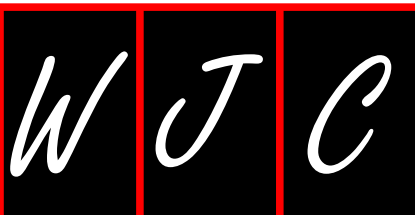


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Brugada phenocopy: A new electrocardiogram phenomenon

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Author contributions: Anselm DD and Branchuk A contributed equally to this work; Anselm DD wrote the manuscript including the initial draft and subsequent revisions; Evans JM revised the paper to meet grammatical and linguistic standards; Branchuk A designed the manuscript, contributed to revisions and served as senior advisor; all authors read and approved the final manuscript.

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Abstract

Brugada phenocopies (BrP) are clinical entities that are etiologically distinct from true congenital Brugada syndrome. BrP are characterized by type 1 or type 2 Brugada electrocardiogram (ECG) patterns in precordial leads V1-V3. However, BrP are elicited by various underlying clinical conditions such as myocardial ischemia, pulmonary embolism, electrolyte abnormalities, or poor ECG filters. Upon resolution of the inciting underlying pathological condition, the BrP ECG subsequently normalizes. To date, reports have documented BrP in the context of singular clinical events. More recently, recurrent BrP has been demonstrated in the context of recurrent hypokalemia. This demonstrates clinical reproducibility, thereby advancing the concept of this new ECG phenomenon. The key to further understanding the pathophysiological mechanisms behind BrP requires experimental model validation in which these phenomena are reproduced under strictly controlled environmental conditions. The development of these validation models will help us determine whether BrP are transient alterations of sodium channels that are not repro-

ducible with a sodium channel provocative test or alternatively, a malfunction of other ion channels. In this editorial, we discuss the conceptual emergence of BrP as a new ECG phenomenon, review the progress made to date and identify opportunities for further investigation. In addition, we also encourage investigators that are currently reporting on these cases to use the term BrP in order to facilitate literature searches and to help establish this emerging concept.

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Key words: Brugada phenocopy; Brugada syndrome; Electrolytes; Myocardial ischemia; Pulmonary embolism; Cardiomyopathy; Electrocardiogram filters

Core tip: Diagnostic distinctions between Brugada phenocopies (BrP) and Brugada syndrome (BrS) are: (1) BrP patients have a reversible underlying condition and upon resolution of this condition, the electrocardiogram normalizes; (2) BrP patients have a low pretest probability of BrS as opposed to a high pretest probability in patients with true congenital BrS; and (3) BrP patients have a negative sodium channel blocker test, while patients with BrS have a positive test. The different electrocardiographic response to the provocative challenge highlights a pathophysiological divergence when comparing BrP and BrS. This suggests alternative underlying mechanisms with various genetic, structural and environmental interactions yet to be elucidated.

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INTRODUCTION

Brugada syndrome (BrS) is a congenitally inherited car-

diac channelopathy characterized by type 1 and type 2 electrocardiogram (ECG) patterns in leads V1-V3 that predisposes individuals to malignant ventricular arrhythmias and sudden cardiac death^[1]. Brugada phenocopies (BrP) are clinical entities that have ECG patterns that are identical to true congenital BrS but are elicited by various other factors, such as myocardial ischemia, metabolic abnormalities, mechanical mediastinal compression and poor ECG filters^[2,3]. In this editorial, we discuss the conceptual emergence of BrP as a new ECG phenomenon, review the progress made to date and identify opportunities for further investigation.

THE BRUGADA ECG PATTERN

True congenital BrS is characterized by two ECG patterns in leads V1-V3: The typical type 1 “coved” or the type 2 “saddleback” patterns. The type 1 pattern has a high take-off ST-segment elevation that is ≥ 2 mm followed by a down-sloping concave or rectilinear ST-segment with a negative symmetric T-wave (Figure 1A)^[1]. The type 2 pattern is defined as a high take-off (r') that is ≥ 2 mm from the isoelectric baseline, followed by ST-segment elevation that is convex with respect to the isoelectric baseline with elevation ≥ 0.05 mV, with variable T-wave in lead V1 and positive or flat T-wave in lead V2 (Figure 2A)^[1].

THE BRUGADA PHENOCOPY

BrP are clinical entities that are etiologically distinct from true congenital BrS. BrP are defined by ECG patterns that are identical to BrS but are elicited by various clinical circumstances. The term phenocopy was chosen because it was previously used to describe an environmental condition that imitates one produced by a gene; therefore, it served as a reasonable and succinct description for all acquired Brugada-like ECG manifestations^[4].

Since the initial reports, type 1 BrP have been reported in the context of an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement (Figure 1B)^[5]; concurrent hyperkalemia, hyponatremia and acidosis (Figure 1C)^[6,7]; acute pulmonary embolism (Figure 1D)^[8,9]; and hypokalemia in the context of congenital hypokalemic periodic paralysis (Figure 1E)^[10,11]. Similarly, type 2 BrP have been reported immediately post-electrocution accidental injury (Figure 2B)^[12], in the context of congenital pectus excavatum causing mechanical mediastinal compression (Figure 2C)^[13]; and as a result of an inappropriate high-pass ECG filter (Figure 3)^[14].

In each of these prior reports, the BrP was observed in the context of a singular inciting clinical event such as myocardial ischemia or metabolic derangement. Finally, the BrP concept was advanced by demonstrating clinical reproducibility in the context of recurrent hypokalemia^[15]. Briefly, a young patient with diarrhea was admitted to hospital due to severe hypokalemia (K 1.5 mEq/L) with concurrent acidosis. The ECG depicted a typical type 1 Brugada ECG pattern (Figure 3A). Upon correc-

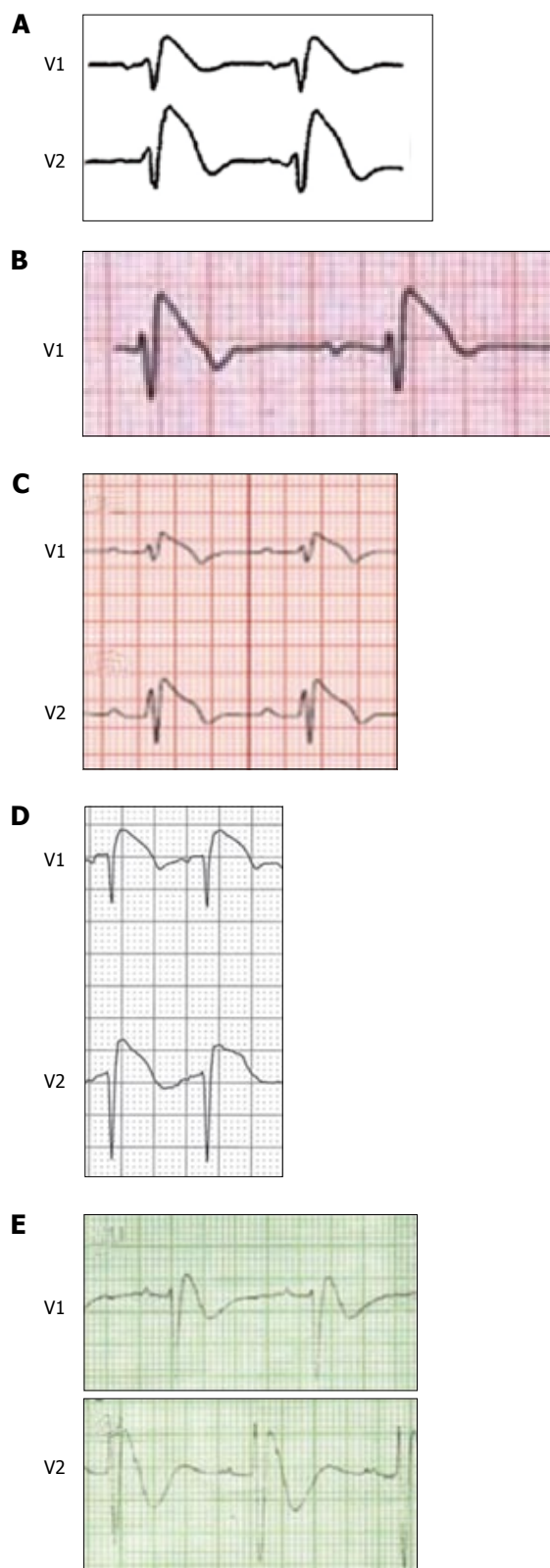


Figure 1 Type 1 Brugada phenocopies. A: True congenital type 1 Brugada electrocardiogram (ECG) pattern; B: Type 1 Brugada phenocopies (BrP) in a patient with an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement; C: Type 1 BrP in a patient with concurrent hyperkalemia, hyponatremia and acidosis; D: Type 1 BrP in a patient with an acute pulmonary embolism; E: Type 1 BrP in a patient with hypokalemia in the context of congenital hypokalemic periodic paralysis.

tion of the metabolic abnormalities, the ECG promptly

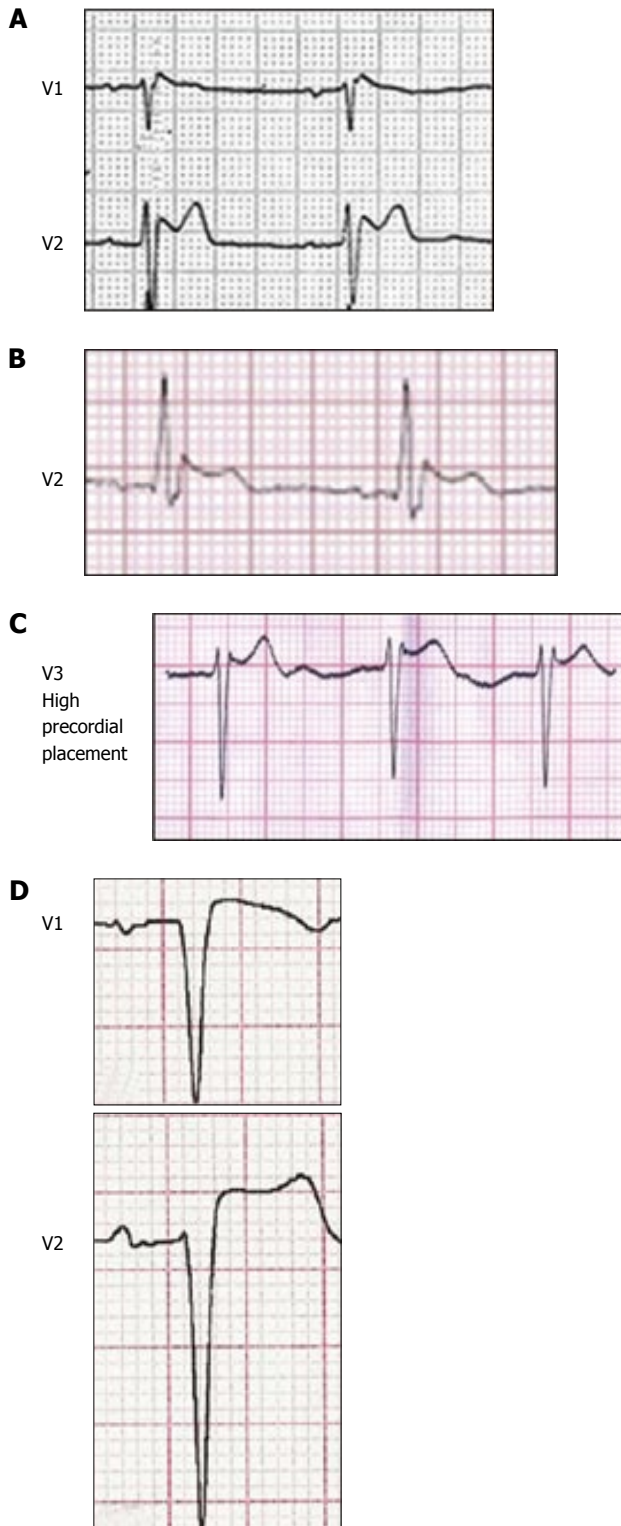


Figure 2 Type 2 Brugada phenocopies. A: True congenital type 2 Brugada electrocardiogram (ECG) pattern; B: Type 2 Brugada phenocopies (BrP) in a patient with an accidental electrocution injury; C: Type 2 BrP in a patient with congenital pectus excavatum causing mechanical mediastinal compression; D: Type 2 BrP as a result of an inappropriate high pass ECG filter.

returned to normal (Figure 3B). A subsequent flecainide provocative challenge did not induce a type 1 Brugada ECG pattern, thereby excluding myocardial sodium channel dysfunction. During the same hospitalization period, the patient experienced ongoing diarrhea with a sec-

Table 1 Brugada phenocopy etiological categories

Etiological category
Metabolic conditions
Mechanical compression
Ischemia and pulmonary embolism
Myocardial and pericardial disease
ECG modulation
Miscellaneous

Reproduced with permission^[9]. ECG: Electrocardiogram.

ond episode of hypokalemia (K 2.6 mEq/L); however, without concurrent acidosis. The ECG again depicted a typical type 1 Brugada ECG pattern (Figure 3C) which resolved after correction of the metabolic abnormality (Figure 3D). This case report is important because it was the first to demonstrate clinical reproducibility of the BrP.

DIFFERENTIATING BRUGADA PHENOCOPY FROM BrS

Currently, a total of 55 case reports, editorials, letters, abstracts and book chapters have been published that discuss the etiology, pathophysiology and conceptual evolution of BrP^[16]. This has led to the current BrP etiological categories (Table 1) and diagnostic criteria (Table 2).

The diagnostic distinction between BrP and true congenital BrS focuses on a few key features. First, patients with BrP have a reversible underlying condition such as adrenal insufficiency, hypokalemia or myocardial ischemia that elicits or induces the Brugada ECG pattern. Once this underlying condition resolves there is prompt normalization of the ECG. This is contrary to true congenital BrS where the ECG manifestations are unmasked by sodium channel blockers, vagotonic agents, febrile states and various metabolic conditions. Second, patients with BrP have a low clinical pretest probability of true congenital BrS as opposed to a high clinical pretest probability in patients with true congenital BrS who have a documented personal history of cardiac arrest, nonvagal syncope or a family history of sudden cardiac death^[1]. Third, patients with BrP have a negative provocative challenge with a sodium channel blocker, while those with true congenital BrS have a positive provocative challenge (Table 2).

The different response to a sodium channel provocative challenge highlights a fundamental pathophysiological divergence when comparing BrP and BrS patients who are exposed to similar environmental stimulus. For example, Postema *et al.*^[17] reported a case of true congenital BrS in the context of hyperkalemia and acidosis. This patient presented with a type 1 Brugada ECG pattern and underwent a positive provocative challenge with ajmaline and negative sodium channel voltage-gated type V α subunit genetic testing. Interestingly, Recasens *et al.*^[6] and Anselm *et al.*^[7] reported a similar case where the patient presented with a type 1 Brugada ECG pattern in the context of hyperkalemia, hyponatremia and acidosis.

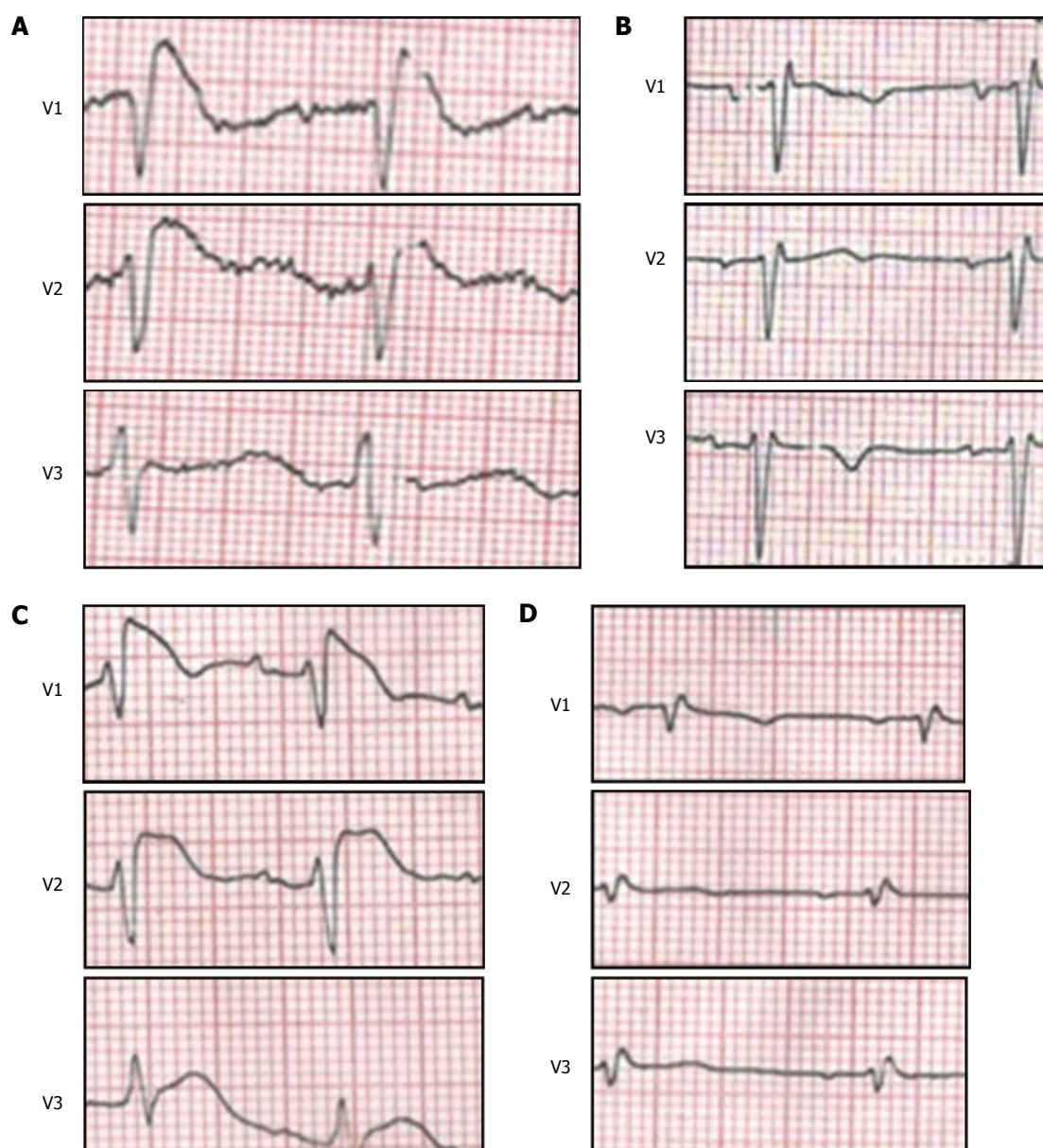


Figure 3 Brugada phenocopy clinical reproducibility. A: Electrocardiogram (ECG) on presentation while the patient is hypokalemic consistent with a type 1 Brugada ECG pattern; B: After correction of the electrolyte abnormality, the ECG normalizes; C: While in hospital, the patient again becomes hypokalemic with recurrence of the type 1 Brugada ECG pattern; D: Subsequent normalization of the ECG pattern after potassium is corrected.

This patient had a negative flecainide provocative challenge. Given the negative sodium channel provocative test, this suggests alternative underlying mechanisms with various genetic, structural and environmental interactions that are yet to be elucidated^[18].

Additionally, while patients with high-risk true congenital BrS are candidates for cardioverter-defibrillator implantation, the clinical implications of patients with BrP remain unknown. Therefore, BrP treatment recommendations at this time would suggest focusing on the resolution of the underlying condition as further intervention has not yet been investigated or validated.

BRUGADA PHENOCOPY: FUTURE DIRECTIONS

The chronological emergence of new ECG phenomena

should include: (1) phenomenological observation; (2) speculation on pathophysiological mechanisms; (3) clinical reproducibility; and (4) experimental model validation. The literature to date has demonstrated steps (1), (2) and (3); however, the key to further understanding the mechanisms behind BrP requires that these phenomena be reproduced under strictly controlled environmental conditions^[19-21]. The development of experimental validation models will help us determine whether BrP are transient alterations of the sodium channels that cannot be reproduced with a provocative sodium channel blocking test, or if they are a malfunction of other myocardial ion channels. Similarly, exposing a genetic model of true congenital BrS to the common conditions that elicit BrP would aid in understanding whether BrP and BrS are entities that belong to the same spectrum of disease, or are completely different entities. In that sense, the model that

Table 2 Criteria to differentiate the Brugada electrocardiogram pattern, Brugada phenocopy and true congenital Brugada syndrome

Brugada ECG pattern
The ECG pattern has a type 1 or type 2 Brugada morphology as currently defined by Bayés de Luna <i>et al</i> ^[1]
Diagnostic criteria for BrP
The ECG pattern has a type 1 or type 2 Brugada morphology
The patient has an underlying condition that is identifiable
The ECG pattern resolves after resolution of the underlying condition
There is a low clinical pretest probability of true BrS determined by lack of symptoms, medical history and family history
Negative provocative testing with sodium channel blockers such as ajmaline, flecainide or procainamide
Provocative testing not mandatory if surgical RVOT manipulation has occurred within the last 96 h
The results of genetic testing are negative (desirable but not mandatory because the SCN5A mutation is identified in only 20% to 30% of probands affected by true BrS)
Features that suggest true congenital BrS
The ECG pattern has a type 1 or type 2 Brugada morphology
There is a high clinical pretest probability of true congenital BrS determined by presence of symptoms, medical history and family history
Positive provocative testing with sodium channel blockers such as ajmaline, flecainide or procainamide. This indicates sodium channel dysfunction consistent with true BrS
Genetic testing is positive in about 20% to 30% of probands

Reproduced with permission^[16]. RVOT: Right ventricular outflow tract; SCN5A: Sodium channel voltage-gated type V alpha subunit; BrP: Brugada phenocopies; BrS: Brugada syndrome.

discovered genetic alterations in patients with acquired long QT^[22] should serve as inspiration to develop the BrP experimental model.

In order to learn about the natural history of BrP, an international online database that allows for longitudinal follow-up is in development at www.brugadaphenocopy.com. We encourage all investigators that are currently reporting on these cases to use the term Brugada phenocopy in order to facilitate literature searches and to help establish this emerging concept^[23,24].

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Peripartum cardiomyopathy: A puzzle closer to solution

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Core tip: The purpose of this review is to highlight the important advances that have brought us nearer to the solution of this puzzle, focusing on what we have learned about peripartum cardiomyopathy (PPCM) since 2000; and what still remains unanswered. There have been many improvements in outcome. Increased understanding of the pathogenesis of PPCM is detailed herein; however, we still do not know the actual triggers that initiate the pathological process; but realize that cardiac angiogenic imbalances resulting from complex pregnancy-related immune system and hormonal changes play a key role.

Abstract

Peripartum cardiomyopathy (PPCM) represents new heart failure in a previously heart-healthy peripartum patient. It is necessary to rule out all other known causes of heart failure before accepting a diagnosis of PPCM. The modern era for PPCM in the United States and beyond began with the report of the National Institutes of Health PPCM Workshop in 2000, clarifying all then-currently known aspects of the disease. Since then, hundreds of publications have appeared, an indication of how devastating this disease can be to young mothers and their families and the urgent desire to find solutions for its cause and better treatment. The purpose of this review is to highlight the important advances that have brought us nearer to the solution of this puzzle, focusing on what we have learned about PPCM since 2000; and what still remains unanswered. Despite many improvements in outcome, we still do not know the actual triggers that initiate the pathological process; but realize that cardiac angiogenic imbalances resulting from complex pregnancy-related immune system and hormonal changes play a key role.

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INTRODUCTION

Peripartum cardiomyopathy (PPCM) represents new heart failure in a previously heart-healthy peripartum patient^[1]. It is necessary to rule out all other known causes of heart failure before accepting a diagnosis of PPCM. Specific echocardiographic criteria define the requirement of systolic heart dysfunction with a left ventricular ejection fraction (LVEF) less than 0.45^[2]. Even if the heart failure has its onset slightly out of the historic definition of time range from one month before delivery to 5 months postpartum, the process is similar, designated as pregnancy-associated cardiomyopathy^[3].

The modern era for PPCM in the United States began with the report of the NIH PPCM Workshop Group^[1] in 2000, describing currently known aspects of the disease; including definition, incidence, potential etiologies, risk factors, diagnosis and management. Since then hundreds

Table 1 Summary of current state of knowledge about peripartum cardiomyopathy

What do we know about PPCM?	What remains unknown about PPCM?
Awareness is important for making an earlier diagnosis with less dysfunction	Actual “triggers” that initiate the process
Hypertension in pregnancy increases risk for development of PPCM	Role of virus in pathogenesis
Most serious complications can be decreased or avoided	Why higher incidence and more severe disease in those with African heritage
Full recovery occurs more frequently than with any other cardiomyopathy	How important role cardiac autoantibodies play in pathogenesis
Autoimmunity (or immune system dysfunction) a part of pathogenesis	The extent and details of genetic factors
Inflammatory cardiomyopathy is common	Importance of the role of prolactin and prolactin inhibition treatment
Higher incidence and more severe disease in those of African heritage	Importance of the role of sFLT1 in pathogenesis
There can be a genetic predisposition	Why do some recovered have a relapse of heart failure with subsequent pregnancy
Effective evidence-based treatment guidelines available	Role of micronutrients and trace metals in pathogenesis
Most recovered do not have a relapse of heart failure in subsequent pregnancy	
Occurs globally, but with geographic variations for incidence and unique characteristics	

PPCM: Peripartum cardiomyopathy.

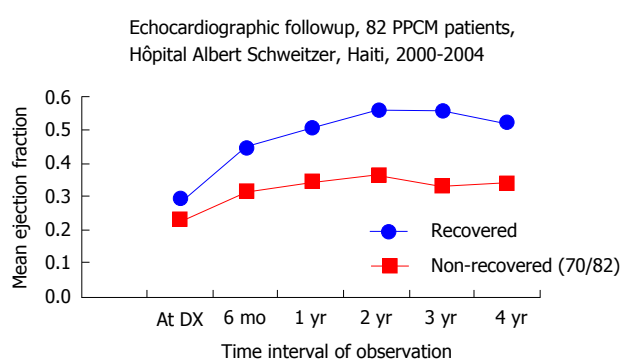


Figure 1 Lower systolic heart function at diagnosis of peripartum cardiomyopathy often means less recovery, “start low, stay low”^[6,14,26]. PPCM: Peripartum cardiomyopathy.

of publications have appeared, an indication of the pressing nature of the disease and the desire to find solutions for its cause and better treatment. There have been numerous excellent recent reviews^[4-8], so this review is not designed to cover the broad basic facets of PPCM. Instead, the purpose of this review is to highlight the important advances that have brought us nearer to the solution of this puzzle; and to identify those key areas that remain without definitive answers. The summarized points of emphasis are listed in Table 1, and discussed individually below.

INCREASING AWARENESS OF PPCM

We know that it helps to have a high index of suspicion that pregnancy-associated heart failure could occur in a previously heart-healthy young woman. Although it is possible that a fulminant myocarditis/cardiomyopathy can suddenly appear without prior warning and awareness, almost all of these women, upon reflection, can recognize that they experienced signs and symptoms earlier by days and weeks. My incessant theme is this: Physicians, nurses and patients must be alert to the possibility that a young woman, despite the lack of any type of heart

problem in her medical history, may develop a serious cardiomyopathy with acute onset of heart failure in the setting of pregnancy^[9].

One reason for the importance of this heightened awareness is that if the patient and her health care providers know about PPCM there is greater potential to recognize it earlier. An earlier detection means that the baseline or diagnostic echocardiographic LVEF is likely to be higher; and when it is in the range of 0.35 or above, the chances for full recovery are much greater (Table 2)^[10-17]. At that level the mortality rate is essentially zero and the full recovery rate approaches 100%. When at-diagnosis LVEF is lower, rate of progression towards recovery is slower, particularly in those of African heritage (See Figure 1 and Table 2).

Studies have shown that lower at-diagnosis LVEF is found when there are delays in diagnosis. This is well demonstrated in the study by Goland *et al*^[10] of 182 United States PPCM patients. They looked at major adverse events, defined as either death or complications that were life threatening. “Delay in diagnosis” referred to patient estimate of time from onset of symptoms to time of confirming the diagnosis of PPCM. 136 PPCM patients who had no adverse events had a mean delay in diagnosis of 1.7 wk while 46 PPCM patients who did have major adverse events had a mean delay in diagnosis of 3.8 wk ($P = 0.02$). Time-of-diagnosis LVEF for those without serious adverse events showed mean value of 0.31, while those with the same serious adverse events showed mean of 0.24 ($P < 0.001$).

HYPERTENSION IN PREGNANCY POSES HIGHER RISK FOR DEVELOPMENT OF PPCM

Up to one-half of PPCM patients have experienced some form of hypertension during their index PPCM pregnancy^[4,5]. Recent clues about the importance of hypertension in pregnancy derive from studies of toxemia of pregnan-

Table 2 Echocardiographic parameters at diagnosis as predictors of recovery (Left ventricular ejection fraction $\geq 50\%$) for peripartum cardiomyopathy *n* (%)

Study	Recovered	Non-recovered	P
Goland <i>et al</i> ^[10,11] (25% African-American)	115 (61.5)	72 (38.5)	
Diagnosis mean LVEF	0.31	0.23	< 0.0001 ^a
Diagnosis mean LVEDd (cm)	5.5	6.1	0.002 ^a
Amos <i>et al</i> ^[12] (51% African-American)	22 (44.9)	27 (55.1)	
Diagnosis mean LVEF	0.23	0.20	0.16
Mean LVEF (%) at 2 mo	43	24	< 0.001 ^a
Diagnosis mean LVEDd (cm)	5.6	6.2	0.01 ^a
Modi <i>et al</i> ^[13] (88.6% African-American)	14 (35)	26 (65)	
Diagnosis mean LVEF	0.29	0.21	0.02 ^a
Diagnosis mean LVEDd (cm)	5.9	6.2	0.16
Fett <i>et al</i> ^[14] (all African heritage)	32 (27.6)	84 (72.4)	
Diagnosis mean LVEF	0.28	0.23	0.002 ^a
Diagnosis mean LVEDd (cm)	5.6	5.9	0.03 ^a
Safirstein <i>et al</i> ^[15] (3.6% African-American)	43 (78.2)	12 (21.8)	
Diagnosis mean LVEF	0.29	0.24	0.13
Diagnosis mean LVEDd (cm)	5.4	5.9	0.21
Diagnostic LVEF > 0.35	25/25	0	< 0.001 ^a
¹ Haghikia <i>et al</i> ^[16]	45 (47)	51 (53)	
Diagnosis mean LVEF	0.28	0.17	< 0.0001 ^a
McNamara <i>et al</i> ^[17] (30% African-American)	59 (65)	32 (35)	
Diagnostic LVEF < 0.30	10/30 (33)	20/30 (67)	0.001 ^a
Diagnostic LVEF ≥ 0.30	58/70 (82.9) ²	21/70 (17.1) ²	0.001 ^a

¹For this group, recovery defined as LVEF 0.55, mean LVEF shown for improved *vs* non-improved; ²Pending last echo late data entry from 12 mo postpartum. LVEDd: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; Recovered: Last LVEF ≥ 0.50 ; Non-recovered: Last LVEF < 0.50;

^aP ≤ 0.05 *vs* non-recovered.

cy (eclampsia and preeclampsia), showing the importance of some biomarkers that assist in early identification of patients at high risk^[18-20]. These same biomarkers appear to be also present in PPCM not only as markers, but strongly suspect as causal factors in the pathogenesis of PPCM^[21]. The functional cardiac abnormalities in severe preeclampsia reflect a diastolic dysfunction, and some of these women also go on to classical systolic dysfunction heart failure that meet diagnostic criteria for PPCM^[22,23].

A recent epidemiology report out of North Carolina^[24] shows that out of 79 PPCM patients, 51 (65%) had some form of hypertension. Eleven, (13.9%) had preeclampsia, 18 (22.8%) had gestational hypertension, 10 (12.7%) had chronic hypertension, 10 (12.7%) had chronic hypertension and preeclampsia, 1 had eclampsia. Only one had hemolysis, elevated liver enzymes and low platelet count syndrome.

PREVENTING SERIOUS COMPLICATIONS OF PPCM

Most serious complications of PPCM can be either avoided or decreased (See Case Reports 1 through 5). The most serious complications of PPCM (ventricular tachyarrhythmias, thromboembolic events, chronic cardiomyopathy) are found when the diagnostic or baseline LVEF is below 0.30 to 0.35^[3-5,9-17]. In the Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study, 5/6 major adverse events (death or transplant or left ventricular assist device) occurred in those with baseline LVEF < 0.30, confirming that women with severe systolic dysfunction at presentation have the poorest out-

comes^[17]. As such, this group may represent a target for future interventional trials.

It is also important to be certain that the best treatment is being implemented for all; but particularly for those in this LVEF under 0.30 category so as to help prevent the major complications: Adequate anticoagulation to help prevent thromboembolic phenomena; heart rhythm monitoring and devices to recognize and treat dangerous arrhythmias; and full use of evidence-based AHA Guideline therapy to help achieve eventual recovery^[25].

REMARKABLE RECOVERY POTENTIAL

Full recovery of heart function occurs more frequently in PPCM than with any other dilated cardiomyopathy. Even with the very limited resources in Haiti, an organized program to diagnose and manage PPCM, with the first population-based PPCM registry, demonstrated the ability to improve full recovery from less than 4% to over one-third of women over a period of 4 years^[26]. The first United States prospective study of PPCM, the IPAC study showed that full recovery (LVEF ≥ 0.50) at 6 mo postpartum came to a remarkable over 65 % of patients^[17]. It is important to note that this level of full recovery occurred without the use of bromocriptine inhibition of the lactating hormone, prolactin. This is discussed in greater detail later. Other studies, all retrospective in nature, have also confirmed high rates of recovery^[11,12,27].

Table 2 confirms the importance of diagnostic levels of systolic heart function (LVEF) to recovery. Health care providers and women in the latter stages of pregnancy are becoming more aware of the importance of

early identification of PPCM; and are becoming more alert about how to differentiate normal late pregnancy signs and symptoms from early heart failure symptoms^[9].

IMMUNE SYSTEM CHANGES IN PATHOGENESIS OF PPCM

Immune system changes (autoimmunity or immune system dysfunction) are an important part of the pathogenesis of PPCM^[28]. Alterations in cellular immunity have been observed in PPCM patients compared to normal postpartum women. An increase in the activation of regulatory T-cells and innate immunity is a necessary part of all pregnancies. However, there is an increase of T cells (CD3⁺ CD4⁺ CD8⁺ CD38) in PPCM patients compared to healthy postpartum patients. Natural killer (NK) cells (CD3⁺ CD56⁺ CD16⁺) are significantly reduced in PPCM patients compared to healthy postpartum women. Furthermore, while the decrease in percent of NK cells is similar in both black and white PPCM patients at entry to the study, this decrease persisted 2 mo later only in blacks^[29-31]. IPAC, with a prospective study of 100 North American PPCM patients, is currently investigating if this immune system activation correlates with recovery outcomes^[17]. (IPAC available at <http://www.peripartumcmnetwork.pitt.edu>). The earlier Investigations of Myocarditis and Acute Cardiomyopathy studies identified comparable findings in their PPCM cohort^[30]. This remarkable finding relating to differences between African heritage and Caucasian PPCM mothers with respect to NK cells is undergoing additional studies^[31].

INFLAMMATORY CARDIOMYOPATHY IN PATHOGENESIS OF PPCM

A cardiomyopathy with inflammatory cytokines is common in PPCM. This inflammatory process may be either cellular or molecular non-cellular or both^[27,32-34]. Mean serum levels of high sensitivity C-Reactive Protein (hsCRP), a simple and inexpensive laboratory estimate reflecting proinflammatory cytokines, were found to be significantly elevated in 22 Haitian PPCM patients compared to 14 non-PPCM Haitian mothers (144.3 mg/L, range 2.8-946 *vs* 5.2 mg/L, range 1.8-9.9, $P < 0.001$)^[14]. In the same population, significantly higher mean serum hsCRP levels were found in recovered PPCM patients compared to non-recovered PPCM patients (417 mg/L compared with 27 mg/L, $P = 0.004$), suggesting that a vigorous inflammatory response favored chances of recovery^[33,34]. Elevated mean serum hsCRP levels have also recently been reported in 52 Chinese PPCM patients compared to 52 non-PPCM controls (28.2 mg/L *vs* 6.2 mg/L, $P < 0.05$)^[35]. In South African PPCM patients at diagnosis, higher levels of serum hsCRP correlated with left ventricular end diastolic diameter ($P = 0.003$) and inversely with LVEF ($P = 0.015$)^[32]. A recent article describing a prospectively identified cohort of 46 PPCM patients in India also reports significantly elevated levels

of serum hsCRP, Tumor Necrosis Factor- α , and Interleukin-6^[36]. These inflammatory markers also helped to predict outcome.

The biomarker of serum hsCRP will only be elevated in the presence of an inflammatory cardiomyopathy, a frequent occurrence in PPCM. However, one would not expect an elevation of serum hsCRP if no inflammatory cardiomyopathy exists, such as in the presence of a familial dilated cardiomyopathy or in a relapse of heart failure in a previously unrecovered PPCM mother in a post-PPCM pregnancy.

Multiple proinflammatory cytokines involved in the pathogenesis of PPCM include Fas, hsCRP, Interferon- γ , Interleukin-6, Transforming Growth Factor- β , Tumor Necrosis Factor- α and others in the process of evaluation^[28,34,37].

GENETIC FACTORS IN PPCM

An important proportion of PPCM patients, around 5%-10%, have either a genetically caused condition (which would make the correct diagnosis familial dilated cardiomyopathy) or a genetic predisposition to develop PPCM when linked with additional factors^[5,38]. Higher incidence of PPCM in those of African origin can be attributed in part to genetic factors, although environmental factors may also play an important role^[39,40]. A genome-wide association of PPCM with chromosome 12p11 locus has been reported by Horne *et al*^[38]. There may also be a genetic predisposition to the development of PPCM, with another factor or factors, involving a complex interaction of pregnancy-associated immune system changes^[41].

It is important to explore further the relationship of PPCM with Idiopathic dilated cardiomyopathy (IDCM) since clinically there are many similarities. Up to one-quarter of familial dilated cardiomyopathy patients and 18% of sporadic IDCM have the presence of TTN, the protein encoding the sarcomere protein titin^[42]. What proportion of PPCM patients also have this gene? Additional studies need to be carried out exploring the finding of a single nucleotide polymorphism, rs258415, to have genome-wide significance in PPCM versus control mothers^[38]. Additional studies are ongoing and will certainly continue to add to our knowledge about inherited patterns and genetic influences in PPCM.

EVIDENCE-BASED TREATMENT OF PPCM

There is effective evidence-based treatment available with the combination of tolerable dosages of diuretics, Angiotensin Converting Enzyme Inhibitors (ACEI) and beta-blockers (BB) as outlined in published Guidelines. There need be no guess work in the application of effective treatment for PPCM since proved effective treatment of heart failure from PPCM is available and clearly defined in the American Heart Association and European Society of Cardiology Guidelines for treatment of heart failure with reduced LVEF^[25,43]. This evidence-based treatment (categories of Class I: "Benefit exceeds risk, should use" and Level of Evidence A: "Data from multiple clinical

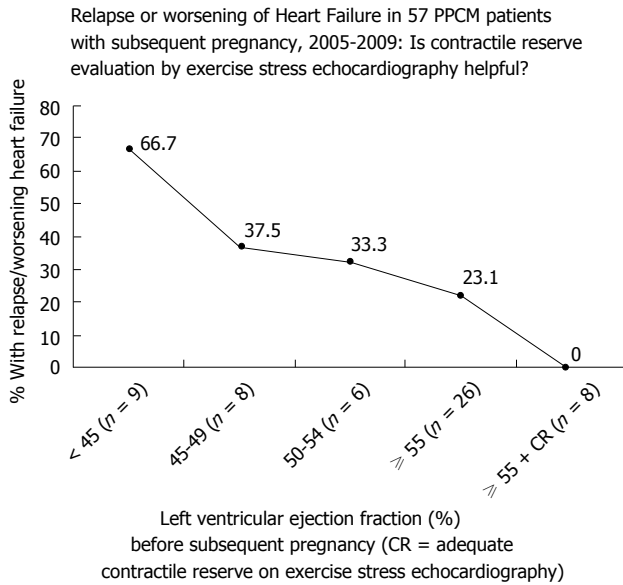


Figure 2 Risk for relapse of heart failure in a post-peripartum cardiomyopathy pregnancy^[53,54]. PPCM: Peripartum cardiomyopathy.

trials and multiple populations”) for systolic heart failure with decreased LVEF consists in giving tolerable dosages of diuretics, ACEI (replaced by hydralazine with or without nitrates if still pregnant or breastfeeding) and BB. Angiotensin receptor blockers (ARB) may be used if there is ACEI intolerance; but just as with ACEI, they are not safe to take during pregnancy or conception. Otherwise, this Guideline-recommended treatment is the same as for heart failure in other non-ischemic cardiomyopathies.

Very severe systolic dysfunction at diagnosis with circulatory collapse will require other treatment for hemodynamic support; and prevent the initial use of BB. As mentioned in the section on thromboembolic events, appropriate anticoagulation until improvement of LVEF above 0.30-0.35 is indicated.

Work by Hilfiker-Kleiner *et al*^[44] and Sliwa *et al*^[45] with respect to potential cardiotoxic prolactin metabolites has stimulated interest in the use of prolactin inhibition by bromocriptine. In regards to the use of bromocriptine, the recent study out of Germany^[16], found the greatest improvement (55 out of 57 or 96%) occurred in PPCM patients receiving combination treatment of BB, ACEI/ARB and bromocriptine (2.5-5 mg/d for 4 wk). These investigators reported “full recovery” (LVEF ≥ 0.55) for 45 out of 96 (47%) PPCM patients; but that there was no statistically significant difference in those who reached full recovery for the 64 who received bromocriptine compared with the 32 who did not receive bromocriptine. Out of 96 PPCM patients, 14 failed to improve. All of these had baseline LVEF ≤ 0.25 .

These European investigators indicate that bromocriptine “may not be sufficiently effective in all patients, especially in PPCM patients with very low baseline EF”^[16]. Their cohort of PPCM patients with very low baseline EF also frequently could not receive BB treatment due to low blood pressure and bradycardia. It is to

be noted that the full recovery rates for these European patients were very similar to those reported by North American IPAC investigators, a study in which bromocriptine had not been a part of the treatment^[17].

The best tolerated dosages of combination BB and ACEI treatment will be the most helpful in moving towards full recovery. A serious deficiency in treatment would be the use of only BB or only ACEI/ARB instead of a combination of the two at tolerated dosages. Very slow and small incremental increases in dosages as needed can circumvent the limiting factor of postural hypotension symptoms. This is the best way to successfully reach the more effective restorative effects with solid increases in LV systolic function.

Aside from hemodynamic benefits, the combination of BB + ACEI may be synergistic; and may depend upon their influence in helping to correct the immune system dysfunction that plays a pathogenic role in PPCM^[46-48]. Anticoagulation to avoid thromboembolic events is extremely important for those who have LVEF < 0.35 . In that lower cardiac function group it is important to monitor heart rhythm to detect and treat ventricular tachyarrhythmias.

Pentoxifylline, as an inhibitor of the proinflammatory cytokine, Tumor Necrosis Factor- α , appeared earlier in South Africa^[49] to be helpful to improve left ventricular function. However, in our trials in Haiti, pentoxifylline failed to show any evidence for improved survival or improved clinical or echocardiographic left ventricular function^[9,50].

Long-term follow-up is important as we continue to see late sudden death in some apparently recovered PPCM mothers; and do not know if this represents sudden cardiac death (SCD) and ventricular tachyarrhythmias as a consequence of PPCM-related scar tissue in the conduction system or from new onset disease, such as coronary artery disease^[51,52].

POST-PPCM PREGNANCIES

The majority of PPCM mothers who experience apparent full recovery (LVEF ≥ 0.50) will not experience a relapse of heart failure with a subsequent pregnancy; or, if they unexpectedly experience a relapse, the treatment, when initiated early, is very effective^[53,54]. In that case, the outcome is still good for mother and baby; and over 90% of those who begin the post-PPCM pregnancy with LVEF above 0.50 will recover to their pre-subsequent pregnancy cardiac function despite relapse^[54]. Risk of relapse of heart failure in a post-PPCM pregnancy increases incrementally in proportion to the systolic dysfunction associated with LVEF < 0.55 (Figure 2)^[54,55]. It is unclear what level of systolic dysfunction constitutes an absolute contraindication to a subsequent pregnancy; however, from extensive experience with post-PPCM pregnancies, it seems to me that the critical level is anything below LVEF 0.40^[54].

The published monitoring strategies^[53] are designed

to help assure early detection of relapse of heart failure, when effective treatment can bring about stabilization and offer excellent potential for another recovery of heart function^[51-56]. Although we may identify “full recovery” for PPCM as those with LVEF ≥ 0.50 , some of these women still go on to a relapse of heart failure in a post-PPCM pregnancy^[53-55] (Figure 2). That must mean that they really did not have a complete recovery or that they have a continuing reason for the development of pregnancy-associated heart failure; and we don't yet know why. It is imperative to attempt to further identify the reasons for this, so that outcomes can still be satisfactory. Evidence supports the observation that even if these apparently completely recovered post-PPCM pregnancy mothers relapse, the treatment of their relapse of heart failure is very effective^[53,54].

The outcome is not nearly so good for post-PPCM pregnancy in those who have not reached the threshold of apparent recovery from the index episode of PPCM^[53,54]. We also do not know if prophylactic beta-blockade will prevent a relapse of heart failure with a post-PPCM pregnancy; or for that matter, if the BB might conceal early diagnosis of relapse, with delay of initiation of effective full treatment.

Even now, there are at least 3 observations that help us to distinguish “full recovery” from “apparent, but incomplete recovery”^[53,54]. First, an LVEF before subsequent pregnancy of 0.55 is a better indicator than an LVEF of 0.50 that the recovery is more likely to be successful without relapse of heart failure in another pregnancy (Figure 2). Secondly, a deterioration of LVEF with the gradual withdrawal of either BB or ACEI treatment is a good indicator that solid recovery has not yet occurred. Thirdly, inadequate contractile reserve on exercise stress echocardiography can be a predictor of likely relapse of heart failure in a post-PPCM pregnancy. With inadequate contractile reserve, it is better to defer subsequent pregnancy and strive for further improvement^[53,54]. It should be emphasized that a history of ventricular tachyarrhythmias warrants the continuation of BB treatment “for life”.

WORLD-WIDE PPCM

Pregnancy associated cardiomyopathy occurs globally, but with geographic variations for incidence, morbidity, mortality and unique characteristics. Cultural practices in Nigeria involving postpartum salt-loading and heated mud beds play an important role in the high incidence of heart failure, a variant of PPCM^[57]. High incidence of PPCM in Haiti seems to reflect the genetic influence of African heritage as well as micronutrient deficiencies, perhaps zinc, involved in immune system dysfunction^[26,58,59]. Overlap of PPCM and high incidence of HIV-disease appear to influence approach to PPCM in South Africa^[60]. Larger proportions of population with African heritage result in greater incidence and prevalence of PPCM^[40,61]. In China, common use of herbal remedies

may influence outcome for PPCM patients, but valid research is limited^[62,63].

WHAT INITIATES PPCM?

We do not yet know what is the actual “trigger” (there may be more than one) that initiates the process resulting in PPCM. This is perhaps the most difficult of all the quandaries about PPCM. We simply do not know. Some entertained the idea that fetal cells crossing into the maternal circulation may have targeted the mother's heart (fetal microchimerism)^[28]. If anything, we now realize that these fetal cells may actually be helpful rather than harmful^[64]. Viral infection, as a trigger, has not been excluded; but neither has there been strong reinforcement of the likelihood. In personal files suggesting a possible link, I have identified 19 patients in whom the time framework of onset of new heart failure associated with pregnancy suggested a viral infection etiology (Table 3)^[65-70]. The largest of these studies^[66] showed similar incidence of the same viruses in endomyocardial biopsy tissue in both PPCM mothers and non-PPCM controls, making it unconvincing that virus played a role in those PPCM patients. It certainly seems likely that viral genomes in myocardial tissue may actually be “innocent bystanders” and not causal of disease, at least for some viruses. On the reverse side, it appears that for some cardiotropic viruses, once sensitization occurs, there may be an ongoing inflammatory process with or without viral genome persistence in the heart^[71].

In any case it seems likely that multiple triggers exist; often in the form of foreign antigens, serving in the role of “molecular mimicry”^[72,73], with epitope spreading, able to initiate an organ specific autoimmune disease^[28,72-74]. It is important to continue to put the pieces of the PPCM puzzle together and eventually the exact trigger or triggers will fit into the overall scheme of things. In the meantime, outcome results continue to improve, despite our lack of knowledge about actual trigger(s) for the process.

PPCM IN THOSE OF AFRICAN HERITAGE

We do not yet know why PPCM has been documented to be both more frequent and a more severe disease in those of African heritage^[13,17,31,75,76]. In the first North American prospective PPCM study, those with African heritage had a lower baseline LVEF and this poorer function persisted throughout the 12 mo study period^[17].

Harper *et al*^[24] identify the birth prevalence in North Carolina, United States, of PPCM for “black, non-Hispanics” as 1 case for every 1087 live births, four times the prevalence for “white, non-Hispanics” at 1 case for every 4266 live births. A California healthcare system reported the incidence of PPCM in blacks to be 1 case for every 1421 deliveries, 2.9 time higher compared with whites^[40]. Amos *et al*^[12], also identified a significant racial disparity in outcomes for PPCM in North Carolina, reporting that in their series of 55 PPCM patients, 51% of whom were

Table 3 Role of viral infection in the etiology of peripartum cardiomyopathy: Pathogenesis or mere presence?

ID	PPCM patient	Virus	Type of test	Comments
1	Author case file, Norway	Parvovirus B19	IgM/IgG + EMB + PCR	EMB = neg myocarditis
2	Case report, Italy ^[65]	Coxsackievirus B	IgM + blood PCR + blood	EMB = lymphocytic myocarditis
3	Case report, Germany ^[66]	Parvovirus B19	EMB + PCR	EMB = borderline myocarditis
4	Case report, Germany ^[66]	Parvovirus B19	EMB + PCR	EMB = borderline myocarditis
5	Case report, Germany ^[66]	E-B Virus	EMB + PCR	EMB = borderline myocarditis
6	Case report, Germany ^[66]	Human Herpesvirus 6	EMB + PCR	EMB = borderline myocarditis
7	Case report, Germany ^[66]	Human Herpesvirus 6	EMB + PCR	EMB = borderline myocarditis
8	Case report, Germany ^[66]	Cytomegalovirus	EMB + PCR	EMB = borderline myocarditis
9	Case report, Germany ^[66]	Parvovirus B19	EMB + PCR	EMB = inflammatory cardiomyopathy
10	Author case file, United States	Parvovirus B19	IgM/IgG + blood	Exposure to PVB19 child during pregnancy
11	Author case file, United States	Parvovirus B19 cytomegalovirus	IgG + blood	Hydrops fetus, stillborn
12	Case report, Japan ^[67]	Influenza A/B	Paired sera antibody rise	EMB = neg. Treatment with IV immunoglobulin
13	Case report, Japan ^[67]	Influenza B	Paired sera antibody rise	EMB neg. Treatment with IV immunoglobulin
14	Author case file, United States	Parvovirus B19	IgG + blood	Exposure to PVB19 child during pregnancy
15	Author case file, United States	Cytomegalovirus	IgM + blood	LVEF 15%, IgG + blood E-B virus
16	Case report, Taiwan ^[68]	PCR neg for all 4 tested	EMB/PCR neg, but myocarditis	2 mo pp, RV/LV failure, patient died VF
17	Author case file, United States	H1N1 Influenza	Nasal swab, no Rx given	LVEF 40% at Dx, day 1 postpartum
18	Case report, United States ^[69]	Parvovirus B19	EMB + PCR	HF 27 wk, g3p2 EMB neg myocarditis
19	Case report, Belgium ^[70]	E-B virus		Postpartum facial palsy full recovery 6 mo

EMB: Endomyocardial biopsy; PCR: Polymerase chain reaction; LV: Left ventricular; LVEF: LV ejection fraction; PPCM: Peripartum cardiomyopathy; PVB19: Parvovirus B19; RV: Right ventricular; VF: Ventricular fibrillation; HF: Heart failure.

“African American”, only 41% of African Americans recovered compared to 74% of “Whites”.

Goland *et al*^[75] recently reported a comparison of 52 African American PPCM patients with 104 white PPCM patients, finding that the rate of left ventricular recovery to LVEF ≥ 0.50 was significantly lower in African Americans (40% *vs* 61%; $P = 0.02$). This negative comparative outcome for those of African heritage has been also documented in Georgia^[75] and Louisiana^[13]. Gentry, in Georgia, United States, indicated that African-American women had a 15.7-fold higher relative risk of PPCM compared to non-African Americans (OR = 15.7, 95%CI: 3.5-70.6)^[76]. These outcomes in United States African American PPCM patients are more comparable to mortality and morbidity reports out of South Africa^[32] and Haiti^[26].

Significantly lower plasma levels of the proinflammatory cytokine, Transforming Growth Factor- β have been documented in both Haiti and South Africa^[32,33]. While it is possible that this is due to genetic factors, we cannot exclude a non-genetic environmental biopathological process. In either case this could result in worse outcomes. This factor has not yet been evaluated in African-American PPCM mothers compared to Caucasian or Hispanic mothers. While zinc deficiency resulting in immune system dysfunction is suggested as a possible nutritional factor in Haiti, this possibility awaits additional study; and certainly plays no role in nations where severe poverty is not an issue^[58,77].

It is important to promote further investigations of the previously mentioned differences in the postpartum

rate of restoration of NK cells in African heritage compared to Caucasian mothers^[31]. This may explain in part the lower diagnostic LVEF and the slower recovery rates found in these African-American mothers. It is possible that NK-T cells promote the expression of cardioprotective cytokines, such as Interleukin-10^[78]. An extra benefit of BB treatment may also be an increase in the percentage of NK T-cells, possibly partially correcting the disparity observed in African-American mothers^[30,79].

ROLE OF AUTOANTIBODIES IN PATHOGENESIS OF PPCM

We do not yet know how important a role cardiac autoantibodies play in PPCM. Are these autoantibodies, common in PPCM patients^[28,80], not only biomarkers of a cardiomyopathy, but also pathogenic in the process (Figure 3)? Some cardiac autoantibodies, such as the antibody targeting the β_1 -adrenergic receptor, appear to be damaging to the heart^[81]. One of the most recent reports^[82] identifies autoantibodies against β_1 -adrenergic receptors and M2-muscarinic receptors to correlate with worse cardiac systolic function. The finding of these serum autoantibodies also in 6/36 (16.7%) normal pregnant women, however, is troubling; and reinforces the need to follow such patients because they may not be actually “normal”^[83]. In our own studies, we found normal postpartum women to have none of the cardiac autoantibodies present in serum^[80].

Preliminary studies suggest that removal of these antibodies results in improved cardiac function^[84-86]. Per-

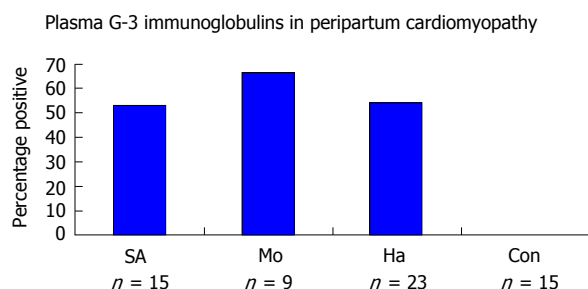


Figure 3 Autoantibodies in peripartum cardiomyopathy. Multiple types of cardiac antigen antibodies are common in PPCM. This Figure illustrates the presence of cardiac myosin heavy chain antibodies in PPCM patients from two African nations and Haiti. None were found in control normal postpartum patients from South Africa^[81]. SA: South Africa; Mo: Mozambique; Ha: Haiti; Con: Controls; PPCM: Peripartum cardiomyopathy.

haps the time has arrived for an interventional trial of immunoadsorption of these antibodies found in PPCM, particularly for those with low baseline LVEF, a group that is least likely to reach full recovery levels? This will not be easily accomplished because of the complicated procedure of apheresis and the precarious condition of the patients who could potentially be most helped by this process. An alternative that holds some promise of help is the use of peptides to neutralize putatively harmful cardiac autoantibodies, such as anti- β 1-adrenoreceptor antibodies, a much simpler process^[87,88].

ROLE OF PROLACTIN METABOLITES IN PATHOGENESIS OF PPCM

We do not yet know for sure that 14/16 kDa-prolactin metabolic products are cardiotoxic in humans; nor if inhibition of prolactin treatment produces better outcomes. As alluded to earlier, a strong foundation has been demonstrated for the cardiotoxic effects of “vasoinhibins”, the cleavage products of normal prolactin under situations of oxidative stress^[44,45]. However, studies to-date testing the effectiveness of prolactin inhibition treatment have given mixed results^[16]. Additional study with randomly-assigned PPCM patients to bromocriptine inhibition of prolactin cohort *vs* no bromocriptine inhibition treatment is underway and should help to clarify this potential treatment modality.

ROLE OF SOLUBLE FMS-LIKE TYROSIDE KINASE IN PATHOGENESIS OF PPCM

We do not yet know for sure that sFLT1 (also known as soluble vascular endothelial growth factor receptor-1) is cardiotoxic in humans; nor if inhibition of sFLT1 treatment will effectively promote the healing process. Soluble FLT1, a recently identified enzyme in the tyrosine kinase family, appears to be anti-angiogenic, cardiotoxic and particularly elevated in both PPCM and preeclampsia^[18,21]. If confirmed in larger series of PPCM patients, such as currently being addressed in the IPAC study, this may lead to

better treatments with promising anti-sFLT1 agents. With respect to preeclampsia, plasma sFLT1 has been found to be significantly elevated very early in some pregnancies, well before the clinical diagnosis of preeclampsia could be made^[89]. Early detection of plasma sFLT1 may also assist in confirming an earlier diagnosis of both PPCM and preeclampsia.

In particular, multiple groups of investigators are defining the clinical importance of finding the higher serum sFLT1/placental growth factor (PLGF) ratios^[19,89]. The highest ratios come about because of those with highest levels of serum sFLT1 (anti-angiogenic) and lowest levels of PLGF (pro-angiogenic) and it appears that this angiogenic imbalance can ultimately lead to heart failure^[88]. In this process, placental hypoperfusion and maternal endothelial dysfunction play important roles^[90]. This may turn out to be a very important development with respect to both diagnosis and management; but we are not yet certain. However, it is important to be alert to the possibility of peripartum heart failure from diastolic dysfunction, despite preserved systolic function with normal LVEF (would not meet current definition criteria for PPCM).

ROLE OF MICRONUTRIENTS IN PATHOGENESIS OF PPCM

Finally, we do not yet know if micronutrient and trace metal deficiencies play a role in the pathogenesis of PPCM in some unique situations. Earlier reports of endemic adolescent dilated cardiomyopathies due to selenium deficiency in China encouraged us to consider this possibility^[91,92]. In the high-incidence PPCM country of Haiti, we searched diligently for this possibility, but could not confirm it^[58]. However, further search led us to think that zinc deficiency could impact immune system functions and contribute to the process^[93-95]. Efforts to facilitate recovery with nutritional supplements in certain situations have provided some support; but remain unconfirmed and need further investigation^[96].

Please see Figure 4 with proposed multifactor hypotheses of the pathogenesis of PPCM. Case reports from the United States are included to illustrate some of the common serious complications that may accompany PPCM. These case reports come from the author's personal case file: PPCM Case Reports With Adverse Events: Note that all cases had diagnostic LVEF < 0.30.

Case 1 (United States): Onset with fetal distress and superior mesenteric artery thromboembolism

A 37 year-old gravida 4, para 2 patient presented in the 40th wk of pregnancy with swollen legs, mild dyspnea and fetal distress. She underwent emergency Cesarean section with rescued male infant. Post-operatively, she developed diffusely tender abdomen with absence of bowel sounds. Computed tomography scan of the abdomen suggested small bowel infarction. Chest X-ray revealed cardiomegaly, small right pleural effusion and increased pulmonary vascularity. An echocardiogram showed left ventricular

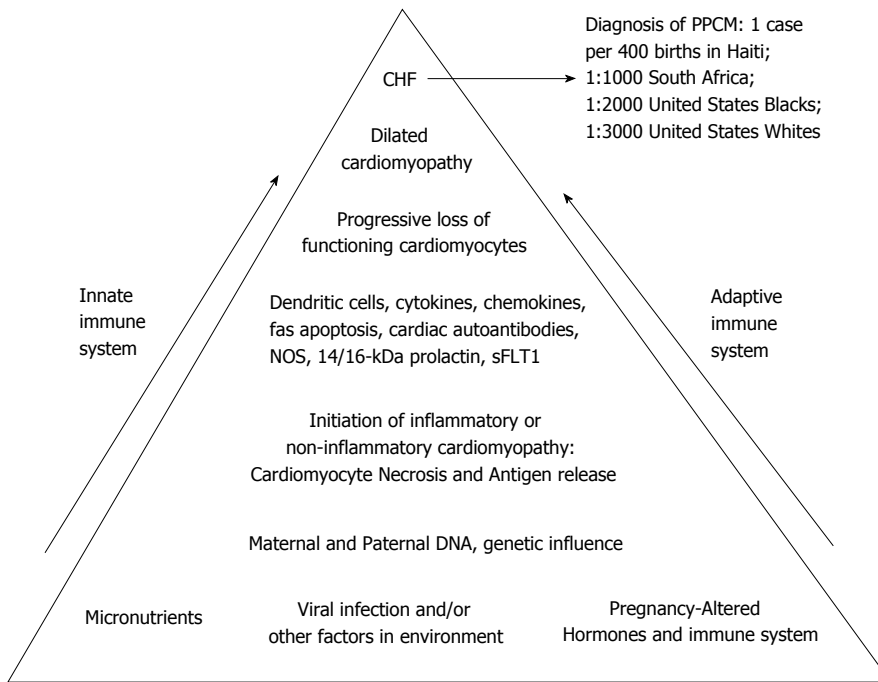


Figure 4 Schematic hypothesis for pathogenesis of peripartum cardiomyopathy. At the base of the pyramid are listed multiple potential contributing factors. Potential viruses include coxsackievirus B3, adenovirus, and parvovirus B19. Dendritic cells are activated by antigen(s) with initiation of a process leading to a cardiomyopathy that may be histologically either inflammatory or non-inflammatory. Cardiomyocyte damage results in the release of previously sequestered cardiac proteins with subsequent production of various autoantibodies, including but not limited to cardiac myosin heavy chain, cardiac Troponin-I, putative cardiac transaldolase, and cardiac beta 1-adrenergic receptor autoantibodies. Production of cytokines, chemokines, nitric oxide synthase (NOS) contribute to the negative inotropic effect. Fas-mediated apoptosis contributes to eventual cardiomyocyte loss. Ultimately, with the progressive loss of functioning cardiomyocytes, dilated cardiomyopathy and congestive heart failure (CHF) ensue, permitting a clinical diagnosis of PPCM. Both innate and adaptive immunity are involved, with participation of both cellular and humoral immune systems. Recently, other potential cardiotoxic substances have been identified, including 14/16 kDa-prolactin metabolites and kinase enzyme system, sFLT1^[21,26,28,32,33,37,38,44,63,66,70,77,80,93]. PPCM: Peripartum cardiomyopathy.

enlargement, end-diastolic diameter of 6 cm and LVEF of 0.17. Exploratory abdominal surgery confirmed necrosis of the small bowel, which was inoperable. She experienced circulatory collapse, cardiac arrest, and unsuccessful resuscitation.

Case 2 (United States): Onset with ventricular tachyarrhythmia, SCD

A 26-year-old gravida 1 patient in her 36th wk of pregnancy collapsed in her garage. She was found by family member who started cardiac cardiopulmonary resuscitation and called emergency services. Her cardiac rhythm normalized and she was taken to the hospital. Her echocardiogram showed mildly dilated left ventricle, end-diastolic diameter 5.1 cm, LVEF at diagnosis 0.17. There was an absence of fetal heart tones, with eventual vaginal delivery of stillborn; but the mother's heart function returned to normal over the next 6 mo.

Case 3 (United States): Onset with cerebrovascular thromboembolism

A 26 year-old gravida 2, para 1 patient in her 37th wk of pregnancy presented with paralysis of the right arm and leg (hemiplegia). Echocardiogram demonstrated thrombus in left ventricle, end-diastolic diameter left ventricle 5.4 cm, LVEF at diagnosis 0.15. Treatment included anticoagulation, hydralazine and metoprolol long-acting.

With stabilization of cardiac function, a Cesarean section was performed with birth of a healthy male infant. Heart function gradually normalized and one year later her only neurological deficit was mild weakness in right leg.

Case 4 (United States): Late diagnosis, chronic severe cardiomyopathy

A 20-year-old primipara developed preeclampsia in her last month of pregnancy. With stabilization of her blood pressure, a Cesarean section was carried out with the birth of healthy twins. She experienced postpartum edema, dyspnea, and abdominal pain. Abdominal ultrasound revealed cholelithiasis and laparoscopic cholecystectomy was performed. Post-operatively, she experienced more edema, dyspnea, and cough. She went to the Emergency Room twice, where blood tests showed abnormal liver function tests; Chest X-ray showed cardiomegaly, An echocardiogram demonstrated LVEF of 0.10. Her hemodynamic instability required a left ventricular assist device. Her LVEF persisted in the range of < 0.20 and she was placed on the transplant list.

Case 5 (United States): Subsequent pregnancy before recovery with eventual chronic dilated cardiomyopathy

A 31-year-old gravida 2, para 2 patient was diagnosed with PPCM two weeks postpartum with echocardiographic LVEF at diagnosis of 0.24. She received treat-

ment with lisinopril and carvedilol with improvement of her LVEF to 0.46. She phased out all medication and 3 years later became pregnant. She delivered a healthy female child; but subsequently experienced dyspnea on exertion and persistent pedal edema 3 d postpartum. An echocardiogram revealed reduction of echocardiographic LVEF to 0.34. She received treatment with lisinopril and carvedilol with gradual improvement of LVEF to 0.42, where it continued unchanged 3 years later.

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Cardioprotection and pharmacological therapies in acute myocardial infarction: Challenges in the current era

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Abstract

In patients with an acute ST-segment elevation myocardial infarction, timely myocardial reperfusion using primary percutaneous coronary intervention is the most effective therapy for limiting myocardial infarct size, preserving left-ventricular systolic function and reducing the onset of heart failure. Within minutes after the restoration of blood flow, however, reperfusion itself results in additional damage, also known as myocardial ischemia-reperfusion injury. An improved understanding of the pathophysiological mechanisms underlying reperfusion injury has resulted in the identification of

several promising pharmacological (cyclosporin-A, exenatide, glucose-insulin-potassium, atrial natriuretic peptide, adenosine, abciximab, erythropoietin, metoprolol and melatonin) therapeutic strategies for reducing the severity of myocardial reperfusion injury. Many of these agents have shown promise in initial proof-of-principle clinical studies. In this article, we review the pathophysiology underlying myocardial reperfusion injury and highlight the potential pharmacological interventions which could be used in the future to prevent reperfusion injury and improve clinical outcomes in patients with coronary heart disease.

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Key words: ST-elevation myocardial infarction; Cardioprotection; Myocardial reperfusion injury; Infarct size; Adjunctive therapy

Core tip: As therapeutic interventions administered at the time myocardial reperfusion have been proven to reduce infarct size in both experimental and clinical models, the existence of a lethal reperfusion injury and its contribution to ischemic cardiac cell death can no longer be ignored. Patients presenting with an acute ST-segment elevation myocardial infarction will likely benefit from therapy aimed at the timely administration of drugs, most likely *via* primary percutaneous coronary intervention, for the reduction/prevention of lethal reperfusion injury. This approach will ensure that patients maximally benefit from the myocardial salvage that results from these therapies.

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INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of mortality and morbidity worldwide. Each year, an estimated 785000 persons will have a new AMI in the United States alone and approximately every minute an American will succumb to one^[1]. In addition, AMI has major psychological and legal implications for patients and society and is an important outcome measure in research studies. The prevalence of AMI provides useful data regarding the burden of coronary artery disease and offers insight into health care planning, policy and resource allocation^[1].

The rapid time course of AMI and the temporal limitation on the maximal effectiveness of reperfusion constitute the pathobiological basis for the contemporary clinical strategies that emphasize early intervention within 1-2 h after the onset of symptoms^[2]. Currently, timely myocardial reperfusion using either thrombolytic therapy or primary percutaneous coronary intervention forms the cornerstone of treatment for acute ST-segment elevation myocardial infarction (STEMI) patients^[3]. However, mortality remains substantial in these patients, with in-hospital mortality ranging between 6% and 14%^[4].

Reperfusion profoundly alters the outcome of an evolving AMI. If instituted in a timely manner, a potential transmural AMI can be prevented and the extent of necrosis greatly reduced and limited to the subendocardium. However, some injured cardiomyocytes at the edge of the wavefront become irreversibly injured during the reperfusion phenomenon, producing a component of lethal reperfusion injury^[5]. After reperfusion, the salvaged myocardium exhibits impaired contractile function, a form of nonlethal reperfusion injury referred to as myocardial stunning. The earlier the reperfusion, the less total necrosis that occurs (including both the ischemia-induced and reperfusion-induced component), as well as the earlier the recovery of contractile function from the transient stunning. Conversely, reperfusion can be rendered less effective by the microvascular damage and obstruction that develop during the ischemic phase; this is known as the no-reflow phenomenon^[6,7].

In this minireview, we provide an overview of myocardial reperfusion injury and highlight potential pharmacological interventions for preventing it in reperfused-STEMI patients.

PATHOPHYSIOLOGICAL MECHANISMS OF MYOCARDIAL REPERFUSION INJURY

There are various pathophysiological mechanisms involved in myocardial injury reperfusion. It has been suggested that mitochondrial permeability transition pore opening, overproduction of oxygen-derived free radicals and intracellular calcium overload might be candidates responsible for reperfusion injury. However, other factors of importance in the pathogenesis of reperfusion injury must be included, such as platelet and neutrophil-mediated injury, the renin-angiotensin system and the

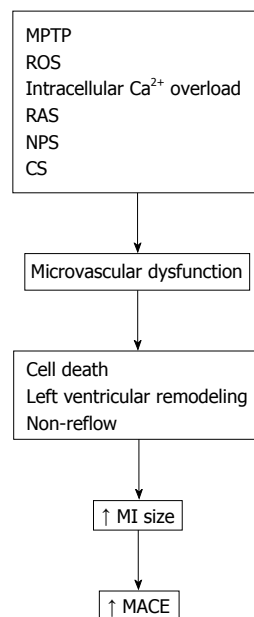


Figure 1 Scheme of mechanism of myocardial injury by a reperfusion process. MPTP: Mitochondrial permeability transition pore; ROS: Reactive oxygen species; RAS: Renin-Angiotensin system; NPS: Neutrophil-Platelet system; CS: Complement system; MI: Myocardial infarction; MACE: Major adverse cardiac events.

complement activation^[8,9] (Figure 1).

Mitochondrial permeability transition pore opening

Multiple lines of evidence have converged to show that the mitochondria have a central role in the pathogenesis of cell injury^[10,11]. In stressed cells, deleterious and salutary effects acting on mitochondria are mediated by death channels and salvage pathways, respectively^[12]. The mitochondrial death channels include the mitochondrial permeability transition pore and the mitochondrial apoptosis channel.

The mitochondrial permeability transition pore is a voltage-dependent channel that is regulated by calcium and oxidative stress^[13]. The opening in the first few minutes of reperfusion of the mitochondrial permeability transition pore, a non-selective channel of the inner mitochondrial membrane, in response to mitochondrial Ca^{2+} overload, oxidative stress, restoration of a physiological pH and ATP depletion, induces the cardiomyocyte death by uncoupling the biochemistry route of oxidative phosphorylation^[14], which leads to a reduction in ATP production.

Overproduction of oxygen-derived free radicals

Cell membranes are composed mostly of phospholipids and proteins. Alterations in membrane proteins by free radicals are among the important factors in the evolution of myocardial ischemia reperfusion damage. Large quantities of oxygen-derived free radicals lead to overwhelming of the cellular endogenous antioxidant defences. This causes, among other effects, the peroxidation of lipid membranes and loss of membrane integrity which results in necrosis and cell death^[15].

Re-introduction of abundant oxygen at the onset of reperfusion evokes a burst of additional toxic oxygen derivatives, including superoxide anion, hydroxyl radical and peroxynitrite, within the first few minutes of reflow. More-

Table 1 Pharmacological cardioprotective strategies for preventing myocardial injury in reperfused-ST-segment elevation myocardial infarction patients

Mitochondrial permeability transition pore opening	Overproduction of oxygen-derived free radicals	Intracellular calcium overload	Neutrophil-mediated injury	Platelet-mediated injury
Cyclosporin A	Adenosine	Glucose-insulin-potassium	Adenosine	Abciximab
Melatonin	Metoprolol	Atrial natriuretic peptide	Abciximab	Melatonin
	Erythropoietin Glucose-insulin-potassium Exenatide Melatonin		Erythropoietin Melatonin	

over, oxidative stress also reduces the bioavailability of nitric oxide (vasodilator compound) during reperfusion^[16].

Intracellular calcium overload

Changes in intracellular calcium homeostasis play an important role in the development of reperfusion injury. Intracellular calcium release at the time of myocardial reperfusion is mediated by damage to the sarcolemmal membrane and oxidative stress-induced dysfunction of the sarcoplasmic reticulum. These changes result in cardiomyocyte hypercontracture, mitochondrial calcium overload and the opening of the mitochondrial permeability transition pore^[17].

Complement system

The complement system is activated during reperfusion injury. This contributes to the formation of the anaphylatoxins C3a, C4a and C5a, as well as the terminal complement complex, the membrane attack complex, which is deposited in cell membranes. The complement factors induce direct cell injury by increasing cell permeability and release of histamine and platelet activating factor. In addition, complement factors, especially C5a, are potent stimulators of neutrophil adherence and superoxide production^[8].

Platelet and neutrophil-mediated injury

Neutrophils are important for the development of reperfusion injury by releasing oxygen free radicals, proteases and pro-inflammatory mediators that further amplify the infiltration of neutrophils into the jeopardized myocardium^[18]. Additionally, the hemorrhagic properties of neutrophils contribute to leukocyte entrapment in the capillaries, leading to microvascular plugging^[19].

Local platelet aggregation and deposition and also microembolization are partially responsible for reperfusion injury, especially in relation to microvascular dysfunction. Reperfusion injury induces platelet activation and this exacerbates the damage to the myocardium. Platelet products may exacerbate microcirculatory spasm, leading to further microvascular congestion, thrombosis and

sluggish coronary flow^[8,20].

Renin-angiotensin system-mediated reperfusion injury

The key product of the renin-angiotensin system, angiotensin II, increases intracellular calcium levels of cardiomyocytes and smooth muscle cells, leading to positive inotropism, impairment of diastolic function and coronary vasoconstriction. At pathophysiological levels, angiotensin II is cardiotoxic and induces myocyte necrosis^[8,21].

POTENTIAL PHARMACOLOGICAL THERAPIES FOR PREVENTING MYOCARDIAL REPERFUSION INJURY

Progress in understanding the basic pathobiology of ischemic heart disease has led to many years of research aimed at developing pharmacological approaches for limiting myocardial ischemic damage. Although myocardial ischemia-reperfusion injury is clearly mediated by several elements (Figure 1), agents aimed against these components of ischemic injury have not been consistently effective in different clinical trials^[2,22]. A number of reasons for the situation have been brought to light^[2,7,23,24].

A number of pharmacological interventions have been tried in the clinical setting to prevent myocardial reperfusion injury in reperfused-STEMI patients, although the results have been largely disappointing. Moreover, several pharmacological agents for preventing myocardial reperfusion injury in reperfused-STEMI patients are currently being tested in proof-of-principal clinical studies (Table 1)^[9,24].

Cyclosporin-A

Cyclosporine is known to inhibit the formation and opening of the mitochondrial permeability transition pore. In a proof-of-concept clinical trial involving 58 patients, cyclosporine administered as a 2.5 mg/kg intravenous bolus at the time of percutaneous coronary intervention was found to reduce the size of the myocardial infarct compared with placebo. Infarct size was reduced by 40%, as measured by creatine kinase release. Evaluation by magnetic resonance imaging also showed less myocardial damage^[25,26]. The ongoing CIRCUS study (NCT01502774) is investigating whether this therapeutic approach can reduce patient death, hospitalization for heart failure and a 15% increase in left ventricular end-diastolic volume.

Exenatide

Exenatide a new antidiabetic drug, has been shown to reduce myocardial infarct size by 23% of area at risk at 90 d, as assessed by magnetic resonance imaging, when given as an intravenous infusion started 15 min prior to primary percutaneous coronary intervention and continued for 6 h^[27,28].

Glucose-insulin-potassium

Of all the agents that have been tested reduce myocardial

infarct size or improve acute clinical outcome of STEMI, perhaps none is more controversial than glucose-insulin-potassium regimen. In the CREATE-ECLA trial, intravenous glucose-insulin-potassium infusion for 24 h was initiated after reperfusion of AMI. This trial had a negative outcome since it showed a difference in mortality at 30 d^[29]. The IMMEDIATE trial has been recently published. In this trial, the intravenous glucose-insulin-potassium infusion for 12 h was started by paramedics in the ambulance prior to reperfusion. The composite of cardiac arrest or in-hospital mortality was lower in 4.4% of glucose-insulin-potassium patients compared to 8.7% in the placebo patients ($P = 0.01$)^[30]. Thus, the use of glucose-insulin-potassium for AMI remains controversial and requires further studies.

Atrial natriuretic peptide

Kitakaze *et al.*^[31] demonstrated that an infusion of carperitide (an atrial natriuretic peptide analogue) during 72 h after reperfusion reduced myocardial infarct size and preserved left ventricular ejection fraction in reperfused-STEMI patients.

Adenosine

Two large multicenter studies, AMI Study of Adenosine (AMISTAD) 1 and AMISTAD 2, showed that a high-dose 3-h intravenous infusion of adenosine started near the time of reperfusion significantly reduced anterior wall myocardial infarct size, as determined by nuclear imaging^[32,33]. Other studies, however, were negative. A total of 112 patients with STEMI were randomized to 4 mg intracoronary adenosine or placebo. There was no benefit of adenosine on myocardial infarct size assessed by magnetic resonance imaging at 4 mo^[34]. Fokkema *et al.*^[35] also studied the effect of high-dose intracoronary adenosine boluses on myocardial infarct size and parameters of myocardial reperfusion. Four hundred and forty-eight patients with acute STEMI were randomized to placebo or 2 bolus injections of intracoronary adenosine. Adenosine did not improve the myocardial infarct size. Thus, the efficacy of the use of adenosine for AMI remains unproven and requires further studies.

Abciximab

In a recent study by Stone *et al.*^[36], 452 patients presenting within 4 h of STEMI with proximal or mid-left anterior descending coronary artery occlusion and undergoing percutaneous coronary intervention plus bivalirudin as an anticoagulant were randomized to bolus intracoronary abciximab, no abciximab, and to manual aspiration thrombectomy versus no thrombectomy in a 2 × 2 factorial design. The authors concluded that in patients with large STEMI undergoing percutaneous coronary intervention with bivalirudin, the addition of intracoronary abciximab bolus significantly reduced myocardial infarct size. Not all recent clinical trials with abciximab have been positive.

Thiele *et al.*^[37] compared intracoronary abciximab bo-

lus during primary percutaneous coronary intervention with an intravenous bolus in patients with STEMI. This large open-label, multicenter trial randomized > 2000 patients to intracoronary *vs* intravenous bolus abciximab followed by a 12 h intravenous infusion. The primary composite end point at 90 d (all-cause mortality, recurrent myocardial infarction or new congestive heart failure) was similar in the intracoronary group versus the intravenous group. Whereas the incidence of death and reinfarction did not differ between groups, fewer patients in the intracoronary group developed new congestive heart failure. The authors concluded that intracoronary abciximab bolus is safe and might be considered to reduce the rates of congestive heart failure. However, other secondary end points in this study, including enzymatic myocardial infarct size, were negative.

Erythropoietin

The large REVEAL study showed no reduction of infarct size^[38] and several other recent trials were negative for infarct size reduction^[39,40].

Metoprolol

The capacity of β -blockers to reduce infarct size was evaluated extensively in the pre-reperfusion era, with inconsistent results^[41]. In the context of reperfusion as the treatment of choice for STEMI, this has been poorly investigated. Experimental data suggest that the β -blocker metoprolol may reduce infarct size only when administered intravenously before reperfusion^[42,43].

Recently, the results have been demonstrated of the Effect of Metoprolol in Cardioprotection During an AMI trial, the first randomized, clinical trial prospectively evaluating the effect of early intravenous β -blockade on infarct size in conjunction with primary angioplasty. A total of 270 patients with anterior STEMI (Killip class II or less) revascularized within 6 h after symptom onset were randomized to receive intravenous metoprolol or not before reperfusion. All patients received oral metoprolol according to clinical guidelines (first dose, 12-24 h after infarction). Infarct size, evaluated by magnetic resonance imaging and creatine kinase release, was significantly reduced in the intravenous metoprolol group with no excess side effects. The left ventricular ejection fraction was higher in the intravenous metoprolol group^[44].

Melatonin

Melatonin, a circadian endocrine product of the pineal gland, is formed and released predominantly during night time. Melatonin has a diverse functional repertoire with actions in essentially all organs, including the heart and other portions of the cardiovascular system^[45-47]. Melatonin reduces the pathophysiological mechanisms that are involved in these benefits, in part due to the detoxification myocardial reperfusion injury, with respect to radical oxygen species and radical of oxygen and nitrogen-based reactants melatonin and its metabolites^[48,49]. Moreover, melatonin has indirect beneficial effects by increasing the

activity of principal antioxidant enzymes^[50]. Recent data also suggest that the mechanism of protection of melatonin appears to involve, at least in part, the inhibition of mitochondrial permeability transition pore opening *via* prevention of cardiolipin peroxidation^[51]. The lack of these cardioprotective effects due to insufficient high endogenous melatonin levels might be associated with several cardiovascular pathologies, including ischemic heart disease^[47,50,52].

Several studies show that humans with cardiovascular disease have noticeably lower circulating melatonin levels than age-matched subjects without significant cardiovascular deterioration^[53]. Recent investigations in patients with STEMI undergoing primary percutaneous coronary intervention confirmed a relationship between melatonin concentrations and ischemia-modified albumin, a biomarker of myocardial ischemia. These data suggest that melatonin can act as a potent antioxidant agent, reducing myocardial damage induced by ischemia/reperfusion^[54].

Because of the available scientific evidence, our group carried out a phase II clinical trial (ClinicalTrials.gov no. NCT00640094) using melatonin. We attempted to document whether intravenous and intracoronary melatonin administration reduces infarct size in STEMI patients treated by primary percutaneous coronary intervention by performing a multicenter, randomized, controlled clinical trial^[55]. The importance of these studies is emphasized by the fact that melatonin is quickly distributed throughout the organism when exogenously administered (oral, intravenous or subcutaneous). It crosses all morphophysiological barriers and enters cardiac cells with ease. The highest intracellular concentrations of melatonin are found at a mitochondrial level^[56]. This is especially important as the mitochondria is a major site of free radical generation and oxidative stress^[57].

Unless the findings in animal investigations are totally misleading, it is expected that melatonin will have similar protective effects benefitting the human heart. Melatonin is easily synthesized in a pharmacologically pure form and is inexpensive. Because of its marked versatility in protecting against oxidative stress and reducing inflammation in patients with myocardial ischemia, melatonin may have significant potential to improve public health.

CONCLUSION

A major determinant of post-infarction mortality and morbidity is the extent of myocardial necrosis after STEMI; therefore, strategies to limit infarct size are important. Several pharmacological interventions have been proposed as potential cardioprotective therapies but their use in clinical practice has been limited.

The list of cardioprotective agents that can be used as adjuvant therapy during to reperfusion is promising. Large multicenter clinical trials with enough statistical power will be necessary to establish the reported beneficial effects and to answer the question of whether they can improve clinical outcomes. To prevent translational

failure, particular attention must be paid to proper selection of patients (who will benefit the most), application (relevant concentration in the early phase of reperfusion) and hard end points.

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Shellfish allergy and relation to iodinated contrast media: United Kingdom survey

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Abstract

AIM: To assess current practice of United Kingdom cardiologists with respect to patients with reported shellfish/iodine allergy, and in particular the use of iodinated contrast for elective coronary angiography. Moreover we have reviewed the current evidence-base and guidelines available in this area.

METHODS: A questionnaire survey was sent to 500 senior United Kingdom cardiologists (almost 50% cardiologists registered with British Cardiovascular Society) using email and first 100 responses used to analyze practise. We involved cardiologists performing coronary angiograms routinely both at secondary and tertiary centres. Three specific questions relating to allergy were asked: (1) History of shellfish/iodine allergy in pre-angiography assessment; (2) Treatments offered

for shellfish/iodine allergy individuals; and (3) Any specific treatment protocol for shellfish/iodine allergy cases. We aimed to establish routine practice in United Kingdom for patients undergoing elective coronary angiography. We also performed comprehensive PubMed search for the available evidence of relationship between shellfish/iodine allergy and contrast media.

RESULTS: A total of 100 responses were received, representing 20% of all United Kingdom cardiologists. Ninety-three replies were received from consultant cardiologists, 4 from non-consultant grades and 3 from cardiology specialist nurses. Amongst the respondents, 66% routinely asked about a previous history of shellfish/iodine allergy. Fifty-six percent would pre-treat these patients with steroids and anti-histamines. The other 44% do nothing, or do nonspecific testing based on their personal experience as following: (1) Skin test with 1 mL of subcutaneous contrast before intravenous contrast; (2) Test dose 2 mL contrast before coronary injection; (3) Close observation for shellfish allergy patients; and (4) Minimal evidence that the steroid and anti-histamine regime is effective but it makes us feel better.

CONCLUSION: There is no evidence that allergy to shellfish alters the risk of reaction to intravenous contrast more than any other allergy and asking about such allergies in pre-angiogram assessment will not provide any additional information except propagating the myth.

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Key words: Shellfish allergy; Contrast allergy; Iodinated contrast allergy; Low osmolarity contrast media; High osmolarity contrast media; Pre-angiography assessment

Core tip: This short survey explains how easily evidence base is missed out from real life practice. There has

never been any evidence to relate shellfish/iodine to contrast media, yet the myth been propagated for decades. Our survey gives a reminder and eye opener to change the practice to evidence base and thus helps in the patient care avoiding unnecessary medications.

Baig M, Farag A, Sajid J, Potluri R, Irwin RB, Khalid HMI. Shellfish allergy and relation to iodinated contrast media: United Kingdom survey. *World J Cardiol* 2014; 6(3): 107-111 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i3/107.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i3.107>

INTRODUCTION

There is a widely held view that a link exists between patient-reported shellfish allergy and increased risk of allergic reaction to iodinated contrast agents. Such agents are widely employed across many medical disciplines, including cardiology. Both invasive and non-invasive (in the case of computed tomography coronary angiography) diagnostic investigations require the use of such agents. Currently, guidance of percutaneous coronary angiography and many structural cardiac interventions mandates the use of iodinated contrast.

Historically the link between shellfish allergy and radio-contrast dates back to the early 1970s. Papers by Witten *et al*^[1] and Shehadi^[2] reported adverse reaction to radio-contrast in patients with history of seafood allergy. It is commonly believed that the individual with reported shellfish allergy is at higher risk of iodinated contrast allergy. It is often further assumed that this is due to the presence of iodine in both situations. Despite little evidence to support this relationship, many physicians still believe that shellfish/iodine allergy increases risk, and this may alter how such patients are treated. Various different methods of managing this perceived increased risk are currently employed, including prophylactic administration of corticosteroids or antihistamine preparations, and even avoidance of iodinated contrast altogether.

Our aims were to assess the current practice of United Kingdom cardiologists with respect to patients with reported shellfish/iodine allergy, and in particular the use of iodinated contrast for elective coronary angiography. Moreover we have reviewed the current evidence-base and guidelines available in this area.

MATERIALS AND METHODS

A questionnaire survey was sent by email to United Kingdom cardiologists. Both secondary and tertiary centres were targeted, as were multiple cardiologists within individual trusts. The aim was to establish routine practice amongst the surveyed cardiologists or specialist nurses for patients undergoing elective invasive coronary angiography. With this in mind, the three main questions posed were: (1) Do you ask about shellfish/iodine allergy history during pre-angiography assessment? (2) If patients

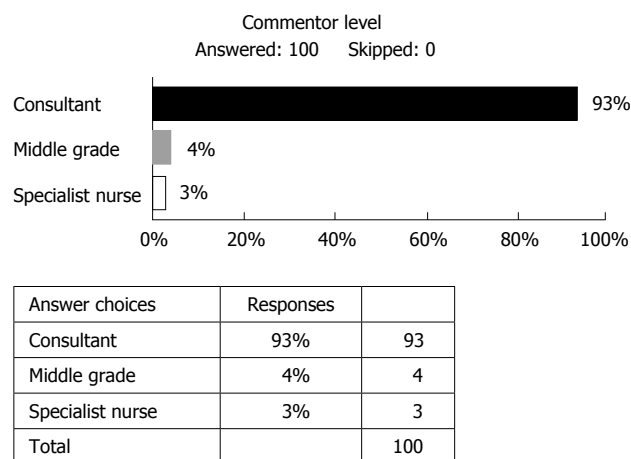


Figure 1 Level of commentor.

have history of shellfish/iodine allergy would you give pre-treatment? and (3) If pre-treatment is offered what is the protocol?

The physicians or specialist nurses completing the questionnaire were encouraged to elaborate and provide additional comments, as they felt necessary.

A comprehensive literature search was performed using PubMed. The following terms were used Shellfish Allergy, Iodinated contrast, and contrast allergy.

RESULTS

The questionnaire was sent to 500 cardiologists across the United Kingdom. A total of 100 responses were received, representing 20% of all United Kingdom cardiologists. Ninety-three replies (Figure 1) were received from consultant cardiologists, 4 from non-consultant grades and 3 from cardiology specialist nurses.

Amongst the respondents, 66% (Figure 2) routinely ask about a previous history of shellfish/iodine allergy while 56% would pre-treat these patients with steroids and anti-histamines (Figure 3). The other 44% do nothing, or do nonspecific testing based on their personal experience.

We found great deal of variation in practice with the following protocols followed: (1) Skin test with 1 ml of subcutaneous contrast before intravenous contrast; (2) Test dose 2 mL contrast before coronary injection; (3) Close observation for shellfish allergy patients; and (4) Minimal evidence that the steroid and anti-histamine regime is effective but it makes us feel better.

DISCUSSION

Shellfish allergy is one of the commonest food allergies in adults, and is a common cause of food-induced anaphylaxis^[3]. Seafood consumption has increased in popularity and frequency worldwide so as the adverse reactions^[3].

Shellfish can be classified into molluscs and arthropoda (crustaceans). Arthropods include crab, crayfish,

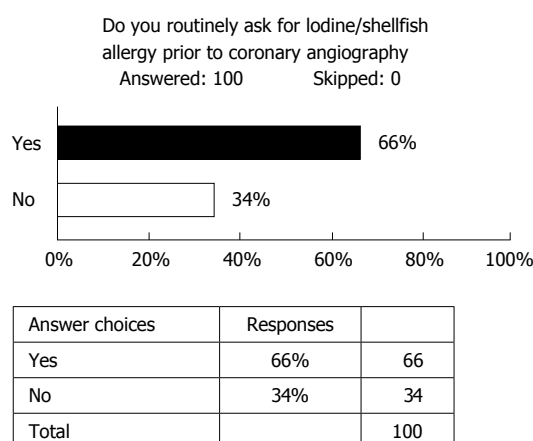


Figure 2 Number/percentage asking question about shellfish/iodine allergy prior to coronary angiography.

lobster, prawn and shrimp. Molluscs is subclassified into gastropod (abalone, conch, limpet, snail and whelk), bivalves (clam, cockle, mussel, oyster and scallop) and cephalopods (cuttlefish, octopus and squid). Four groups of allergens have been identified in shellfish: Tropomyosin, arginine kinase, myosin light chain and sarcoplasmic calcium-binding protein. Among the allergens identified, tropomyosin, a contractile protein, is considered a major allergen for prawn, and other crustaceans, such as shrimp, crayfish, lobster, crab and barnacles^[4].

The overall prevalence of shellfish allergy in the western world (United States, Canada and Europe) is approximately 0.6%, ranging between 0% to 10%^[5]. Of the shellfish, prawns are most frequently implicated (62% of shellfish allergy), followed by crab, lobster and then the molluscan species^[6]. Symptoms of shellfish allergy can range from mild urticaria to life threatening anaphylaxis. Most reactions are Immunoglobulin E (IgE)-mediated with rapid onset and may be gastrointestinal, cutaneous, or respiratory. Symptoms may be limited to transient oral itching or burning sensation within minutes of eating shellfish. Management of allergy is the same as for any other allergies *i.e.*, antihistamines, corticosteroids and adrenaline in severe or life-threatening reactions.

Shellfish allergy is mainly due to tropomyosins and iodine has in fact no role to play in allergic reactions. Moreover, iodine is an integral part of human body and essential for survival, therefore iodine itself cannot be considered an allergen. Radio-contrast media is composed of anions (iodide) and cations (sodium or meglumine). Iodine molecule is an effective X-ray absorber in the energy range therefore iodinated contrast media allow enhanced visibility of vascular structures and organs during radiographic procedures. There are two basic types of contrast media: ionic high osmolality contrast media (HOCM) and non-ionic low osmolality contrast media (LOCM), and both contains iodine molecule. HOCM (ionic) creates more charged particles and have more osmolality whereas LOCM (non-ionic) generates less dissociation and therefore have low osmolality. Examples of currently used ionic and non-ionic contrast media

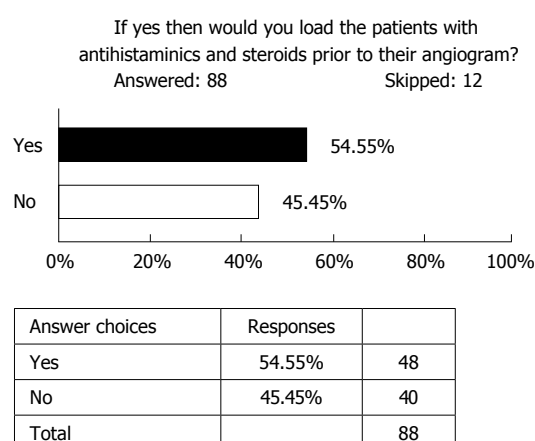


Figure 3 Patients treated with steroids and anti-histamines before coronary angiogram.

are: Perflutren-protein type-A microspheres injection (optison), iohexol injection (omnipaque), and non-ionic iodixanol injection (Visipaque).

Reactions to intravenous contrast are not truly allergic^[7] and not mediated *via* IgE. Instead there is direct stimulation of mast cells and basophils to release mediators leading to “anaphylactoid” reactions (pseudo-allergy). This may lead to urticaria, bronchospasm, hypotension, and even cardiac arrest. Previous allergic reactions to shellfish would create IgE sensitized to those allergens, but this sensitized IgE would play no role in allergic reactions to contrast media as they are not IgE mediated. Moreover, the cause of “anaphylactoid” reactions to contrast media is not the iodine in the contrast but is thought to be its hyper-osmolality compared to blood^[8].

Hyperosmolar contrast regardless of its composition is an irritant and will cause vasodilatation, increased vascular permeability, and direct cardiotoxicity and nephrotoxicity. Non-ionic contrast (LOCM) still uses iodine as a radiopacification agent, but fewer iodinated molecules are created with different side chains that reduce dissociation in solution. Fewer molecules in solution decrease the osmolality and therefore cause fewer side effects and reactions. These compounds are usually about one-half to one-third as osmotically active as the ionic forms^[9] and associated with fourfold or greater reduction in all adverse reaction and fivefold decrease in severe adverse reactions^[9]. The risk of reactions to intravenous contrast media ranges from 0.2%-17%, depending on the type of contrast used, the severity of reaction considered, and the prior history of any allergy^[9].

High risk patients include patients with previous intravenous contrast reactions, asthma, multiple true allergies, those taking beta-blockers or metformin, females, elderly and diseases that increase the risk of adverse reactions *e.g.*, pheochromocytoma, hyperthyroidism, thyroid cancer, renal failure^[10,11]. Atopy, in general, confers an increased risk of reaction to contrast administration, but the risk of contrast reaction is low, even in patients with a history of “iodine allergy”, seafood allergy, or prior contrast reaction. Allergies to shellfish, in particular, do not increase

the risk of reaction to intravenous contrast any more than of other allergies. A history of prior reaction to contrast increases the risk of mild reactions to as high as 7%-17%, but has not been shown to increase the rate of severe reactions^[9].

Mild reactions including warmth, nausea and vomiting occur only for short duration and do not require any treatment. Moderate reactions (*e.g.*, vomiting, sweating and swellings) occur in 1% of patients and frequently require treatment. Severe reactions occur in 0.02%-0.5% and deaths in 0.0006%-0.006%; neither has been related to "iodine allergy", seafood allergy, or prior contrast reaction^[9]. The most severe reactions, including death, have been reported to occur at similar rates with both types of contrast Media^[12].

Pre testing for contrast allergy is challenging and has been proposed in patients with a history of an anaphylactic reactions^[13]. Skin testing and Radioallergosorbent test have not been helpful in the diagnosis of contrast allergy as only a fraction of patients with severe reactions have a positive skin test^[14]. Small test doses are also not useful not only because severe reactions can occur even with small doses but also because of severe reactions to large doses of contrast media observed in patients who have tolerated small doses well. Therefore, no valid single test available to diagnose contrast allergy except only when symptoms occur after the contrast injection. However one can identify patients who are at high risk of contrast allergy^[15] and be prepared for adverse reactions.

Despite the increased use of non-ionic LOCM, and a decrease in the incidence of mild to moderate, and possibly severe reactions, pre-medications are still widely used in clinical practice. On the basis of observational data, Greenberger *et al*^[16] concluded in 1991 that patients with a previous reaction to high osmolality iodinated contrast media should receive oral prednisone and diphenhydramine with or without adrenaline. Since then, professional organisations have recommended a variety of regimens and combinations of methyl-prednisolone with or without an antihistamine^[17], oral prednisolone or methyl-prednisolone^[18], or intravenous hydrocortisone and intramuscular diphenhydramine^[19].

Steroid pre-medications reduce the incidence of respiratory symptoms due to contrast media from 1.4% to 0.4%, and the incidence of combined respiratory and hemodynamic symptoms from 0.9% to 0.2%^[20]. Thus, to prevent one episode of a potentially life threatening, iodinated contrast medium related reaction, about 100 to 150 patients need to receive steroids prophylactically^[20]. Disastrous anaphylactic complications after administration of iodinated contrast media seem to be rare. In the analysed trials, more than 10000 patients received an iodinated contrast medium but no reports of death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stay was reported^[20].

Although it has been noted that steroid pre-medication decreases the total number of adverse events, it does not reduce the number of severe events. No significant effect is seen when steroids are given within 3 h before

administration of intravenous contrast media^[17]. Even with longer protocols, steroid premedication has not shown a statistically significant improvement in severe adverse reaction rates^[9].

For antihistamines, limited evidence shows that they may prevent some reactions. One may conclude that valid data supporting the efficacy of drug combinations or the use of premedication in patients with a history of allergic reactions are completely lacking^[20]. Severe allergic reactions due to contrast media seem to be rare; this may explain why no reports of disastrous reactions exist.

The treatment of an acute reaction to contrast media is no different from any other anaphylactic reaction. Treatment may include injectable epinephrine and antihistamines, as well as the use of intravenous fluids for low blood pressure and shock^[20].

In a conclusions, There is widespread variation in the management of patients who report previous shellfish allergy by United Kingdom cardiologists.

There is no evidence that allergy to shellfish alters the risk of reaction to intravenous contrast more than any other allergy, and this is due to: (1) Shellfish allergy is not related to iodine; instead the vast majority are due to tropomyosin; (2) Shellfish allergy is IgE mediated, whilst intravenous contrast allergy is due to direct stimulation of mast cells and basophils. Hence previous exposure to shellfish allergens and subsequently sensitized IgE, would play no role; and (3) Contrast pseudo allergic reactions are due to hyper-osmolality of contrast (free iodine molecule) rather than the bound iodine molecule.

It may be concluded therefore that there is no additional information gained by inquiring about previous shellfish/iodine allergy during pre-angiogram assessment. There is no specific relevance to this particular allergy, and such questioning potentially propagates the myth. If patients ask question about shellfish/iodine allergy they should be reassured and explained that there is no relation to contrast allergy.

There is no compelling evidence that anti-histamines have a role in prevention of allergic events, although corticosteroid pre-medication has shown benefit in reducing minor reactions, but no significant benefit in decreasing severe and fatal reactions.

It would be appropriate to use low osmolality, non-ionic contrast for patients with atopy, patients with previous reaction to intravenous contrast, and patients with systemic disease that increase their risk for contrast reaction. Almost all the life threatening reactions to intravenous contrast occur immediately or within 20 min of contrast injection so all patients with previous allergic reactions should be monitored and treat severe reactions the same way you would treat any severe anaphylactic reaction.

COMMENTS

Background

Radio-contrast is commonly used in both invasive and non-invasive diagnostic investigations but relation of the contrast media to shellfish and iodine allergy

is poorly understood.

Research frontiers

The authors conducted a questionnaire-based survey in United Kingdom to find out practice in relation to Shellfish/iodine allergy. They also looked at the current literature available and evidence base to establish the relationship between contrast media and shellfish/iodine allergy, if there was any.

Innovations and breakthroughs

The authors' survey found the more than 50% of the Cardiologists ask about shellfish/iodine allergy and pre-treat patients undergoing coronary angiography assuming that there exists a relation between the two. Looking at the evidence there is no such relation and by asking such questions in pre-angiography sessions they are propagating the myth.

Applications

The authors' research suggests no pre-treatment required for patient with history of shellfish/iodine allergy undergoing coronary angiography. This also prevents un-necessary medication use and stay in the hospital.

Terminology

LOCM: Low osmolality contrast media, HOCM: High osmolality contrast media, IgE: Immunoglobulin E.

Peer review

The present study showed at first the current practice of United Kingdom cardiologists with respect to patients with reported shellfish/iodine allergy, and in the use of contrast agent for elective coronary angiography. Second, the differences between shellfish and contrast allergy were explained in details including those mechanisms. Finally, the author stated the meaning of the pre-medication using antihistamines and/or steroids for the prevention of the contrast induced allergy. The suggestions in this manuscript seems to be very interesting, instructive and valuable, and the information in which may be of great use for many physicians in the real clinical setting.

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Steal syndrome secondary to coronary artery fistulae associated with giant aneurysm

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Abstract

Giant coronary artery aneurysms and coronary artery fistulae are uncommon pathologies. We present the case of an elderly woman who was referred to cardiology for investigation of possible ischaemic heart disease prior to orthopaedic surgery. The patient had developed chest pain in the setting of a septic total knee replacement associated with changes on electrocardiography. Coronary angiography revealed multiple coronary arteriovenous fistulae associated with giant coronary artery aneurysm causing steal syndrome in the setting of haemodynamic stress.

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Key words: Coronary angiography; Coronary disease; Myocardial ischaemia; Coronary aneurysm; Vascular fistula; Chest pain

Core tip: This case report presents the angiographic findings of a rare occurrence of multiple coronary arteriovenous fistulae associated with giant coronary artery aneurysm and steal syndrome in the setting of haemodynamic stress.

INTRODUCTION

This case report presents the angiographic findings of a rare occurrence of multiple coronary arteriovenous (AV) fistulae associated with giant coronary artery aneurysms and steal syndrome in the settings of haemodynamic stress.

CASE REPORT

A 76-year-old lady was referred to cardiology for investigation of ischaemic heart disease (IHD) prior to orthopaedic surgery.

The patient was undergoing staged revision of a septic total knee replacement. After the first revision surgery, she experienced ischaemic chest pain. She had a history of chronic rate-controlled atrial fibrillation but no history of IHD. Her cardiovascular risk factors include hypertension, type 2 diabetes mellitus, age and post-menopausal status. There was no associated troponin rise however the electrocardiography revealed anterior T-wave inversion (Figure 1). Transthoracic echocardiography demonstrated mild tricuspid regurgitation, mild pulmonary hypertension, normal left ventricular function, and mild to moderately dilated right ventricle.

A coronary angiogram was performed *via* transradial approach. The study revealed two fistulae arising from distal left main coronary artery and proximal left anterior descending artery supplying a large aneurysm (Figure 2). The aneurysm, measuring 2.4 cm × 1.6 cm, drained into the pulmonary artery (PA) through multiple AV fistulae. The remainder of the coronary vasculature did not reveal any significant pathology.

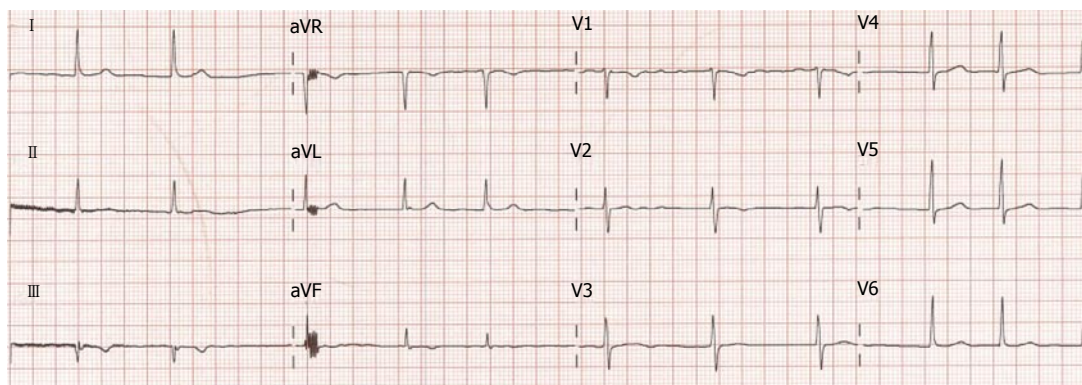


Figure 1 The patient's electrocardiography, demonstrating new anterior T wave inversion.

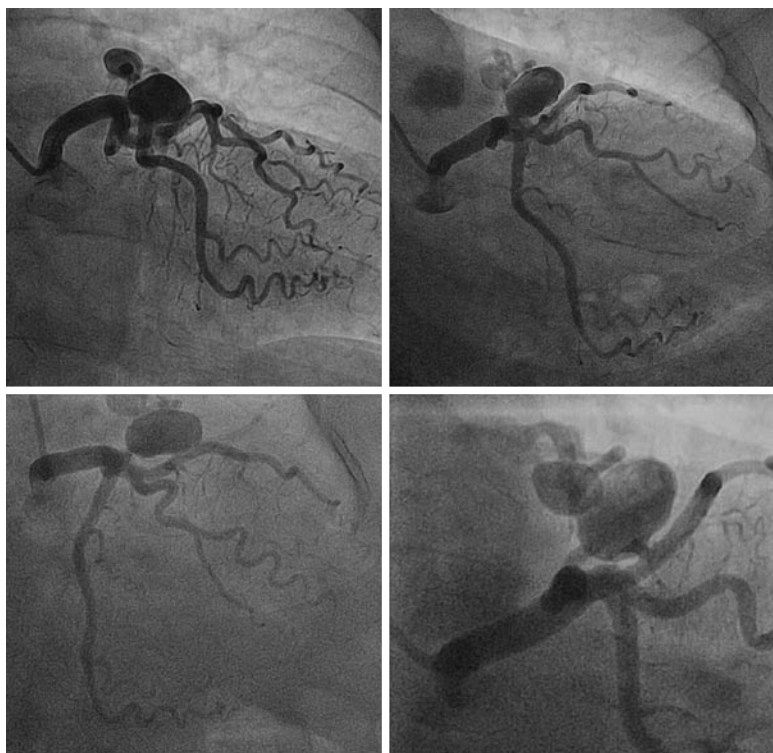


Figure 2 Coronary angiogram images demonstrating two fistulae arising from distal left main coronary artery and proximal left anterior descending artery supplying a large aneurysm. The aneurysm drains into the pulmonary artery through the arteriovenous fistulae.

In this case, the coronary artery aneurysm with associated fistulae was not deemed amenable to transcatheter closure/coiling given the size and multiple openings. Surgical repair was considered appropriate because of the risks of aneurysm rupture, endocarditis, thrombosis/embolism or heart failure^[1,2]. However the risk of significant periprocedural myocardial ischaemia secondary to upcoming orthopaedic procedure was small relative to the risk of undergoing cardiac surgery particularly in the context of underlying sepsis. The definitive management was therefore delayed until the patient's full recovery from sepsis and surgery.

DISCUSSION

Coronary artery aneurysms are fairly uncommon, being found in less than five percent of patients undergoing coronary angiography, most commonly in the right coro-

nary artery^[3,4]. Males are more commonly affected than females^[4]. The most common cause of coronary artery aneurysm in adults is atherosclerosis. As such, the same risk factors that predispose patients to atherosclerotic disease are also risk factors for coronary artery aneurysm formation^[3,4]. Other disease processes that damage the coronary arteries can also predispose to aneurysm formation; these include arteritis (infectious or inflammatory), syphilis, connective tissue diseases, Kawasaki's disease and metastatic malignancy. In addition, traumatic insult to the vessels, as in trauma, coronary angiography/intervention and aortic dissection, are implicated. Congenital malformations also increase the risk of developing coronary artery aneurysm^[3].

Coronary artery fistulae are rare, with an observed prevalence of less than one percent of patients on coronary angiography^[3-7]. Again, the right coronary artery is more commonly affected than the left coronary ves-

sels^[5,7]. The fistulae drain into the right cardiac chambers more commonly than the left, with the most common drainage sites being the right ventricle, right atrium or PA, and less frequently the coronary sinus, left atrium, left ventricle or superior vena cava^[5,7].

Coronary artery fistulae may be either congenital or acquired^[1,5-8]. Congenital fistulae may occur as an isolated anomaly or in conjunction with other congenital heart anomalies/malformations^[7]. Causes of acquired coronary fistulae include disease processes that damage the vessels, such as infection, inflammation and malignancy^[7,8]. In addition, trauma to the vessels, whether iatrogenic (as in cardiothoracic surgery and interventional procedures) or non-iatrogenic, may lead to fistula formation^[6-8].

Coronary artery aneurysm with associated fistula (CAAAF), being a combination of two uncommon pathologies, is extremely rare. As of 2005, only 50 cases had been reported^[1,4]. Little information is available about the aetiology of CAAAF but it has been observed that “most of the aneurysms were observed at the termination site of the fistulae”^[4].

Risks associated with CAAAF include aneurysm rupture, endocarditis, thrombosis/embolism, myocardial ischaemia and heart failure^[1,2]. Transcatheter, surgical or conservative management may be considered depending on the size, location and clinical context for the individual patient^[1,2].

COMMENTS

Case characteristics

An elderly lady with chest pain in the setting of sepsis.

Clinical diagnosis

Ischaemic heart disease was the most likely clinical diagnosis given the description of chest pain and the risk factor profile.

Differential diagnosis

Musculoskeletal or gastroesophageal reflux disease as exacerbation of chest pain with exertion could not be assessed given the patient's mobility was significantly limited by her orthopaedic condition.

Laboratory diagnosis

Serial troponin levels were negative.

Imaging diagnosis

Coronary angiography demonstrated multiple arteriovenous (AV) left main and left anterior descending coronary artery fistulae associated with giant aneurysm.

Treatment

The patient was medically managed for her hypertension, diabetes mellitus,

atrial fibrillation and ischaemic chest pain.

Related reports

Coronary angiogram images and electrocardiography are provided in the case report.

Term explanation

Coronary artery aneurysm refers to an abnormal dilatation of a coronary artery segment, relative to adjacent segments or other coronary arteries. Coronary artery (vascular) fistula refers to an abnormal connection between a coronary artery and another vessel or cardiac chamber.

Experiences and lessons

Coronary artery fistulae may only become symptomatic in the context of haemodynamic stress.

Peer review

The authors present a rare case report of multiple coronary AV fistulae with giant coronary artery aneurysms and steal syndrome. The manuscript is clearly written and well organized.

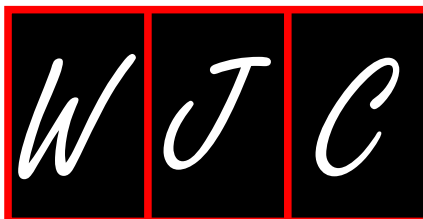
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Acknowledgments

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- 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

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- 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]

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

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

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- 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

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

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

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

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