fibronectin Reduced heart rate and increased stroke volume Increased heart glycogen content, myofibrillar protein content and turnover Reduced glycogen phosphorylase expression and activity	Rosiglitazone induced cardiac hypertrophy *via* the mTOR pathway	[16]
Meta-analysis in T2DM (n = 15565, control = 12282)	Received rosiglitazone more than 24 wk	Increased the risk of myocardial infarction Increased cardiovascular death incidence	Rosiglitazone increased in the risk of myocardial infarction and borderline increased in risk of cardiovascular death	[11]
RECORD study (n = 4447)	Received rosiglitazone with mean follow-up time of 3.75 yr	Increased the risk of heart failure	Rosiglitazone increased risk of heart failure, but did not increase the risk of cardiovascular death or all cause mortality	[18]
RECORD study (n = 4447)	Received rosiglitazone with mean follow-up time of 5.5 yr	Increased the risk of heart failure	Rosiglitazone increased risk of heart failure Suggestion of contraindication for rosiglitazone to be used in patients developing symptomatic heart failure	[65]
Case-control analysis of a retrospective cohort study (n = 159026)	Treated with TZDs at least 1 yr	Increased risk of heart failure Increased mortality Increased risk of acute myocardial infarction	Rosiglitazone was associated with risk of heart failure, acute myocardial infarction, and mortality	[19]
Retrospective, double-blind, randomized clinical studies with rosiglitazone (n = 14237)	Received rosiglitazone 24-52 wk	Increased heart failure incidence Increased events of myocardial ischemia	Rosiglitazone increased the risk of heart failure and myocardial infarction	[13]
A meta-analysis of randomized controlled trials (n = 6421, control = 7870)	Received rosiglitazone at least 12 mo	Increased risk of myocardial infarction and heart failure No increased risk of cardiovascular mortality	Rosiglitazone increased risk of myocardial infarction and heart failure, without increased risk of cardiovascular mortality	[23]

I/R: Ischemia/reperfusion; PPAR: Peroxisome proliferator-activated receptor; T2DM: Type 2 diabetes mellitus; RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; ANP: Atrial natriuretic peptide; BNP: B-type natriuretic peptide; ERK: Extracellular signal-regulated kinase; TZD: Thiazolidinedione; mTOR: Mammalian Target of Rapamycin pathway

regarding MI and heart failure, but not cardiovascular mortality[23,52,65].

Lipscombe *et al*[19] also demonstrated that rosiglitazone therapy in patients with T2DM was associated with a significantly increased risk of congestive heart failure, acute MI, and death. Similarly, results from a meta-analysis demonstrated that rosiglitazone treatment for at least 12 mo was associated with a significantly increased risk of MI and heart failure[23]. A retrospective analysis also suggested that rosiglitazone may increase the risk of heart failure[13]. These data from the clinical trials and meta-analysis in recent years strongly indicated that rosiglitazone could have adverse effects on the cardiovascular outcome due to increased risk of MI and heart failure, resulting in increased mortality in patients treated over a long period with rosiglitazone[14,18,22,23]. A meta-analysis demonstrated that patients treated with both rosiglitazone and pioglitazone had a 1.7-fold increase in risk of congestive heart failure with a slightly greater increase in risk with rosiglitazone than with pioglitazone (1.3-fold)[67].

The association between TZDs and heart failure is well recognized as a class effect. An increased plasma volume rather than direct effects on cardiac function is thought to be the mechanism responsible for heart failure[12]. Fluid retention is mediated through increased sodium reabsorption of the renal PPARγ-dependent pathway in the collecting tubules[68].

Unlike the mechanism responsible for heart failure, the mechanism of increased MI risk of rosiglitazone is still controversial. An unfavorable effect of the lipid profile has been proposed, in which rosiglitazone increases low density lipoprotein cholesterol to a greater extent than pioglitazone, and decreases the triglyceride level to a smaller extent than pioglitazone[69].

DISCREPANCY IN FINDINGS FROM ROSIGLITAZONE USE

As summarized in Table 1 for the beneficial effects and Table 2 for the adverse effects of rosiglitazone, these controversial reports are still debated. Although each side for and against the use of rosiglitazone has its own supporting documentation, the growing number of reports of serious adverse cardiovascular effects cannot be taken lightly. It is possible that the controversy on the cardiovascular effects of rosiglitazone could be due to differences in species which could have different drug metabolism, different experimental models, different drug administration methods as well as different time intervals of drug treatment which relates to the effects of the drug. The differences in patients' clinical characteristics may also contribute to the differences in outcomes, in which older patients with preexisting cardiovascular disease are more likely to have serious cardiovascular events.

Regardless of this controversy, since evidence from clinical reports indicated potential cardiovascular risks of rosiglitazone, the European Medicines Agency suggested that the anti-diabetes drug rosiglitazone (Avandia®) should be suspended from the EU market due to its excessive cardiovascular risk[61,70]. As a result, rosiglitazone has been withdrawn from the EU market[61]. However, rosiglitazone is still available in the US but remains under close monitoring from the US Food and Drug Administration[61-63,71].

CONCLUSION

Rosiglitazone is a potent agent in the treatment of hyperglycemia in patients with T2DM because it is an insulin sensitizer and improves glucose uptake. Despite previous reports on its beneficial effects, growing evidence indicates that rosiglitazone increases cardiovascular risks in patients taking this drug. Although this drug has been withdrawn from the EU market, it is still can be used elsewhere. It is important that future large clinical trials should be done to evaluate the definitive cardiovascular outcome of the drug and the interplay between rosiglitazone and other available anti-hyperglycemic agents. In addition, large meta-analyses are also essential and must be carefully interpreted in order to elucidate the effects of rosiglitazone on cardiovascular risks and outcomes.

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GUIDELINES CLINICAL PRACTICE

Clinical evidence of interaction between clopidogrel and proton pump inhibitors

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Abstract

Clopidogrel is approved for reduction of atherothrombotic events in patients with cardiovascular (CV) and cerebrovascular disease. Dual antiplatelet therapy with aspirin and clopidogrel decreases the risk of major adverse cardiac events after acute coronary syndrome or percutaneous coronary intervention, compared with aspirin alone. Due to concern about gastrointestinal bleeding in patients who are receiving clopidogrel and aspirin therapy, current guidelines recommend combined use of a proton pump inhibitor (PPI) to decrease the risk of bleeding. Data from previous pharmacological studies have shown that PPIs, which are extensively metabolized by the cytochrome system, may decrease the ADP-induced platelet aggregation of clopidogrel. Results from retrospective cohort studies have shown a higher incidence of major CV events in patients receiving both clopidogrel and PPIs than in those without PPIs. However, other retrospective analyses of randomized clinical trials have not shown that the concomitant PPI administration is associated with increased CV events among clopidogrel users. These controversial results suggest that large specific studies are needed. This article reviews the metabolism of clopidogrel and PPIs, existing clinical data regarding the interaction between clopidogrel and PPIs, and tries to provide recommendations for health care professionals.

Key words: Antiplatelet therapy; Aspirin; Clopidogrel; Proton pump inhibitor

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INTRODUCTION

Clopidogrel is approved for reduction of atherothrombotic events in patients with acute coronary syndrome (ACS)[1]. Clopidogrel usually is prescribed as an alternative to aspi-

rin for patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) who are intolerant of aspirin. A few randomized trials in patients with ACS have shown that clopidogrel plus aspirin produces significant relative risk (RR) reductions of 10%-20% in cardiovascular (CV) events compared with aspirin alone[2,3]. Current guidelines recommend clopidogrel plus aspirin for ≥ 1 mo after a bare metal coronary artery stent, ≥ 1 year after a drug-eluting stent (DES), ≥ 1 mo and ideally ≥ 1 year after unstable angina or non-ST-elevation MI managed without intervention, and 1 year after ST-elevation MI[4-6]. These antiplatelet agents have recognizable risks of gastrointestinal (GI) complications such as ulceration and related bleeding. These risks may be further compounded by the ancillary use of other adjunctive medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anticoagulants. Given the high prevalence of antiplatelet therapy in clinical practice, coupled with an increased emphasis on their extended use, especially after implantation of a DES[7-9], it is important that physicians should know the potential benefits and the associated risks of antiplatelet therapy for secondary prevention of cardiac ischemic events.

Recently, two relevant cautions about clopidogrel therapy have been raised if one intends to administer aspirin and clopidogrel therapy together. One is antiplatelet non-responsiveness or resistance, and the other relates to interaction between clopidogrel and proton pump inhibitors (PPIs). Previous experience has found that the expected antiplatelet effect from oral aspirin and/or clopidogrel does not occur, and a significant number of patients experience increased risks of adverse ischemic events despite antiplatelet therapy. This phenomenon is considered to be aspirin and/or clopidogrel non-responsiveness or resistance[10-14]. The reported mean prevalence of clopidogrel resistance is 21% (95% CI: 17%-25%) in a systemic review[15]. The issue of clopidogrel resistance has been discussed elsewhere [10,11,14-18]. This paper does not discuss clopidogrel resistance, but focuses on interaction between clopidogrel and PPIs.

PPIs are often prescribed prophylactically with initiation of clopidogrel to reduce the risk of GI bleeding while taking dual-antiplatelet therapy. A randomized, double blind OCLA (Omeprazole Clopidogrel Aspirin) study that assessed the influence of omeprazole on clopidogrel efficacy has demonstrated that omeprazole significantly decreases the clopidogrel inhibitory effect on platelet P2Y12, as demonstrated by vasodilator-stimulated phosphoprotein phosphorylation test[19]. It suggests that PPIs reduce the inhibitory effect of clopidogrel on platelet aggregation. In a population-based study, we have reported that concomitant use of PPIs and clopidogrel is associated with an increased risk of rehospitalization (HR: 1.23, 95% CI: 1.07-1.41, $P = 0.003$) and mortality (HR: 1.65, 95% CI: 1.35-2.01, $P < 0.001$)[20]. It was consistent with previous studies that concomitant use of clopidogrel and PPIs is associated with a higher risk of acute MI, death or target vessel failure[21,22]. Similarly, three larger retrospective cohort studies of 38 531 patients have reported an increased risk of CV events for patients receiving combined PPI and clopidogrel compared with clopidogrel alone[23-25]. In contrast, results of the retrospective analyses of three large clinical trials of 41 000 clopidogrel-treated patients [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), Platelet Inhibition and Patient Outcomes (PLATO), Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7)] have shown no significant effect of concomitant PPI administration on the clinical efficacy of clopidogrel therapy[26-28]. Due to the fact that these studies had conflicting results, it opens the question of whether the efficacy of clopidogrel is influenced by concomitant use of PPIs. This report aims to review the metabolism of clopidogrel and PPIs, relevant articles of clinical and pharmacological studies, and tries to provide recommendations for the combined use of clopidogrel and PPIs.

CLOPIDOGREL METABOLISM

Clopidogrel, a thienopyridine, is a prodrug that is transformed to an active metabolite, which subsequently blocks platelet activation and aggregation. After ingestion of clopidogrel, the majority (85%) of the prodrug is immediately inactivated by plasma esterases to an inactive from (SR26334). Approximately 15% of an absorbed clopidogrel dose is converted to an active thiol metabolite (R-130964); mainly by the hepatic cytochrome P450 isoenzymes[19,29]. The metabolism of clopidogrel is a complex process that involves a number of cytochrome P450 isoenzymes to varying degrees. The active metabolite is formed in the liver through the cytochrome P450 (CYP) system after two sequential reactions that involve CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, with CYP2C19 playing a major role (Figure 1)[29-32]. Clopidogrel and its active metabolite are relatively short lived in plasma. With repeated 75 mg daily doses, plasma concentrations of the parent compound and its active metabolite fall below the lower limit of quantification after 2 h[29-33]. Despite a short half-life, the irreversible binding of the active metabolite of clopidogrel to the platelet receptor leads to a prolonged pharmacodynamic effect. Inhibition of platelet aggregation by clopidogrel lasts for several days, with platelet function returning to baseline about 5 d after stopping the drug[34].

It has been reported that patients with reduced-function genetic polymorphisms of CYP2C19 are associated with reduced conversion of clopidogrel to its active metabolite and a reduction in inhibition of ADP-induced platelet aggregation by clopidogrel[29,30].

Another report has shown that the effect of clopidogrel in reducing the rate of the primary efficacy outcome was similar in patients who were heterozygous or homozygous for loss-of-function alleles, and in those who were not carriers of the alleles[31]. Although the role of CYP2C19 genetic polymorphisms is still controversial, sever-

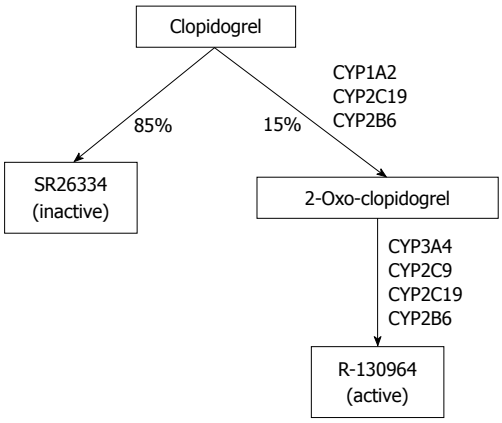

Figure 1 Metabolism of clopidogrel. Clopidogrel undergoes two-step metabolism that can involve several different cytochrome P450 enzymes (from[29], reproduced with permission from the publisher of *Annals of Pharmacotherapy*, Copyright 2011).

al cohort studies have shown that patients with prior MI, ACS, or percutaneous coronary intervention (PCI) who are prescribed clopidogrel have significantly increased RR of CV events, which includes death from CV causes, MI, stroke, or stent thrombosis (1.5-4), with CYP2C19 reduced-function genetic variants[19,32,33]. This increased risk is apparent even among patients who are heterozygous for reduced-function allelic variants[19,32,33]. Mega and his colleagues have found that carriers of a reduced-function CYP2C19 allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse CV events. Specifically, common polymorphisms in the *CYP2C19* gene, seen in approximately 30% of caucasians, 40% of blacks, and > 55% of East Asians[34], significantly diminish the pharmacokinetic and pharmacodynamic responses to clopidogrel by approximately one quarter to one third. Genetic polymorphisms of *CYP2C19* modulate clopidogrel pharmacokinetics and pharmacodynamics in healthy volunteers[12,35], as well as in patients[14,36,37]. As compared with subjects with no *CYP2C19* variant allele, subjects with one or two *CYP2C19* loss-of-function alleles have been shown to have lower plasma concentrations of the active metabolite of clopidogrel and a decrease in the ADP-induced platelet aggregation of clopidogrel[12]. In addition, investigators have demonstrated that, among individuals treated with clopidogrel, patients with a reduced-function *CYP2C19* allele tend to have significantly lower levels of the active clopidogrel metabolite, diminished platelet inhibition, and a higher rate of major adverse CV events[32], including stent thrombosis[37].

PPI METABOLISM

PPIs are prodrugs that are transformed nonenzymatically in the acid environment of gastric parietal cells to active derivatives, which bind covalently to H^+ K^+-ATPase (proton pump)[38,39]. This irreversible inhibition of the proton pump leads to long-term acid suppression for up to 36 h[38]. Li *et al*[40] have compared the degree of CYP2C19 inhibition by the currently used PPIs (e.g. omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole), and the inhibition of CYP2C19 by the PPIs was measured *in vitro* using S-mephenytoin 4-hydroxylation as a marker reaction. They have found that lansoprazole is the most potent inhibitor of CYP2C19, whereas pantoprazole and rabeprazole are the least potent. The currently available PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. All PPIs are hepatically metabolized to an extent *via* the cytochrome P450 mixed oxidase system. The isoenzymes CYP3A4 and particularly, CYP2C19, are the major isoforms that cause PPI biotransformation. The relative contribution of this latter pathway in general metabolism differs among drugs and has been reported to be omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole[41]. In contrast to the situation with clopidogrel, reduced CYP2C19 function results in less inactivation of PPI and an increase in pharmacodynamic effect (greater acid inhibition). Poor CYP2C19 metabolism has been associated with improved clinical outcomes such as healing of esophagitis or eradication of *Helicobacter pylori* (*H. pylori*)[10].

Gilard *et al*[19], using a novel surrogate marker (vasodilator-stimulated phosphoprotein phosphorylation platelet reactivity index, or PRI) for CV events, have reported that there is a higher PRI in patients taking clopidogrel plus PPI than in those taking clopidogrel without PPI. In another double-blind, placebo-controlled trial, patients undergoing coronary artery stent implantation received dual antiplatelet treatment, and were randomized to receive omeprazole or placebo for 7 d to compare the PRI value between the two groups. The authors found significantly more poor responders, as measured by PRI, in the omeprazole group than in the placebo group[10]. In the PRINCIPLE-TIMI 44 trial, mean inhibition of platelet aggregation was significantly lower for patients on a PPI than for those not on a PPI after a 600 mg clopidogrel loading dose (P = 0.02). This indicates that PPI users have significantly less inhibition of ADP-induced platelet aggregation than non-users[26]. Metabolism of PPIs and clopidogrel involves CYP2C19, therefore, the CYP2C19 isoform is the key enzyme in the metabolism of many PPIs, which are also inhibitors of the CYP2C19 and CYP3A4 isoenzymes to varying degrees. This has led to the assumption that some PPIs have the ability to inhibit metabolic activation of clopidogrel[41,42]. The ability of a PPI to inhibit CYP2C19 activity could reduce R-130964 generation and cause a diminished clopidogrel response. Thus, concomitant PPI therapy can further reduce clopidogrel metabolism, which predisposes patients to such adverse CV events and death[43-45].

SEARCH STRATEGY TO IDENTIFY ARTICLES RELEVANT TO THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PPIs

The PubMed and Medline searches were conducted

Table 1 Clinical evidences support the interaction between clopidogrel and proton pump inhibitors

Study design	Follow-up	Number of patients on clopidogrel with/without PPI	End point	Results	Ref.
Population-based study	6 yr	PPI: 572; no PPI: 2706	Rehospitalization (due to AMI or angina); mortality	Rehospitalization in PPI *vs* no PPI groups: HR: 1.23 (95% CI: 1.07-1.41, $P = 0.003$); mortality: HR: 1.65 (95% CI: 1.35-2.01, $P < 0.001$)	Huang *et al*[20]
Retrospective cohort study	1 yr	Low PPI: 712; high PPI: 5.03%(?); without PPI: 4800	MI	Acute MI rate: non-PPI: 1.38% (66/4800); low PPI exposure: 3.08% (22/712); high PPI exposure: 5.03% (?) ($P < 0.05$ for high *vs* no PPI use)	Pezalla *et al*[21]
Retrospective nested case-control	3 mo	Cases: 734 (PPI: 194); controls: 2057 (PPI: 424)	Death or readmitted for MI	Readmission for acute MI, adjusted OR 1.27 (95% CI: 1.03-1.57); pantoprazole OR: 1.02 (95% CI: 0.70-1.47); other PPIs (omeprazole, lansoprazole and rabeprazole) OR: 1.40 (95% CI: 1.10-1.77)	Juurlink *et al*[23]
Retrospective cohort study	October 2003 and January 2006	PPI: 5244; without PPI: 2961	Death or rehospitalization for MI or unstable angina	Death or rehospitalization: non-PPI *vs* PPI groups: 20.8% *vs* 29.8% OR: 1.25 (95% CI: 1.11-1.41); omeprazole OR: 1.24 (95% CI: 1.08-1.41); rabeprazole OR: 2.83 (95% CI: 1.96-4.09)	Ho *et al*[24]
Retrospective cohort study using the National Medco Integrated Database	1 yr	PPI: 6828; without PPI: 9862	Stroke or TIA, ACS, CV death, coronary revascularization	MACE rate in the PPI *vs* non-PPI groups: 25.1% *vs* 17.8% (adjusted HR of 1.57, 95% CI: 1.39-1.64); Omeprazole: 25.1% HR: 1.39 (95% CI: 1.22-1.57), esomeprazole: 24.9% HR: 1.57 (95% CI: 1.40-1.76), lansoprazole: 24.3% HR: 1.39 (95% CI: 1.16-1.67) and pantoprazole: 29.2% HR: 1.61 (95% CI: 1.44-1.81)	Kreutz *et al*[25]
Retrospective cohort within RCT	28 d and 1 yr	PPI: 366; without PPI: 1750	Death, MI, stroke at 1 yr; Death, MI, UTVR at 28 d	Death, MI, stroke at 1 yr: HR: 1.55, 95% CI: 1.031-2.341, $P = 0.035$; Death, MI, UTVR at 28 d, HR: 1.63, 95% CI: 1.015-2.627, $P = 0.043$	Dunn *et al*[46]
Retrospective cohort study	1 yr	PPI: 318; without PPI: 502	CV death, Q-wave MI, coronary revascularization and stent thrombosis	Major MACE event rate in the PPI *vs* non-PPI groups: 13.8% *vs* 8% ($P = 0.008$); HR of MACE: 1.8 (95% CI: 1.1-2.7, $P = 0.01$); overall mortality: 4.7% *vs* 1.8% ($P = 0.02$)	Gaglia *et al*[48]
Retrospective observational study (FRENA registry)	15 mo	PPI: 519; no PPI: 703	MI, stroke, critical limb ischemia, death	Incidence of events of PPI *vs* no PPI groups: MI: 4.4% *vs* 2.1%, HR: 2.5 (95% CI: 1.3-4.8, $P = 0.003$); stroke: 3.7% *vs* 2.3%, HR: 1.9 (95% CI: 1.03-3.7, $P = 0.039$); critical limb ischemia: 4.7% *vs* 3.4%; HR: 1.6 (95% CI: 0.95-2.8, $P = 0.077$); death: 7.5% *vs* 3.3%, HR: 2.2 (95% CI: 1.3-3.7, $P = 0.003$)	Muñoz-Torrero *et al*[49]

PPI: Proton pump inhibitor; TIA: Transient ischemic attack; MI: Myocardial infarction; AMI: Acute MI; ACS: Acute coronary syndrome; CV: Cardiovascular.

using the keywords "clopidogrel" and "proton pump inhibitors" to identify studies that evaluated a potential interaction between clopidogrel and PPIs. Reference lists of recent publications on these topics were also evaluated for relevant publications. An initial screen to identify relevant papers by reading the abstracts or titles was performed. The original studies but not the review articles were included. The second screening was based on full-text review. Studies were selected if they reported on the incidence of major cardiac adverse events or mortality. Studies were excluded if the primary end point was only biological or GI safety driven, or if there was inappropriate group comparison. These articles are subsequently separated into two different categories depending upon that support or against the drug-drug interaction between clopidogrel and PPIs.

CLINICAL EVIDENCES SUPPORT DRUG INTERACTION

Recent studies of the influence of PPIs on clinical outcomes with clopidogrel therapy are summarized in Table 1. We have conducted a nationwide, population-based study in 3278 patients with coronary artery disease who had taken clopidogrel after PCI, using the Taiwan National Health Insurance database[20]. According to the Kaplan-Meier analysis, the incidence of rehospitalization due to acute MI (AMI) or angina ($P = 0.001$) and mortality ($P < 0.001$) was significantly greater for patients with concomitant PPI use ($n = 572$) than for those without ($n = 2706$). Multivariate analyses showed that concomitant PPI use was associated with an increased risk of rehospitalization (HR: 1.23, 95% CI: 1.07-1.41, $P = 0.003$) and mortality (HR: 1.65, 95% CI: 1.35-2.01, $P < 0.001$)[20]. Due to the fact that the prevalence of CYP2C19 loss-of-function alleles is much greater among East Asians than among other populations, we believe that concomitant use of clopidogrel and PPIs may have the possibility of low response to clopidogrel in East Asians patients who have undergone PCI. Pezalla *et al*[21] have assigned their patients into three groups: no PPI exposure group (control), low PPI exposure group, or high PPI exposure group based on the adherence rates to PPIs. They have found that the 1-year AMI rate was 1.38% (66 of 4800 patients) in the control group, 3.08% (22 of 712 patients) in the low PPI exposure group, and 5.03% in the high PPI exposure group. Using the control group MI inci-

dence as the expected MI rate, the difference in MI rates between the control and high exposure groups (1.38% *vs* 5.03%) was significant ($P < 0.05$).

A large epidemiological study has investigated the medical records of the Ontario Public Drug Program[23]; the investigators isolated 13 636 patients with prescriptions for clopidogrel within 3 d of AMI. This study found that there was a significant association between occurrence of AMI and concurrent use of PPI (adjusted OR: 1.27, 95% CI: 1.03-1.57). A stratified analysis based on the specific PPI user revealed that pantoprazole was not associated with an increased risk of MI in patients taking clopidogrel. In contrast, the other PPIs were associated with a 40% increase in the risk of recurrent MI (OR: 1.40, 95% CI: 1.10-1.77). Therefore, the pantoprazole may be safer than other PPIs in terms of the subsequent risk due to recurrent MI in patients taking clopidogrel.

Ho *et al*[24] have performed a retrospective cohort study of 8205 patients with ACS who were taking clopidogrel after discharge from hospital. Using pharmacy refill data, the investigators found that 64% ($n = 5244$) of the patients were prescribed a PPI at discharge or during follow-up, while 36% ($n = 2961$) were not. There was a significantly higher rate of death or rehospitalization for ACS in patients prescribed clopidogrel plus a PPI (adjusted OR: 1.25, 95% CI: 1.11-1.41). This finding supports the theory of an interaction between PPI and clopidogrel. In the Clopidogrel Medco Outcomes Study[25], researchers analyzed integrated data on pharmacy and medical records claims from > 10 million patients, including 16 690 patients taking clopidogrel for a full year following coronary stenting. This retrospective cohort study found that the risk of major adverse CV events [including stroke or transient ischemic attack (TIA), ACS, coronary revascularization, or CV death] was raised from 17.9% to 25.1% in patients also taking PPIs (HR: 1.51, 95% CI: 1.39-1.64, $P < 0.0001$). The overall risk of major cardiac events was 51% higher among patients taking any PPIs. These included a 70% increase in the risk of MI or unstable angina, a 48% increase in the risk of stroke or TIA, and a 35% increase in the need for urgent target vessel revascularization[25].

The Clopidogrel for Reduction of Events during Observation trial was a large, randomized, double-blind study[46]. The investigators evaluated both the 28-d incidence of death, MI, or urgent target vessel revascularization and 1 year rate of death, MI, or stroke for patients on clopidogrel with or without a PPI, and placebo with or without a PPI. The results showed that baseline PPI use was independently associated with adverse CV events at 28 d and 1 year in the overall population (OR: 1.633, 95% CI: 1.02-2.63 at 28 d; OR: 1.55, 95% CI: 1.03-2.34 at 1 year)[46]. The phenomenon that concomitant use of PPIs and clopidogrel was associated with an increased risk of recurrent MI is not only observed for omeprazole, but may also be seen for most PPIs[23-25]. A recent has also found that there was a slightly increased risk (< 20%) of MI hospitalization or death in older patients who started both clopidogrel and a PPI compared with those without a PPI[47].

Gaglia *et al*[48] have examined the effect of a PPI at discharge after PCI with DESs on the incidence of major adverse cardiac events (MACE) in patients with (318 cases) or without (502 cases) a PPI. The MACE included death, Q-wave MI, target vessel revascularization, and stent thrombosis. All patients were taking clopidogrel. Using the univariate survival analysis, there was a greater rate of MACE (13.8% *vs* 8.0%, $P = 0.008$) and overall mortality (4.7% *vs* 1.8%, $P = 0.02$) in the PPI group. After multivariate analysis, the adjusted MACE HR for PPI at discharge was 1.8 (95% CI: 1.1-2.7, $P = 0.01$). Another multicenter, observational (FRENA) registry was conducted in Spanish hospitals to evaluate the influence of concomitant use of PPI on outcome in 1222 patients receiving clopidogrel[49]. PPI users had a higher incidence of MI (rate ratio: 2.5, 95% CI: 1.3-4.8), ischemic stroke (rate ratio: 1.9, 95% CI: 1.03-3.7), and a nonsignificantly higher rate of critical limb ischemia (rate ratio: 1.6, 95% CI: 0.95-2.8) than nonusers. On multivariate analysis, concomitant use of clopidogrel and PPIs was independently associated with an increased risk for subsequent ischemic events; both in the whole series of patients (HR: 1.8, 95% CI: 1.1-2.7) and in those with cerebrovascular disease or peripheral artery disease (HR: 1.5, 95% CI: 1.01-2.4)[49]. The authors have concluded that concomitant use of PPIs and clopidogrel is associated with a nearly doubling of the incidence of subsequent MI or ischemic stroke in patients with established arterial disease.

A recent systematic review and meta-analysis of 25 articles has also described that administration of PPIs together with clopidogrel corresponded to a 29% increased risk of combined MACE (RR: 1.29, 95% CI: 1.15-1.45) and a 31% increased risk of MI (RR: 1.31, 95% CI: 1.12-1.53), but does not influence the risk of death[50]. In summary, these reports indicated that concomitant use of PPI and clopidogrel might be associated with an increased risk of CV events.

CLINICAL EVIDENCE AGAINST DRUG INTERACTION

In a retrospective analysis of the National Medco Integrated Database, the authors identified 1641 patients who had undergone a PCI/stent procedure[25]. These patients were divided into two cohorts: one with patients taking PPIs ($n = 234$) and one not taking PPIs ($n = 1407$). Over the 12-mo study period, the incidence of CV events was 24.8% for patients taking a PPI, and 20.8% for those who were not. There was no significant difference in the risk of any event between the two groups. In the National Heart Lung and Blood Institute dynamic registry, a univariate analysis of a cohort study found that patients prescribed both PPI and clopidogrel were not associated with adverse clinical outcomes after PCI[51]. In the nationwide French registry of 2208 patients presenting with AMI who received clopidogrel therapy, the authors

Table 2 Clinical evidences against interaction between clopidogrel and proton pump inhibitors

Study design	Follow-up	Number of patients on clopidogrel with/without PPI	End point	Results	Ref.
Cohort study	12 yr	PPI: 83; no PPI: 176	MI, CV death, urgent revascularization	No significant effect of use of PPIs	Collet *et al*[43]
Retrospective cohort study	180 d	PPI: 3996; no PPI: 14569	MI, death or coronary revascularization	Adjusted RR for MI or death: 1.22 (95% CI: 0.99-1.51); for revascularization, 0.97 (95% CI: 0.79-1.21)	Rassen *et al*[47]
Retrospective cohort study	1-yr	PPI: 397; no PPI: 138	MI, death, CABG or repeat PCI	Death, MI events with PPI *vs* non-PPI groups: 6.7% *vs* 9.6% (P = 0.32); CABG with PPI *vs* non-PPI groups: 3.1% *vs* 4.1% (P = 0.53); revascularization with PPI *vs* non-PPI groups: 15.8% *vs* 14.2% (P = 0.65)	Ramirez *et al*[51]
Prospective, double-blind placebo- controlled multicentre RCT	Median of 133 d	PPI: 1801; no PPI: 1826	Cardiovascular events (death, non-fatal MI, CABG or PCI, or ischemic stroke)	Cardiovascular events: HR: 1.02, 95% CI: 0.70-1.51	Bhatt *et al*[53]
Double-blind randomized trial	6 mo	PPI: 2257; no PPI: 4538	MACE (CV death, MI, stroke)	MACE in PPI *vs* no PPI groups after adjustment for potential confounders: 11.8% *vs* 12.2%, adjusted HR: 0.94 (95% CI: 0.80-1.11, P = 0.46)	O'Donoghue *et al*[26]
Retrospective cohort study (FAST-MI Registry)	1 yr	PPI: 1453; no PPI: 900	Death, MI, or stroke	No in-hospital difference in death, reinfarction, or major bleeding in PPI *vs* no PPI groups; Death, MI, or stroke at 1 yr in PPI. no PPI groups: 12% *vs* 14% (P = 0.72), adjusted OR: 0.98 (95% CI: 0.90-1.08)	Simon *et al*[54]

PPI: Proton pump inhibitor; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; RR: Relative risk; CV: Cardiovascular.

found that the use of any PPI had no effect on the clinical response to clopidogrel[52]. Further evidence against drug interactions was from the randomized Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), in which 3627 patients taking aspirin after ACS or stent implantation were randomized to clopidogrel alone or with low-dose omeprazole[53]. The primary GI end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The primary CV end point was a composite of death from CV causes, nonfatal MI, revascularization, or stroke. The trial was terminated prematurely when the sponsor lost financing. However, the results of COGENT revealed that omeprazole was associated with a 45% reduction in the risk of GI events and no increase in the risk of CV events, including secondary analysis of AMI or revascularization. The authors concluded that among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper GI bleeding. However, there was no apparent CV interaction between clopidogrel and omeprazole.

O'Donoghue *et al*[26] have used a multivariable Cox model with propensity score to assess the association of concomitant use of clopidogrel (n = 6795; 300 mg loading dose, 75 mg daily maintenance dose) and PPI with clinical outcomes. The primary endpoint was a composite of CV death, nonfatal MI, or stroke. Results revealed that in the clopidogrel group, the Kaplan-Meier rate of the primary endpoint throughout long-term follow-up was 11.8% for individuals on a PPI and 12.2% for those not on a PPI. After adjustment for potential confounders and the propensity to treat with a PPI, no significant association remained between use of a PPI and risk of the primary endpoint (adjusted HR: 0.94, 95% CI: 0.80-1.11, P = 0.46). Recently, the French Registry of Acute-ST-Elevation and Non-ST Elevation Myocardial Infarction has reported their experience in assessing the clinical impact of PPI treatment on the efficacy of clopidogrel therapy[54]. This study found that PPI use was not associated with an increased risk for any of the main in-hospital events (in-hospital survival, reinfarction, stroke, bleeding, and transfusion). Besides, PPI treatment was not an independent predictor of 1-year MI, stroke, or death (HR: 0.98, 95% CI: 0.90-1.08, P = 0.72) in patients administered clopidogrel for recent MI (Table 2).

In summary, these articles did not show drug interactions between PPIs and clopidogrel in terms of increasing the risk of CV death, nonfatal MI, or stroke in patients with ACS.

DISCUSSION/RECOMMENDATIONS

ADP-induced platelet aggregation of clopidogrel has been shown to be reduced in patients receiving omeprazole or other PPIs[19,29,43,55,56], previous retrospective cohort studies[21,23-25,46,48] and a meta-analysis[50] have indicated that concomitant use of PPIs and clopidogrel may be associated with an increased risk of CV events. However, a systematic review and meta-analysis have claimed that these previous studies had significant heterogeneity, which indicates that the evidence is biased, confounded or inconsistent. They have proposed that prospective randomized trials are required to investigate whether a cause-and-effect relationship truly exists regarding PPI-clopidogrel drug interactions[50]. Other articles have opposite opinions; many studies have reported that the use of PPIs had no effect on the clinical response to clopidogrel[26,38,39,51,53]. It is possible that biological differences

detected by platelet function tests are not large enough to have clinical relevance. It is very common that clopidogrel and statins are used together in patients with coronary artery disease. There is some evidence to support a possible pharmacokinetic interaction between statins and clopidogrel. However, real-life interactions including hard end point studies seem to lack an association between the two drugs[57]. The United States FDA, on November 17, 2009, updated the public and health care professions about new safety information concerning a drug interaction between omeprazole and clopidogrel. The FDA recommends that co-administration of omeprazole and clopidogrel should be avoided because omeprazole reduces the effectiveness of clopidogrel[58]. This concern also extends to the use of esomeprazole when taken with clopidogrel. The results of new studies performed by the manufacturers of clopidogrel and submitted to FDA have indicated that co-administration of omeprazole and clopidogrel reduces plasma concentrations of the active metabolite of clopidogrel by about 45%, and the effect on platelet inhibition is reduced by as much as 47%. Other potent inhibitors of CYP2C19 including esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine and ticlopidine are expected to have a similar effect as omeprazole and should also be avoided[58]. The European Medicines Agency, has also indicated that concomitant use of PPI and clopidogrel-containing medicines should be avoided unless absolutely necessary[59]. Nevertheless, the current totality of evidence does not justify a conclusion that PPIs are associated with CV events among clopidogrel users. How to respond to the PPI-clopidogrel interaction remains a matter of debate. Some have suggested that PPIs should simply be avoided in patients taking clopidogrel. This is not good advice and reflects oversimplification of an exceedingly complex topic. Others have argued that the PPI-clopidogrel interaction is of no consequence. Although it is probably true for many patients, the interactions do occur in a considerable number of cases. Health-care providers must make decisions for their patients in the present situation of conflicting evidence, and we therefore propose the following recommendations.

Patients who require clopidogrel should start and continue their therapy

The occurrence of stent thrombosis in patients with DESs may be associated with a poor outcome such as AMI or sudden cardiac death. In the Swedish Coronary Angiography and Angioplasty Registry, where 13 738 bare-metal stents (BMSs) and 6033 DES patients were followed up for 3 years[60], the authors found that late stent thrombosis in the DES group was associated with an increased rate of death. Patients with DESs had an 18% increase in the relative long-term risk of death, compared with patients with BMSs. The FDA and advisory reports from the American Heart Association (AHA), American College of Cardiology, Society for Cardiovascular Angiography and Interventions, and American College of Surgeons have recommended that antiplatelet agents such as aspirin or clopidogrel should be used for at least 1 year following the use of a DES[58,61]. Similar reports have also stressed the importance of 12 mo dual antiplatelet therapy after placement of a DES in patients with a low risk for bleeding[62,63]. Thus, continued clopidogrel therapy is recommended because it is beneficial for decreasing the adverse outcome in patients who require the drug.

Identify the risk of GI ulcer and bleeding; high-risk patients should receive PPI therapy

A meta-analysis of 22 trials of daily low-dose aspirin *vs* placebo in > 57 000 patients revealed an RR of 1.7 for major bleeding and 2.07 for significant GI bleeding, without any difference between a daily dose of 75-162.5 mg and 162.5-325 mg[64]. Upper GI events, such as symptomatic or complicated ulcers, occur in 1 in 20 NSAID users and in 1 in 7 older adults using NSAIDs[65], which accounts for 30% of related hospitalization and death[66,67]. Endoscopic trials suggest that the GI toxicity of a coxib plus aspirin is additive, which results in an overall risk of endoscopic ulcer formation[68,69]. In the Clopidogrel in Unstable angina to prevent Recurrent Events study, 1.3% of patients who received clopidogrel on top of aspirin had major GI hemorrhage as compared to 0.7% of patients treated with aspirin alone. This indicates that the risk of major bleeding is increased among patients treated with clopidogrel in addition to aspirin[70]. A consensus document approved by the American College of Cardiology Foundation (ACCF), American College of Gastroenterology and AHA in 2008 strongly recommends the administration of PPIs to decrease peptic ulcer or GI bleeding in high-risk patients[71]. Patients that receive aspirin or dual antiplatelet therapy may have a high risk of peptic ulcer or GI bleeding if they present with symptoms of dyspepsia or persistent epigastric pain, or have a history of previous GI bleeding, and concomitant use of NSAID or oral anticoagulants. These patients should receive PPIs to decrease peptic ulcer or GI bleeding in high-risk patients[71].

Consider using pantoprazole when a PPI is indicated

This recommendation is based on the observation that pantoprazole is less potent than omeprazole to inhibit CYP2C19[40] and does not appear to attenuate the pharmacodynamic response to clopidogrel[72,73]. Co-administration of pantoprazole may enhance the antiplatelet effect of enteric-coated aspirin in patients with ACS, who are undergoing PCI and dual antiplatelet therapy[74]. Furthermore, it has been reported that pantoprazole had no association with recurrent MI in a large population-based, case-control study of patients receiving clopidogrel[23].

Histamine-2-receptor antagonist can be used as an alternative to PPIs for GI protection

Concomitant use of clopidogrel and an NSAID (including

low-dose aspirin) has been associated with impaired healing of asymptomatic ulcers[75] and disruption of platelet aggregation[76], with a consequent increase in serious upper GI events (OR: 7.4, 95% CI: 3.5-15)[77]. Histamine-2-receptor antagonists are able to decrease peptic ulcer or esophagitis in low-dose aspirin users[78]. Famotidine is a histamine H2-receptor antagonist that is well tolerated and able to prevent and heal peptic ulcers in patients who are receiving conventional NSAIDs[79,80]. The FAMOUS trial (Famotidine for the Prevention of Peptic Ulcers in Users of Low-dose Aspirin) was a randomized, double-blind, placebo-controlled trial, which demonstrated that famotidine prevented gastric and duodenal ulcers, and erosive esophagitis in patients taking low-dose aspirin (i.e. 75-325 mg)[81]. Concerning the long-term use of PPIs, an alternative management strategy has been proposed, including the use of H2-receptor antagonists[81,82]. In other words, H2-receptor antagonists such as famotidine might be considered as a useful alternative in patients with drug interactions between clopidogrel and PPIs.

Think about other alternative antiplatelet therapy to avoid interaction between clopidogrel and PPIs

Prasugrel is a third-generation thienopyridine with more consistent and efficient metabolism than clopidogrel. Prasugrel appears less susceptible to genetic variation and drug interactions, which is the limitation of clopidogrel in antiplatelet activity[83-85]. Previous studies have reported that the prasugrel has greater potency and more rapid platelet inhibition than clopidogrel, and has a comparable safety profile[86,87]. In a retrospective analysis of the TRITON-TIMI 38 study, a randomized controlled trial that compared prasugrel and clopidogrel in > 13 000 patients with ACS, there was a 19% RR reduction in the composite CV endpoint with prasugrel *vs* clopidogrel, but with increased major bleeding[88].

Another direct-acting inhibitor of the ADP receptor P2Y12 is ticagrelor, which has a more rapid onset and more pronounced platelet inhibition than clopidogrel[89]. Gurbel *et al*[90] has recently reported that ticagrelor therapy may overcome the nonresponsiveness to clopidogrel, and in their study, almost all clopidogrel nonresponders and responders treated with ticagrelor had platelet reactivity below the cut-off points associated with ischemic risk. An important randomized, double-blind, multicenter, clinical study, the PLATO trial has recently been conducted to compare the efficacy of ticagrelor and clopidogrel in 18 624 patients with ACS. Treatment with ticagrelor compared with clopidogrel significantly reduced the rate of death from vascular causes, MI, or stroke (HR: 0.84, 95% CI: 0.77-0.92, $P < 0.001$), without an increase in the rate of overall major bleeding, but with an increase in the rate of non-procedure-related bleeding[27]. In view of the above evidence and the drug interaction between clopidogrel and PPIs, newer drugs such as prasugrel or ticagrelor may have the potential to overcome the limitations of clopidogrel.

When dual therapy is necessary, separation of PPI and clopidogrel for > 12 h

PPIs and clopidogrel are each given once daily and both have relatively short half lives of 1-2 h and 4-6 h, respectively[39,91]. The clopidogrel concentrations should be very low or unmeasurable at 4-6 h after ingestion[91]. Besides, clopidogrel is most effective when taken before a meal. Thus, separation of 12-15 h between these two drugs should theoretically prevent any competitive inhibition of CYP2C19 metabolism and avoid any adverse clinical effects. We therefore suggest taking PPI before breakfast and clopidogrel at bedtime.

CONCLUSION

To date, there remains significant ongoing controversy regarding the clinical outcomes of patients taking clopidogrel and PPIs. From the ACCF Task Force on Clinical Expert Consensus Documents, clinicians should pay attention to gastroprotection strategies that involve PPIs in patients with a high risk of GI bleeding, and eradication of *H. pylori* in patients with peptic ulcer history who receive dual-antiplatelet therapy[71]. In situations when both clopidogrel and a PPI are indicated, pantoprazole should be used because it is the PPI that is least likely to interact with clopidogrel. Famotidine may be an appropriate alternative for patients who require acid-lowering therapy[78,81]. Until further reliable data become available, wide separation of PPIs and clopidogrel could minimize the potential clinical drug interactions.

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CASE REPORT

Percutaneous endovascular management of atherosclerotic axillary artery stenosis: Report of 2 cases and review of literature

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Abstract

With recent advancement in percutaneous endovascular management, most atherosclerotic peripheral arterial diseases are amenable for intervention. However, there is limited published literature about atherosclerotic axillary artery involvement and its endovascular management. We report two cases of atherosclerotic axillary artery stenosis, which were successfully managed with stent angioplasty using self expanding nitinol stents. The associated coronary artery disease was treated by percutaneous angioplasty and stenting. The long term follow-up revealed patent axillary stents in both cases.

Key words: Angioplasty; Atherosclerosis; Axillary artery; Coronary artery; Endovascular; Self expanding stent

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INTRODUCTION

The successful percutaneous endovascular intervention of atherosclerotic peripheral arterial disease (PAD) of various locations is well described in the literature. However, there is very little published literature about atherosclerotic axillary artery stenosis and its endovascular management. We hereby describe two cases of atherosclerotic axillary artery stenosis in association with coronary artery disease (CAD), which were successfully managed by percutaneous stent angioplasty.

CASE REPORT

Case 1

In March 2007, a 48-year-old chronic smoker, hypertensive, manual worker presented at the emergency room (ER) with acute anterior wall myocardial infarction. He was given intravenous streptokinase injection within 5 h of the onset of chest pain. Post-thrombolysis he had mild, persistent chest pain and ST elevation in V_1-V_4 chest leads. The systolic blood pressure in the right upper limb was 80 mmHg, for which intravenous dopamine infusion was started in the ER. Later, it was realized that there was a disparity in systolic blood pressure in the two upper limbs - in the right arm blood pressure was 80 mmHg while in the left arm it was 130 mmHg. On further inquiry, he revealed a history of right upper limb claudication on doing manual work during the last 6 mo. There was no history of trauma of the right upper limb, or radiation therapy in the neck or chest region for

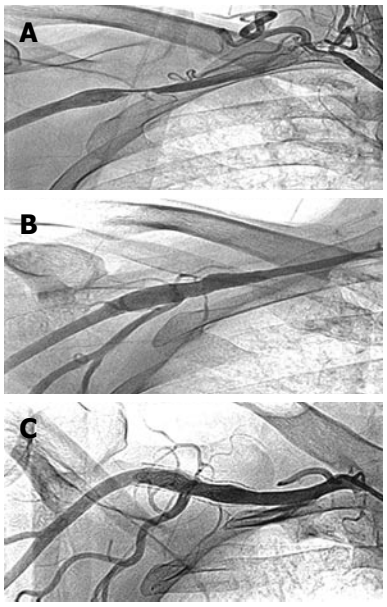

Figure 1 Peripheral angiogram of axillary artery stenosis and its endovascular treatment in case 1. A: Angiogram showing 90% short segment stenosis of proximal part of right axillary artery; B: Brisk flow with no residual stenosis of axillary artery following a 8 mm × 40 mm self expanding nitinol stent deployments; C: At 10 mo of follow-up, patent axillary stent with no in-stent restenosis and brisk flow across it.

any malignancy. The general physical examination was unremarkable other than feeble right upper limb arterial pulses. Cardiovascular examinations revealed a left ventricular third heart sound, but the rest of the systemic examination was normal. His 2-dimensional echocardiogram showed a left ventricular ejection fraction of 0.30, a hypokinetic anterior wall and septum, and no mitral regurgitation. His routine biochemistry, including fasting blood sugar, renal and liver function tests, were within normal limits. His fasting lipid profile revealed total cholesterol 117 mg%, HDL 26 mg%, LDL 67 mg%, and triglycerides 101 mg%. Forty-eight hours after admission, he underwent coronary and peripheral angiography *via* the trans-femoral route. Coronary angiography revealed 90% proximal left anterior descending (LAD) tubular bifurcation stenosis; left main, left circumflex and dominant right coronary arteries (RCA) were normal. A peripheral angiogram revealed 90% eccentric right axillary artery stenosis (Figure 1A). Bilateral subclavian, renal, common and internal carotid arteries were normal.

Following written informed consent, he was taken for coronary and peripheral intervention. The left coronary artery was cannulated with a Judkins Left 3, 6F guide catheter, the proximal LAD lesion was stented with a 3 mm × 18 mm Bx Sonic stent (*Cordis Co., Miami, Florida*). TIMI-3 flow was achieved in the LAD. Then, the right subclavian artery was cannulated with a 7F sheath (*Cook, Bloomington, Indiana, USA*) and the axillary artery lesion was crossed with a 0.014 inch All Track guide wire (ATW) (*Cordis*). The lesion was pre-dilated with a 4 mm × 20 mm balloon. An 8 mm × 40 mm PRECISE™ self expanding nitinol stent (*Cordis*) was deployed across the lesion. It was post dilated with a 7 mm × 20 mm OptaPro balloon (*Cordis*). Brisk flow was achieved in the axillary artery (Figure 1B). The systolic blood pressure in both upper limbs became equal following the intervention. At follow-up, his right upper limb claudication symptom was absent. However, he had class Ⅱ dyspnea on exertion, which was attributed to his low left ventricular ejection fraction (0.25). He was managed with optimal doses of diuretics, angiotensin converting enzyme inhibitors and β-blockers.

In January 2008, at 10 mo of follow-up, he underwent a diagnostic angiogram. Coronary angiogram revealed 100% diffuse in-stent restenosis of the proximal LAD bare metal stent, with grade Ⅲ retrograde filling of the distal LAD from intra-coronary collaterals; the rest of the coronary arteries were normal. The left ventricular angiogram in RAO 30° view showed an ejection fraction of 0.25, antero-lateral and apex region akinetic. The axillary stent was patent with brisk flow across it (Figure 1C). A stress Thallium test was performed following the angiogram, which revealed scarred non-viable anterior wall of the left ventricle myocardium, and a resting ejection fraction of 0.25. He was continued on optimal medical treatment. At 4 years follow-up in February 2011, he was doing well with no right upper limb symptoms and equal blood pressure in both upper limbs.

Case 2

In July 2009, a 65-year-old non-smoker, normotensive, non-diabetic, right handed gentleman presented with left upper limb claudication on doing minimal manual work during the last 3 mo. He also complained of class Ⅱ dyspnea on exertion of the same duration. There was no history of chest pain, syncope, left upper limb numbness or discoloration. There was no history of radiation therapy in the neck or chest region for any malignancy. On general physical examination, his left brachial and radial pulses were not palpable and blood pressure in left upper limb was not recordable. The left upper limb was warm and viable with no discoloration, epilation, brittle nails or gangrenous changes. Other arterial pulses were well palpable. Systemic examination was unremarkable. His ECG was within normal limits, 2-dimensional echocardiography revealed no regional wall motion abnormality, and his left ventricular ejection fraction was 0.60. His routine biochemistry, including blood sugar, liver and renal function tests, were normal. The fasting lipid profile was total cholesterol 121 mg%, HDL 32 mg%, LDL 65 mg% and triglycerides 102 mg%. He was subjected to cardiac catheterization and a peripheral angiogram. Coronary angiography performed *via* the right trans-femoral route, revealed 50% diffuse stenosis of major obtuse marginal 1, 70% diffuse stenosis of the proximal-distal LAD, dominant RCA having mid cutoff with grade Ⅲ antegrade filling of the distal RCA. A peripheral angiogram revealed total cutoff of the left axillary artery at the level of the head of the humerus (Figure 2A). Bilateral carotid, subclavian and renal arteries were normal.

Following a written informed consent, he was taken-up for coronary and peripheral interventions. The left

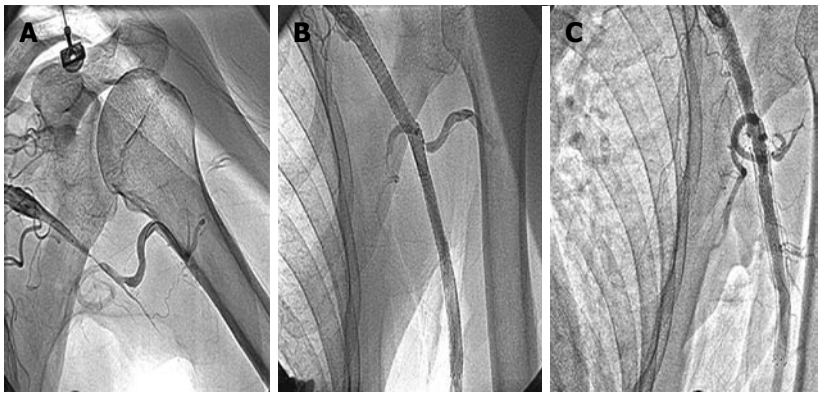

Figure 2 Peripheral angiogram of axillary artery stenosis and its endovascular treatment in case 2. A: Total occlusion of distal part of left axillary and brachial artery; B: Brisk flow across the axillary-brachial segment following two 8 mm × 80 mm, 8 mm × 60 mm self expanding nitinol stent deployment; C: At 5 mo of follow-up, patent axillary stent and brisk flow across it.

coronary artery was cannulated with an Extra Back-Up 3.5, 6F (*Medtronic*) guide catheter *via* right trans-femoral approach. The LAD lesion was crossed with a 0.014 inch ATW coronary guide wire (*Cordis*), pre- dilated with a 2 mm × 20 mm Sprinter (*Medtronic*) balloon, and stented with 3.5 mm × 28 mm and 3.5 mm × 18 mm Multi-Link Vision (Abbott Vascular, Santa Clara, CA, USA) stents at 14 atms. The whole stented LAD segment was post-dilated with a 3.5 mm × 15 mm non-compliant Sprinter (*Medtronic*) balloon at 18 atms. TIMI-3 flow was achieved in LAD. Thereafter, the left subclavian artery was cannulated with a Judkins Right 3.5, 7F coronary guide catheter, and the totally occluded axillary-brachial segment was crossed with a 0.014 inch All Track coronary guide wire (*Cordis*) with a 2.5 mm × 20 mm balloon support. After successful crossing of the lesion with the guide wire, it was dilated with a 2.5 mm × 20 mm followed by a 3.5 mm × 28 mm balloon. There was a long segment dissection across the occluded axillary-brachial artery, which was stented with two 8 mm × 80 mm and 8 mm × 60 mm SMART® CONTROL self expanding nitinol stents (*Cordis*). The whole stented segment was post-dilated with a 7 mm × 20 mm OptaPro balloon (*Cordis*). Brisk flow was achieved in the left upper limb (Figure 2B). The blood pressure in both the upper limbs became equal. On follow-up, his claudication symptom of the left upper limb had been relieved.

However, 5 mo later in November 2009, he presented with angina on rest and dynamic ST-T changes in anterior chest leads. A check angiogram revealed 90% in-stent restenosis of the LAD. The left axillary stent was patent (Figure 2C). He was advised to undergo coronary artery bypass surgery for underlying triple vessel disease. At 20 mo of follow-up in February 2011, his left brachial and radial arteries were well palpable, blood pressure in both upper limbs was equal and ultrasound Doppler showed a patent axillary stent.

DISCUSSION

The axillary artery is the continuation of the subclavian artery, commences at the outer border of the first rib, and ends at the lower border of the tendon of the Teres major muscle, where it continues as the brachial artery[1]. The commonly reported etiologies of axillary artery stenosis are Takayasu's aorto-arteritis[2], giant cell arteritis[3], radiation induced arteritis[4] and crutch related injuries[5]. Though atherosclerosis is known to involve the arterial bed at various sites, it is uncommon to encounter atherosclerotic axillary artery stenosis in clinical practice[6-8]. We have reported two cases of atherosclerotic axillary artery stenosis - the first case had short segment isolated axillary artery stenosis, while the second case had diffuse, long segment axillary-brachial occlusion. The associated CAD in both cases suggests atherosclerosis as a common etiology. In the absence of systemic symptoms, non-ostial involvement of coronaries, and absence of other major artery involvement, which are classic of Takayasu's and giant cell arteritis, the inflammatory etiology in these two cases is very unlikely. Both cases required intervention to relieve the symptoms of claudication in the affected upper limb. There are reports of percutaneous transluminal angioplasty of the axillary artery stenosis from 1990 onwards[8-11]; however the limited success rate, early and late re-occlusion are a few of the limitations of plain angioplasty, which has improved over the decade with stent angioplasty. In 1994, McBride *et al*[12] reported the first case of stent angioplasty in radiation induced axillary artery stenosis and in 2000, Oran *et al*[5] reported another case of stent angioplasty in crutch related axillary artery stenosis. There is only one original article about atherosclerotic stent angioplasty of the axillary artery stenosis published by Müller-Hülsbeck *et al*[6] in 2007. As the axillary artery is located at the mobile shoulder joint, the self expanding stent instead of balloon expandable stent is preferable as the earlier one is more flexible, compressible, and non-deformable in comparison to the balloon expandable stent[13].

The limited published literature about axillary artery disease and its endovascular management is possibly because more attention is given by the endovascular specialist to critical limb ischemia of lower limbs and proximal

subclavian artery disease in comparison to the distal arterial bed of the upper limb. Another reason may be that ther is a good collateral circulation across the shoulder joint and adequate distal flow in the limb, which results into fewer symptoms. Both our cases had long term patency of axillary stents. Though a 1 year patency rate of > 90% has been reported for self expanding stents of the iliac artery[14], similar studies are required for short and long term outcomes of stent angioplasty of the axillary artery.

One interesting observation in our cases was that there was significant in-stent restenosis of coronary bare metal stents. Though the risk factors for in-stent restenosis like bare metal stents, long lesions (in case 2), smaller diameter of stents (3 mm stent in case 1) were there, an associated PAD is also being considered as one of the risk factors for repeat target vessel revascularization in CAD patients[15].

In conclusion, this is a report about two uncommon cases of atherosclerotic axillary artery stenosis, which were successfully treated with endovascular stents and had a favorable long term outcome.

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Events Calendar 2011

January 25
Moving towards a national strategy for Chronic Obstructive Pulmonary Disease
London, United Kingdom

Februrary 24-26
Abdominal Obesity 2011 - 2nd International Congress on Abdominal Obesity
Buenos Aires, Argentina

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
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

June 2-5
CODHy 2011 - The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 26-29
EHRA EUROPACE 2011
Madrid, Spain

June 29-July 1
Hands-on Cardiac Morphology - Summer Edition
London,
United Kingdom

August 27-31
ESC 2011 - European Society of Cardiology Congress 2011
Paris, France

October 23-26
9th International Congress on Coronary Artery Disease
Venecia, Italy

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 352 experts in cardiology from 41 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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Aims and scope

The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research.

Columns

The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

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Format

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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