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Scientific integrity: Any doubt about the data should be reported to the Editorial Office as soon as raised.
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Peak Atrial Longitudinal Strain (PALS): Better Call it Stretch?

Michael Y Henein$^{1,2}$, Matteo Cameli$^3$, Per Lindqvist$^4$, Urban Wiklund$^5$, Giulia E Mandoli$^3$, Sergio Mondillo$^3$

1. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
2. Molecular & Clinical Sciences Research Institute, St George University London, UK
3. Department of Cardiovascular Diseases, University of Siena, Siena, Italy
4. Department of Surgery and peri-operative sciences, Umeå University, Umeå, Sweden
5. Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden

Corresponding author:
Dr. Giulia Elena Mandoli
Ambassador for Italy of EACVI Heart Imagers of Tomorrow, European Society of Cardiology
Department of Cardiovascular Diseases, University of Siena
Siena, Italy
Email: giulia_elena@hotmail.it

Abstract

Left atrial (LA) strain is gaining more and more relevance in medical literature, with many applications in different clinical settings. The term "strain", meaning deformation, is applied to the contraction phase of the left ventricle (LV), due to its myocardial shortening along the longitudinal axis, to the LA relaxation phase, correlated to its distensibility and elastic compliance in receiving blood from the pulmonary veins, and even to LA contraction consequent to the electric activation of LA myocardium. This manuscript describes the main anatomical and physiological characteristic of the left atrium and discusses the use of the term strain from terminological and conceptual points of view.

Keywords: Left atrium; strain; stretch

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Introduction

The left atrium (LA) is an important cardiac chamber with a dual function, conduit and pump. The foundation of the LA function is its anatomical and myocardial fibre orientation.[1]

In essence, the myocardial fibre orientation almost mirrors the one of the left ventricle (LV). The pectinate fibres occupy the basal region of the LA, similar to the circumferential fibres at the base of the LV, control the modest systolic function of the basal region.[2] On the other hand, the predominant muscle layer is the longitudinal fibres which controls the longitudinal shortening of the cavity. These fibres originate at the back of the LA and insert around the circumference of the mitral annulus, thus pulling the base of the atrium towards its back during atrial systole, after the P wave, and as they relax they bring the annulus back to its resting position at end-diastole and the onset of the Q wave of the electrocardiogram (ECG). This phase is followed by LV systole during which its longitudinal subendocardial fibres contract to shorten the cavity along its long axis by pulling the mitral annulus, the site of their insertion, toward the LV apex.

During LV systole, the LA cavity is stretched longitudinally while its pressure drops and hence its filling from the pulmonary veins. For the LA, this phase is referred to as ‘reservoir’ at the end of which the intracavitary pressure increases and as it exceeds that of the LV the mitral valve opens and the onset of LV filling starts with fast acceleration. The deceleration of LV early diastolic filling is dictated by the diastolic pressure difference when LV pressure rises. LV diastasis follows early diastole before the start of atrial systole (Figure 1).

LA structure measurements in the form of longitudinal and transverse diameters, cavity area and volume are well established. LA function is historically assessed in the form of area change and volume fall during atrial systole, i.e, late diastole. Also, three-dimensional assessment of LA volume changes during different phases of the cardiac cycle have been recently invoked, with promising potential. While these measurements reflect overall LA cavity function, they do not assess intrinsic myocardial properties. Myocardial velocities have been used to overcome this limitation at different sites of basal LA segments,
lateral, septal, anterior and posterior. Those measurements have been found to reflect the old differentiated M-mode velocities.[3] While these velocities reflect the longitudinal LA segments, using the time of their peak played an important role in studying and assessing LA synchronicity.[4]

Recently, studying myocardial intrinsic function has become possible using speckle tracking 2D echocardiography technology, from which myocardial segmental and global strain can be evaluated.[5] Despite the technology was originally developed to assess LV deformation, it has been applied for studying LA deformation too with great success.[6] LA myocardial strain during atrial systole can now be accurately measured and is referred to as peak atrial contraction strain (PACS), with its respective strain rate. Changes happening in LA myocardium during LV systole have been referred to as peak longitudinal strain (PALS) (Figure 2).

In addition, LA myocardium with its elastic component acts as a hemodynamic mediator between LV and the pulmonary circulation. It has to ensure optimum filling of the LV while protecting the pulmonary capillary bed from possible pressure and volume overloads. In order to achieve that, particularly during its reservoir phase (assessed by PALS) three important factors contribute to LA function; its myocardial ultrastructure (ratio between elastic fibres and fibrous tissue), LV filling pressures and severity of volume overload. Thus, LA function reservoir function cannot be seen as purely passive as a consequence of mitral plane movement towards the apex. This is further evidenced by the strong relationship found between PALS and the invasively estimated LV filling pressures, over and above other standard echo parameters.[7] Likewise, LA compliance which negatively correlates with severity of mitral regurgitation.[8]

According to the principles of physics, the term ‘strain’ describes the deformation of the tissues based on the relative displacement of the speckles, as a result of a force applied to the tissue. However, the direction of the deformation must be specified. Applying the LA physiology described above shows that changes happening to LA myocardial fibres in two opposite directions, i.e. active shortening in late diastole and stretching during LV systole, can make it ambiguous for both to be synonymously called ‘strain’. Does LA ‘strain’ then reflect a deformation caused by external or internal forces? PACS involves electric activation of LA myocardium, development of action potential, and ionic movements in and out of the myocytes; none of these electric-chemical-mechanical interactions occur during PALS. Furthermore, elastic properties of the LA do not require electric activation but are able to store potential energy that is converted to kinetic energy successively used in the early filling phase, a component that is lost in the presence of LA fibrosis. Thus, the basis of LA deformation during the two phases of diastole are quite different.

In view of the above it seems clear that PALS can not reflect absolute LA myocardial active function, but is a reflection of complex atrio-ventricular interaction in early diastole. If the echocardiography community elect to continue using ‘Strain’ as a reflection of myocardial contraction, as in the case of left and right ventricles, the scientific accuracy would be improved by replacing PALS by ‘peak atrial longitudinal stretch’, similar to LV longitudinal stretch during atrial systole i.e. late diastole.

Declarations of Interest
The authors declare no conflict of interest

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The authors state that they abide by the authors’ responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal [9].

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9. Shewan LG, Coats AJS, Henein MY. Authors’ Responsibilities and Ethical Publishing. International Cardiovascular Forum Journal 2018;13:3-4, DOI: 10.17987/icfj.v13i0.525
Epidemiology of Peripartum Cardiomyopathy in Africa

Kamilu M Karaye1,2, Abdulrazaq G Habib1, Karen Sliwa3,4
1. Department of Medicine, Bayero University & Aminu Kano Teaching Hospital, Kano, Nigeria
2. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.
3. Hatter Institute for Cardiovascular Research in Africa, Department of Internal Medicine & Cardiology, Faculty of Health Sciences, University of Cape Town, South Africa.
4. Mary McKillop Institute, ACU, Melbourne, Australia.

Corresponding author:
Prof Kamilu M Karaye.
Department of Medicine, Aminu Kano Teaching Hospital, PO Box 4445, Kano, Nigeria.
Email: kkaraye@yahoo.co.uk

Abstract
Peripartum cardiomyopathy (PPCM) is a disease that predominantly affects Black African women. The history of peripartum cardiac failure in Africa dates to the 1960s, before the availability of echocardiography. With the availability of echocardiography in the late 1970s, studies on well-characterised PPCM began to be reported. To date, there is no population-based PPCM study in Africa. However, hospital-based studies have reported incidence rates as high as 1:100 deliveries in Nigeria and representing up to 52% of all cardiomyopathies. For reasons that are not yet very clear, there are obvious wide disparities in incidence and prevalence within and between African Countries. Likewise, prevalence of suggested risk factors for the disease such as increased age, gravidity or parity, twin pregnancy, obesity, poor socioeconomic status/malnutrition and selenium deficiency vary widely between studies. However, the disease seems to be more common among the poor rural population. Clinical outcomes are much worse in Africa than in Western Europe and North America. Mortality rates as high as 24.2% at 6 months and 47.4% at 1 year of follow-up had been recorded in Kano, Nigeria, 48.3% over 4 years in Burkina Faso, 11.6% over 6 months in Zimbabwe and 13.0% over 6 months in South Africa. It is hoped that the ongoing peripartum cardiomyopathy in Nigeria (PEACE) Registry and the worldwide EURObservational Research Programme (EORP) on PPCM will soon shed more light on the epidemiology of PPCM in Africa. The present article aimed to review the epidemiology of the disease in Africa, where the disease is relatively more common.

Keywords: peripartum cardiomyopathy; epidemiology; Africa; Nigeria

Introduction
Peripartum cardiomyopathy (PPCM) is “an idiopathic cardiomyopathy presenting with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the LV Ejection Fraction (LVEF) is nearly always reduced below 45%”,[1] Although the disease was first described by Gouley and colleagues in 1937, its aetiology is still unknown and large scale epidemiologic studies began only recently.[2, 3, 4] However, several case series of HF around the puerperium dating back to 1961, many predating the wide availability of echocardiography and most not confirmed with autopsy, have been reported from Africa (Table 1). With the availability of echocardiography in the late 1970s in parts of Africa however, many of those postpartum HF cases were shown not to be due to a cardiomyopathy.[5-9]

Given that African ancestry is believed to be a strong risk factor for PPCM, the present article aimed to review the epidemiology of the disease in Africa, where the disease is relatively more common.[1]

Epidemiology
PPCM is a global disease with epidemiology that varies widely and with multifactorial aetiology.

Prevalence/incidence of PPCM
The true incidence or prevalence of PPCM in Africa and in some other populations is unknown. This is largely because to date there is no population-based study on PPCM in Africa, and very few such studies were carried out elsewhere. However, from available data, PPCM tends to be rare in some parts of the world and more common in others.[10-14] For example recent population-based studies suggest an estimated incidence of PPCM of 1 in 1,741 deliveries in South Korea, 1 in 3,790 deliveries (925 patients in 15
The reasons for the variation in incidence between and within countries remain unknown, but probably reflect both environmental and genetic factors.

PPCM risk factors
PPCM has been associated with several risk factors over the years, but there is significant inconsistency between studies of their association with the disease. The suggested risk factors include increased age, gravidity or parity, African origin, pre-eclampsia, use of tocolytics, twin pregnancy, obesity, poor socioeconomic status/malnutrition, customary birth practices and selenium deficiency.[19-21]

Increased age: Although PPCM is thought to be more prevalent in the upper and lower extremes of childbearing age, and in older women of high parity, it is important to note that the disease could affect such women regardless of their age or parity.[19-22] In our recent series comprising of 54 PPCM patients in Kano, Nigeria, the age of the patients ranged from 18 to 45 years with a mean of 26.6 ± 6.7 years, and 35.2% were between 18 and 20 years, and only 20.4% were older than 30 years.[21] In comparison to controls who were lactating mothers from the same locality as the patients, increased age was not a risk factor for the disease.[23]

Gravidity/parity: Although several studies have suggested that high parity is an important risk factor for PPCM, it is important years in Taiwan, 1 in 10,149 deliveries in Denmark (61 patients in 10 years), 1 in 3,189 live births in the United States of America and 1 in 20,000 deliveries in Japan.[10-14] Studies that estimated incidence in Africa used hospital-based data, arriving at values such as 1 in 1000 live births in South Africa, 1 in 100 deliveries in Sokoto, Nigeria, and 1 in 3,800 in Burkina Faso.[15-17] Prevalence of PPCM was also estimated in a multicentre study in Kano, Nigeria.[18] It was the most prevalent type of idiopathic myocardial failure in Johannesburg in African women before the menopause.

The reasons for the variation in incidence between and within countries remain unknown, but probably reflect both environmental and genetic factors.

Table 1. Some pioneer studies on peripartum HF in Africa

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Echo?</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seftel H &amp; Susser M, 1961.5</td>
<td>South Africa (Johannesburg)</td>
<td>23</td>
<td>No</td>
<td>The commonest type of idiopathic myocardial failure in Johannesburg in African women before the menopause. Two-thirds developed symptoms within first 10 weeks postpartum. A significant relationship is shown between incidence on the one hand and high parity, high childbearing age, and twinning on the other. Poor prognosis is significantly related to high age and parity; prolonged lactation after presentation and presence of cardiomegaly or LVH on ECG. Early onset followed by prompt medical attention is associated with a favourable outcome.</td>
</tr>
<tr>
<td>Brockington IF, 1971.6</td>
<td>Nigeria (Ibadan)</td>
<td>50</td>
<td>No</td>
<td>The clinical findings are of biventricular myocardial failure with mild transitory hypertension. Clinical syndrome is more compatible with a hypertensive origin than with intrinsic myocardial disease.</td>
</tr>
<tr>
<td>Davidson NM, et al, 1974.7</td>
<td>Nigeria (Zaria)</td>
<td>224</td>
<td>No</td>
<td>PPCF patients recruited from 1969-1972. 96% were Hausa or Fulani in origin, compared with 70% for women admitted to the medical wards (Controls). 58% of the patients lived in rural areas, compared with only 37% of Controls. Incidence of PPCF in Zaria about 1% of Hausa deliveries, with a peak in July. Only 1% of Hausa PPCF patients did not take postpartum baths, 3% did not lie on hot beds, and 6% took no “Kanwa” at all. Authors believed that the customs of Hausa women in Zaria were important in the pathogenesis of PPCF, although they may not be wholly responsible for the syndrome.</td>
</tr>
<tr>
<td>Davidson NM et al, 1978.8</td>
<td>Nigeria (Zaria)</td>
<td>224</td>
<td>No</td>
<td>Results of 2-5-year follow-up. Post-partum hypertension was found in 87% of PPCF patients and 61% of Controls. Digoxin and diuretics were rapidly effective, causing a mean weight loss of 29% in 15 days, resolution of hypertension, and a fall in the cardio-thoracic ratio (CTR). During the 1st year after diagnosis, the CTR became normal in 82% of patients, and the ECG in 60%. PPCF recurred, again with the same seasonal variation, after 19 per cent of subsequent pregnancies. During follow up for 2 to 5 years, 22% of the patients became hypertensive, and 11% died. The prognosis was worst in those with an arrhythmia, hypertension, sustained cardiomegaly or aged 30 or more.</td>
</tr>
<tr>
<td>Sanderson JE, et al, 1979.9</td>
<td>Nigeria (Zaria)</td>
<td>43</td>
<td>Yes</td>
<td>Left ventricular function and systolic time intervals were relatively good. Estimated cardiac output were high. Findings not compatible with a severe heart muscle disorder, or cardiomyopathy.</td>
</tr>
</tbody>
</table>

N, total number of patients; ECG, electrocardiogram; LVH, left ventricular hypertrophy; CTR, cardiothoracic ratio; PPCF, peripartum cardiac failure.
to note that 24–37% of cases may occur in young primigravid/primiparous patients.[1,3,19-23] Of the 43 patients studied in Harare, Zimbabwe, 34.9% were primiparous, and 16.3% had parity of 4 or more.[24] The average parity among PPCM patients was 2 in South Africa and Burkina Faso, but 4 to 5 in Nigeria and up to one-third was primiparous.[16,17,20,21] In comparison, PPCM patients in the PPCM EORP recruited from European countries had a median parity of 2 and only 18.6% were primiparous, while those from non-European countries had median parity of 3 and 12.1% were primiparous.[3] In our cohort, multiparity was also not associated with PPCM because it was even more common in the Control (84%) than PPCM (74.4%) groups (p=0.296).[23]

African origin: There seems to be a strong relationship between African ancestry and PPCM, although Elkayam et al clearly showed that PPCM in the United States is not limited to black women.[25] However, there was a significantly higher incidence in African American women as compared with other races.[26] Gentry et al conducted a case-control study in Augusta, Georgia, and Memphis, and found almost a 16-fold higher incidence of PPCM in African American compared with non-African American women.[26] Furthermore, African ancestry seems to confer worse prognosis among PPCM patients, likely due to poorer access to medical care and the presence of guanine nucleotide-binding proteins β-3 subunit (GNB3) TT genotype, which is more prevalent in blacks and associated with worse outcomes.[27] In subset analysis by race, black women with the GNB3 TT genotype had a significantly lower mean LVEF at entry compared to C allele carriers (0.28±0.09 vs. 0.35±0.08; p=0.04).

The ongoing worldwide PPCM EORP aims to delineate the impact of socioeconomic factors versus ethnicity on a number of management and outcome parameters.[3]

Preeclampsia: It has been suggested that preeclampsia and PPCM share a common pathophysiological mechanism that leads to the clinical syndrome of HF, and both are possibly related to the secretion of antiangiogenic factors, including soluble fms-like tyrosine kinase-1 (sFLT1) from the placenta in pregnancy.

[28,29] Although epidemiologic studies have reported a strong association between preeclampsia and PPCM, with a prevalence of preeclampsia in patients with PPCM of about 20%, previous studies from Africa have not reported such an association.[16,20-24,30] It is hoped that the ongoing PEACE Registry in Nigeria will shed more light on this.[4] In itself, preeclampsia occurs in 10% of pregnancies in Africa, which is significantly higher than the global average of approximately 2%.[31]

Systemic hypertension: A review by Elkayam described hypertension as a strong ‘associated condition’, and not an aetiological factor of PPCM,[32] However, in societies where both PPCM and sustained hypertension are common in women, differentiating PPCM from hypertensive heart disease could be difficult if high blood pressure (BP) is considered a clinical feature of PPCM. In support of this point, we found eccentric left ventricular hypertrophy, irrespective of gender, to be the most common type of abnormal LV geometry in hypertensive subjects in Kano, Nigeria.[33] These patients tend to present in HF with similar clinical and echocardiographic features to PPCM, except for the high BP or history of hypertension.[33] Some PPCM registries have shown that high BP in PPCM is rare, as reported by Sliwa et al from South Africa (2%) and Fett et al from Haiti (4%).[34,35] In contrast, we recently found hypertension among 41% of untreated PPCM patients and 28% of controls (p=0.197).[23]

A retrospective study in Japan similarly reported the incidence of hypertension in PPCM as 41%, which is substantially higher than in the overall pregnant population.[14,36] Moreover, Kamiya et al revealed that the hypertension is independently associated with a shorter hospital stay and higher LVEF.[14,36] However, hypertensive patients with and without PPCM had the same LV size and systolic dysfunction at diagnosis and discharge. In addition, parameters such as LV systolic diameter, fractional shortening, and LVEF showed greater improvement in the hypertensive patients. Thus, they concluded that the hypertensive state is not causative in the development of PPCM and might be a subset of PPCM that is characterized by relatively swift recovery, except in fatal cases.[14]. Similarly, Ntusi et al showed different modes of recovery in patients presenting with PPCM versus those with hypertensive disorders of pregnancy presenting with LV dysfunction and HF in a South African cohort.

[37] In addition to important differences in the ages, time of onset of HF, clinical, ECG and echocardiographic features, 5 of the 30 PPCM patients died over 3.5 years as against none of the 53 hypertensive patients over 6 years of follow-up.[37] In a retrospective analysis of data from 6 States in the USA, Kao et al also reported a significantly higher prevalence of hypertension among PPCM patients (46.9%) than Controls (6.4%), and considered it a strong PPCM risk factor.[38] Similarly in the Investigations of Pregnancy-Associated Cardiomyopathy (iPAC) study, hypertension was found in 45% of the PPCM patients and was commoner in Blacks (70% Vs 34%) but not associated with worse outcomes.[39] Placental ischaemia seems to be the main pathogenic mechanism of pregnancy-induced hypertension. This is followed by the placental release of vasopressor substances that are involved both in generalised endotheliosis that characterizes the disease, and in hypertension.[40] From the foregoing, it clear that the relationship between hypertension and PPCM needs further research.

Poor socio-economic status/malnutrition: It was observed more than 40 years ago that peripartum cardiac failure is a disease that predominates among the poor, living in poor social conditions.

[5,8] In Kano (Nigeria), it was also observed that among women referred for echocardiography, PPCM almost always occurred in women with low income (7.3% Vs 0%).[41] The most plausible explanations for this observation could be poor nutrition and poor medical care. However, the occurrence of the disease in well-nourished patients had put this theory to doubt. A more recent study in Kano has further questioned the theory of poor socioeconomic status as a risk factor for PPCM by finding no significant differences in income and educational level between PPCM patients and controls.[23]

Customary birth practices: About 4 decades ago in Zaria (northern Nigeria), women of the Hausa tribe appeared to have a high incidence (1:100) of a form of HF within the time frame of PPCM, termed postpartum cardiac failure (PPCF).[9,42] This was believed to be related to some local Hausa postpartum customary practices, mainly twice daily hot baths by new mothers, regular ingestion of a thick drink made from millet and rich in dry lake salt, ‘Kunun Kanwa’ (in Hausa Language), and lying on heated mud beds, starting from shortly after giving birth and continuing for
About 3 months.[9,42] Although these practices were intended to stimulate breastmilk production, protect from the harmful effects of “cold” and improve the general wellbeing of the new mother, they were also believed to cause significant volume overload and vasodilatation, resulting in PPCF.[8,9,42] When echocardiography became available in Zaria in the late 1970s, Sanderson et al confirmed that PPCF was mainly a “high-output HF with well-preserved ventricular function”, and not a cardiomyopathy.[9] For this reason therefore, PPCF is an entity different from what we know today as PPCM, going by the current definition.[1]

Among a well-characterised cohort of 21 PPCM patients, Danbauss SS reported from Zaria that all of them practised the postpartum customs, while Isezu et al reported from Sokoto (northern Nigeria) that up to 81.5% of PPCM patients practised the hot baths for at least 30 days.[16,43] When compared with apparently healthy controls however, the practices were found to be even more common among them than the PPCM patients (hot baths, 82% Vs 35.1%; Kunun Kanwa, 78% Vs 23.1%; p<0.001; respectively), clearly implying that the practices were simply common cultural habits among the Hausas that are not related to PPCM.[23] It is important to note that traditional customary birth practices are not limited to the Hausas or Fulanis in Nigeria. Okeke et al reported that in the immediate postpartum period, 25.2% of 420 women in Enugu, South Eastern Nigeria drank various forms of alcoholic beverages to induce lactation while 80.2% of them applied hot compresses on the lower abdomen to aid lochia drainage and involution of the uterus, 75% of them sat in hot salt water solution (sitz bath) in the immediate postpartum to aid lochia drainage, aid perineal wound healing and improve vaginal tone.[44] Although the results of PEACE Registry are still being awaited, it is common knowledge that PPCM is relatively more common in northern than other regions of Nigeria, and the relevance of the traditional birth practices in PPCM would be clarified.[4,7-9]

Selenium deficiency: Selenium is a naturally occurring element found in soil, rocks and water [37]. The selenium content in foods principally depends on the concentration and physico-chemical forms existing in the soil [45]. However, levels of serum selenium are determined by many factors, including its availability in foods, absorption, cooking, lactation, alcohol, chronic illnesses, etc [37,41]. Cenac et al reported for the first time from Niger Republic, where PPCM is an endemic disease, that selenium deficiency may be an important problem in Sahelian African patients with PPCM, akin to what was described for Keshan disease [47,48]. In support of the PPCM selenium theory by Cenac et al, our results have shown critically low selenium levels among 76.9% of the studied PPCM patients [23,47]. Further analysis of our data (unpublished) shows that selenium levels increase the odds of having PPCM to 1.08 (95% confidence interval = 1.043- 1.118; p<0.001).[23] North-western Nigeria shares a long border, geography and customs with Niger republic, hence the common food types and dietary habits, which are the sources of selenium. Our results have shown that PPCM patients had significantly lower serum selenium levels and significantly higher prevalence of rural residency than controls despite similar income and educational levels. In addition, rural residency significantly increased the odds of having critically low serum selenium levels. Our observation of high prevalence of rural residency among PPCM patients was similarly made for PPCF decades ago in Zaria and Johannesburg.[5,7,8,23] It is well known that in Nigeria, most rural residents are subsistence farmers who tend to consume the locally produced foods and grown animals. Urban residents on the other hand are more exposed to imported foods and animals, from regions where there is no selenium deficient soil and animals. Therefore, it is reasonable to hypothesize that most women in Kano (and the Sahel region) develop PPCM if they depend on locally produced foods and animals. The serum selenium levels among PPCM patients in Kano (61.7±14.9µg/L) and Niamey (48.0±25µg/L) were similar, most likely because of their geographical and cultural similarities which explains the heavy burden of the disease in the region, in comparison with respective values in Haiti of 110µg/L (range 67-145µg/L) [23,47,49]. It is hoped that the ongoing PEACE Registry will further clarify the relationship between PPCM and selenium deficiency. This study aims to describe the relationship between selenium deficiency, oxidative stress and PPCM, the impact of sodium selenite supplementation on LV reverse remodelling, change in New York Heart Association (NYHA) functional class and survival in PPCM, and the prevalence of selenium deficiency and its relationship with cardiac function in apparently healthy pregnant women.[4]

Clinical outcomes
LV function recovery and mortality rates for PPCM vary widely across the globe due to various reasons. Mortality rates as high as 24.2% at 6 months and 47.4% at 1 year of follow-up had been recorded in Kano, Nigeria, 48.3% over 4 years in Burkina Faso, 11.6% over 6 months in Zimbabwe and 13.0% over 6 months in South Africa (Table 2).[17,20,21,24] In comparison, mortality rates were much lower in the United States (4.1% over 1 year); 2.4% at one month post-hospital discharge in the EORP study, in-hospital mortality of 1% in South Korea, and 0% at 6 months in Germany; possibly a reflection of the higher standard of health care.[3,10,39,50] Although some researchers didn’t identify any predictors of mortality, others inconsistently reported younger age at diagnosis, lower body mass index (BMI) and some echocardiographic variables as independent predictors of mortality.[20,21,34] Whitehead et al reported that mortality increased with maternal age, in women with parity of more than 4, and in black women, who were 6.4 times more likely to die compared with whites.[51] In the IPAC study, 30% of patients were Black, and clinical outcomes were significantly worse in Black women as only 59% achieved a final LVEF >50% versus 77% of whites or others, whereas 26% of black women had either an event or a final LVEF <35% versus only 8% of whites or others (p<0.03).[39] However, in the EORP program, 106 (25.8%) patients were Black Africans, but mortality rate at one month post discharge did not differ between patients from ESC and non-ESC countries (p=0.216).[3]

LV reverse remodelling (LVR) was recently shown to involve both LV systolic and diastolic functions, and maximum improvement seems to occur within the first 6 months of PPCM diagnosis. [20,21,23,38] In our cohort, 47.1% satisfied the criteria for LVR while 29.4% recovered LV systolic function at 1 year follow-up; somewhat similar to the prevalence of LVR of 28% over 2 years reported from Haiti and of 21% in South Africa over 6 months (Table 2).[20,21,34] Blauwet et al found older age and smaller LV end-systolic dimension (LVESD) to be significant predictors of LV recovery among PPCM patients in South Africa.[20] In addition,
Right ventricular (RV) systolic and diastolic dysfunction (RVSD and RVDD respectively) have been recently studied in PPCM, representing up to 52% of all cardiomyopathies. For reasons that are not very clear, there are wide disparities in the epidemiology of PPCM in Africa, and it is hoped that the ongoing peripartum cardiomyopathy in Nigeria (PEACE) Registry and the worldwide EURObservational Research Programme (EORP) on PPCM will soon shed more light on the epidemiology of PPCM in Africa.

Declarations of interest
The authors declare no conflict of interest.

Acknowledgements
The authors state that they abide by the authors’ responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal [59].

References


Table 2. Pattern of mortality and LVRR among PPCM patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients at follow up</th>
<th>Mortality</th>
<th>LVRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria (1 year)</td>
<td>16</td>
<td>33</td>
<td>47.4%</td>
</tr>
<tr>
<td>South Africa (6 months)</td>
<td>15</td>
<td>141</td>
<td>13%</td>
</tr>
<tr>
<td>Burkina Faso (6 months)</td>
<td>12</td>
<td>29</td>
<td>48.3%</td>
</tr>
<tr>
<td>Zimbabwe (6 months)</td>
<td>19</td>
<td>35</td>
<td>13%</td>
</tr>
<tr>
<td>United States (1 year)</td>
<td>42</td>
<td>100</td>
<td>4%</td>
</tr>
<tr>
<td>EORP (1 month)</td>
<td>3</td>
<td>411</td>
<td>2.4%</td>
</tr>
<tr>
<td>Haiti (2 years)</td>
<td>29</td>
<td>98</td>
<td>15.3%</td>
</tr>
<tr>
<td>South Korea (hospital)</td>
<td>5</td>
<td>795</td>
<td>1%</td>
</tr>
<tr>
<td>Germany (6 months)</td>
<td>48</td>
<td>45</td>
<td>0%</td>
</tr>
</tbody>
</table>

LVRR, left ventricular reverse remodelling; EORP, EURObservational Research Programme on PPCM.

**Conclusion**

The history of peripartum cardiac failure in Africa dates to the 1960s and early-mid 1970s, before the availability of echocardiography. To date, there is no population-based PPCM study in Africa to the best of our knowledge. However, hospital-based studies have reported incidence rates as high as 1:100 deliveries in Nigeria and representing up to 52% of all cardiomyopathies. For reasons that are not very clear, there are wide disparities in the epidemiology of PPCM within and between African Countries. However, the disease seems to be more common among the poor rural population. With the availability of echocardiography and other investigation tools, well characterised PPCM patients have been studied in Africa. One of the first studies on RV function in PPCM had come from Nigeria, and subsequent studies elsewhere have further described the bi-ventricular nature of the disease. Clinical outcomes are much worse in Africa than in Western Europe and North America. It is hoped that the ongoing peripartum cardiomyopathy in Nigeria (PEACE) Registry and the worldwide EURObservational Research Programme (EORP) on PPCM will soon shed more light on the epidemiology of PPCM in Africa.


The Impact of Diurnal Fasting During Ramadan on Patients with Established Cardiac Disease: A Systematic Review

Marwan M. Refaat¹, Nadim El Jamal¹, Hebah M. El-Rayess¹, Anthony Gebran¹, Amar M. Salam²

1. Department of Internal Medicine, American University of Beirut Faculty of Medicine and Medical Center, Beirut, Lebanon
2. Cardiology Department, Weill Cornell Medical College-Qatar and Hamad Medical Corporation, Doha, Qatar

Corresponding author:
Marwan M. Refaat,
Associate Professor of Medicine
Department of Internal Medicine, Cardiovascular Medicine/Cardiac Electrophysiology
Department of Biochemistry and Molecular Genetics
American University of Beirut Faculty of Medicine and Medical Center
3 Dag Hammarskjold Plaza, 8th Floor, New York, NY 10017, USA
Email: mr48@aub.edu.lb or marwanrefaat@alumni.harvard.edu

Abstract
During the month of Ramadan, Muslims abstain from eating before dawn until after sunset for a month. This study reviews most recent literature on the effect of Ramadan fasting on the Cardiac patient specifically, excluding any study done on patients with no diagnosis of Cardiac disease to help cardiologists better deal with their patients who would wish to fast during Ramadan. As such, a Medline and Pubmed search was conducted to retrieve studies investigating the effects of fasting during Ramadan specifically on the cardiac patient with regard to incidence of cardiac disease and change in cardiovascular risk parameters. The search was conducted by combining the key word “Ramadan Fasting” with multiple cardiac diseases and cardiovascular risk parameters. Only studies reporting results on patients already diagnosed with a cardiac disease were included. fourteen were included. Most studies have shown, with a few exceptions, that Ramadan fasting has no adverse effects on incidence of cardiovascular disease or the number of hospitalizations due to cardiac disease events. Thus patients with controlled disease may fast with the consultation and monitoring of their physician.

Keywords: Ramadan Fasting; Cardiac Disease; Cardiovascular Risk Factors.

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Introduction
Fasting in the month of Ramadan of the Islamic calendar is one of the pillars of Islam. It is an obligation for all Muslim adults. In Ramadan, Muslims refrain from the consumption of food and fluids from the rising to the setting of the sun, and have two meals; one at the breaking of the fast (iftar) and one before sunrise (Suhur). On top of its religious significance, recent studies showed several benefits of fasting that promote cellular regeneration, reversing immunosuppression and diabetes. [1, 2] Other recent studies demonstrated a possible benefit of fasting in cancer prevention, ameliorating toxicity and efficacy of chemotherapy,[3-9] preserving cognitive performance,[10] and improving outcome in studies on neurodegenerative diseases. [11, 12]

In light of its religious importance and the benefits fasting might have, physicians are asked by their patients if it is safe for them to fast. Of particular interest to us is the cardiac patient as many seek the advice of their cardiologist regarding their ability to fast. This review aims to investigate the available evidence-based literature on the effects of Ramadan fasting on the cardiac patient.

Methods
The studies addressed in this review were obtained by a Medline and Pubmed search using the key word “Ramadan fasting” combined with the mesh terms “Coronary Heart Disease”, “Heart Failure”, “atrial fibrillation”, “angina”, “myocardial Infarction”, “arrhythmia”, “cardiovascular disease”, “cardiovascular disease AND diabetes”, OR “stroke”. The search period was set until 31 December 2017. Titles and abstracts were examined
independently by two investigators for relation to our topic. Those related, were in the same way examined according to the following inclusion and exclusion criteria. All articles, letters, and reports describing statistical, experimental, or case studies on the effects of Ramadan fasting on cardiac patients, the incidence of cardiac disease, and cardiovascular risk factors in these patients were included. The criteria for exclusion were reviews, articles not written in English, and studies depicting effect of Ramadan fasting on parameters in previously healthy individuals since our study is concerned with the cardiac patient. Studies that investigated effects of Ramadan fasting on incidence of cardiovascular events or cardiovascular risk factors in all patients, but specified results for previously diagnosed cardiac patients, were included and only data on cardiac patients was extracted. Studies that fit the inclusion criteria were then examined and their results extracted into a database and noted for the presence or absence of any significant difference attributed to Ramadan Fast. Secondary outcomes of studies were also extracted and analysed. Risk of bias and the quality of the studies were assessed by using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[13]

Results

The search yielded 178 results after removing duplicates. The process of screening the articles is represented in the flow diagram of Figure 1. Of the search, fourteen met our inclusion criteria; i.e. relating fasting to effects on cardiac patients, along with two case studies. Of these nine reported a relation between incidence of cardiovascular disease or hospitalization due to cardiac events and Ramadan fasting (Table 1). These were important to include as they indicated effects of fasting on patients already diagnosed with these conditions or who previously had these conditions. Five studies investigated effects of Ramadan fasting on cardiovascular risk factors in patients diagnosed with cardiac disease, or with previous cardiac disease (Table 2). Most studies included had a good or fair quality rating after quality assessment by the NIH quality assessment tool (Table 3). The search also yielded two case studies. One of which reported polymorphic ventricular tachycardia in a patient with known brugada syndrome after a large meal and a month of fast.[14] The other case study reports a patient with hypertension, hyperlipidemia, and diabetes type 2 who experienced angina while fasting during Ramadan, symptoms were relieved with medical treatment after the fast, but then the patient suffered a new thrombotic occlusion leading to four vessel bypass surgery.[15]

3.1 Effects of Ramadan Fasting on Incidence of Cardiovascular Events in Patients with Heart Disease:

Most studies tabulated in Table 1 showed no significant difference between Ramadan and non-Ramadan months regarding incidence of cardiovascular events (Stroke, Myocardial Infarction, Unstable Angina, Atrial Fibrillation, Heart Failure) in the different categories of cardiac patients.[13, 16-23] However patients with a previous MI were shown to be less likely to be hospitalized for CHF,[16] and for Atrial Fibrillation during Ramadan compared to other months. In a study involving 4175 patients Salam et al. reported that patients admitted for hospitalization due to Heart Failure during Ramadan were more likely to have previous CAD compared to non-Ramadan months.[23] Moussavi et al.[24] and Chamshi Pasha at al.[17] reported no significant effect of Ramadan fasting on chest pain, discomfort, or precipitation of cardiac events.

3.2 Effects of Ramadan Fasting on Lipid Profile in Cardiac Patients:

Effects of Ramadan fasting on HDL levels during Ramadan fast in patients with previous cardiovascular disease, Khafaji et al. reported a significant decrease in HDL levels in stable cardiac patients.[26] Also the study by Khafaji et al. is the only study reporting a significant increase in LDL in fasting, while the rest report either no significant change in LDL levels.[25] All studies that measured total cholesterol in cardiac patients reported no significant change in its levels during fasting[19, 25, 26] except Nematy et al. who reported amelioration in lipids profile.[27]

3.3 Effects of Ramadan Fasting on Cardiovascular Risk Factors in Patients with Cardiovascular Disease:

Regarding fasting blood sugar levels, no study showed a significant change during fasting compared to non-fasting months in cardiovascular patients.[25, 27] Inflammatory profiles, and vasculoprotective indicators were reported to either not change significantly,[26, 27] or to ameliorate[25] in Ramadan in patients with cardiovascular disease. Nematy et al. also reported an improvement in 10 year coronary heart disease risk in patients with cardiovascular disease during Ramadan.[27]

Discussion

Ramadan is an obligation that millions of Muslims worldwide observe. It is a month of the lunar year and thus it occurs at different times in consecutive years according to Gregorian calendar. As such Ramadan could fall in the winter where
Table 1. Incidence of Cardiac Disease in Cardiac Patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Patient with</th>
<th>Number of Patients</th>
<th>Parameter Measured</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Suwaidi et. Al[16]</td>
<td>2004</td>
<td>Qatar</td>
<td>Prior MI</td>
<td>238</td>
<td>Incidence of CHF</td>
<td>Less likely to be hospitalized for CHF during ramadan (25%) than a month before (33.5%), after (35.9%), and a 9-month average (29.1%)(p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hx Coronary Artery Bypass Surgery</td>
<td>86</td>
<td>Incidence of CHF</td>
<td>No statistically Significant Difference in hospitalization for CHF between Ramadan (7.2%) a month before before ramadan (8.8%), after ramadan (9.6%), and a 9month average (9.7%),(p&gt;0.05)</td>
</tr>
<tr>
<td>Al Suwaidi et al.[13]</td>
<td>2004</td>
<td>Qatar</td>
<td>Hx of AMI</td>
<td>75</td>
<td>Incidence of AMI</td>
<td>No statistically Significant Difference one month before Ramadan (15%), During (19%) and after (19%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hx Coronary Artery Bypass Surgery</td>
<td>59</td>
<td>Incidence of AMI</td>
<td>No statistically significant difference one month before Ramadan (3.2%), during (3.5%), and after (3%)</td>
</tr>
<tr>
<td>Al Suwaidi et al.[17]</td>
<td>2005</td>
<td>Gulf Countries</td>
<td>Cardiac Disease (general not specified)</td>
<td>465</td>
<td>Comfort and incidence of Cardiac Events</td>
<td>27% felt better, 6.7% felt worse, 4.5% developed cardiac events.</td>
</tr>
<tr>
<td>Bener et al. [18]</td>
<td>2006</td>
<td>Qatar</td>
<td>AMI</td>
<td>201</td>
<td>Hospitalization for Stroke</td>
<td>No statistically Significant Difference (53.3% of stroke patients had AMI before ramadan, 62% during, and 69% after)</td>
</tr>
<tr>
<td>Comoglu et al. [20]</td>
<td>2003</td>
<td>Turkey</td>
<td>Cardiac Disease (general not specified)</td>
<td>319</td>
<td>Hospitalization for Stroke</td>
<td>No statistically Significant Difference (41.1% of stroke patients had a Cardiac Disease before ramadan, 42.5% during, and 37.5% after)</td>
</tr>
<tr>
<td>Chamsi-Pasha et al. [19]</td>
<td>2004</td>
<td>Saudi Arabia</td>
<td>Cardiac Disease (general not specified)</td>
<td>86</td>
<td>Hospitalization Non Required</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiac Disease (general not specified)</td>
<td>86</td>
<td>NYHA Class</td>
<td>No Significant Change During Fast (mean class: 1.4 before Ramadan, 1.2 after, p=0.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coronary Artery Disease</td>
<td>46</td>
<td>NYHA Class</td>
<td>No Significant Change During Fast (mean class: 1.2 before Ramadan, 1.1 after, p=0.57)</td>
</tr>
<tr>
<td>El Mitwalli et al.[21]</td>
<td>2010</td>
<td>Egypt</td>
<td>Cardiac Disease (general not specified)</td>
<td>138</td>
<td>Stroke Admissions</td>
<td>No statistically Significant Difference (30.2% of stroke patients had a Cardiac Disease before ramadan, 24.1% during, p=0.1)</td>
</tr>
<tr>
<td>Mousavi et al. [24]</td>
<td>2014</td>
<td>Iran</td>
<td>CAD</td>
<td>148</td>
<td>Chest Pain and Dyspnea</td>
<td>No statistically significant difference in incidence of chest pain or dyspnea between fasting and non fasting groups (P = 0.141, OR = 0.416, and 95% CI, 0.126-1.374)</td>
</tr>
<tr>
<td>Salam et al [22]</td>
<td>2013</td>
<td>Qatar</td>
<td>Prior MI</td>
<td>236</td>
<td>Hospitalization for Afib</td>
<td>Less likely to be hospitalized for Afib during Ramadan (9.1% of Afib Patients had prior MI before Ramadan, 9.8% during, 23.2% after p=0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Previous HF</td>
<td>133</td>
<td>Hospitalization for Afib</td>
<td>No Significant Difference (22.1% of Afib Patients had prior HF before Ramadan, 20.3% during, 36.5% After,p=0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Valvular Heart Disease</td>
<td>14</td>
<td>Hospitalization for Afib</td>
<td>No Significant Difference (2.9% of Afib Patients had prior Valvular disease before Ramadan, 3.5% during, 1.3% After,p=0.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AMI</td>
<td>37</td>
<td>Hospitalization for Afib</td>
<td>No Significant Difference (9% of Afib Patients had prior HF before Ramadan, 3.5% during, 7.3% After,p=0.21)</td>
</tr>
<tr>
<td>Salam et al [23]</td>
<td>2017</td>
<td>Gulf Countries</td>
<td>Known Systolic LV dysfunction</td>
<td>1919</td>
<td>Hospitalization for HF</td>
<td>No statistically Significant Difference (46.4% of HF patients had Systolic LV dysfunction during Ramadan, 46.1% in non-Ramadan months,p=0.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Known CAD</td>
<td>1928</td>
<td>Hospitalization for HF</td>
<td>Admitted patients were more likely to have CAD prior (54.6% of HF patients had prior CAD during Ramadan, 47.1% in non Ramadan Months,p=0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital Heart Disease</td>
<td>32</td>
<td>Hospitalization for HF</td>
<td>No statistically Significant Difference (0.3% of HF patients had congenital disease during Ramadan, 0.8% in non-Ramadan months , p=0.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Valvular Heart Disease</td>
<td>578</td>
<td>Hospitalization for HF</td>
<td>No statistically Significant Difference (12.7% of HF patients had valvular disease during Ramadan, 14% in non-Ramadan months,p=0.54)</td>
</tr>
</tbody>
</table>
daylight hours are short, or it could fall in the summer where the fasting hours could reach up to 18 hours depending on the geographical location. These long fasting hours will require rescheduling of medication time and adequate fluid intake. Most studies have shown that Ramadan fasting has no adverse effects on incidence of various cardiovascular diseases, or the number of hospitalizations due to cardiac disease events.

An important exception to this is that patients with chronic kidney disease (GFR< 30/min/1.73 m²) would be advised not to fast. Those with early stage CKD (GFR< 30 ml/min/ 1.73 m²) could fast after a trial of few days and documenting no increase to this, hypertensive patients can fast but should pay attention to meals they might take that might raise their blood pressure abruptly, as can be concluded by the rise of blood pressure after meals reported by Khafaji et al.\[26\]

The studies above have been done in different countries and have thus assessed different populations and socioeconomic classes. Cultures and sub-cultures differ in their dietary habits during Ramadan. Different populations and classes are bound to have differences in the type of foods consumed during Ramadan. For example, eating habits in Morocco are not usually present in countries like Iran and Kuwait. Measures taken by physicians to avoid health risks during Ramadan must therefore come after careful examination of the lifestyle and eating habits of the patients.

It is important to note the effects of fasting on hypertension since hypertension is well known risk factor for cardiovascular events. Some studies showed a decrease in blood pressure during fasting,\[20, 28, 29\] but Topacoglu et al reported an increase in the number of admissions for hypertension to the ED during Ramadan,\[30\]. The discrepancies can be explained by the following; amelioration in blood pressure can be due to dehydration effects during long fasting time.\[28\] It can also be attributed to decreasing day time activity which leads to a decrease in sympathetic tone.\[31\]

The effect of Ramadan fasting on patients with Coronary Artery Disease was shown to be somewhat protective with regard to incidence of CHF,\[16\] or Afib.\[22\] However, Salam et al reported in a recent large sample size study, a higher likelihood that patients admitted for HF during Ramadan have prior CAD.\[23\]

Even though both studies regarding HF we done in the same country, the differences in results between these two studies on HF hospitalization in CAD patients may be attributed to the

### Table 2. Cardiovascular Risk Parameters in Cardiac Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>Parameters Measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamsi Pasha et al.[19]</td>
<td>2004</td>
<td>Saudi Arabia</td>
<td>86</td>
<td>Hematologic and Biochemical Parameters</td>
<td>No significant Change during the fast (all p&gt;0.05)</td>
</tr>
<tr>
<td>Khafaji et al.[26]</td>
<td>2011</td>
<td>Qatar</td>
<td>56</td>
<td>TC, TG, HDL-C, LDL-C, hs-CRP, Serum Leptin in stable cardiac patients</td>
<td>Improvement in 10 year coronary heart disease risk (13.0 ± 8 before Ramadan and 10.8 ± 7 after Ramadan, P = 0.001), total cholesterol, triglycerides, VLDL-c, LDL-c, cholesterol/HDL and LDL/HDL ratio were significantly decreased (P = 0.02 for cholesterol and P &lt; 0.001 for rest) and HDL-c increased significantly (P &lt; 0.001); dec. in SBP (132.9 ± 16 mmHg vs 129.9 ± 17 mmHg, P = 0.03); no change in DBP (80.2 ± 9 vs 78.6 ± 11 mmHg, P = 0.14); no significant change in FBS, insulin, HOMA-IR, hcy, hs-CRP (P = 0.33, P = 0.58, P = 0.76, P = 0.06 and P = 0.07 respectively)</td>
</tr>
<tr>
<td>Nematy et al.[27]</td>
<td>2012</td>
<td>Iran</td>
<td>82</td>
<td>10 year coronary heart disease risk, Lipids Profile, BP, FBS, insulin, HOMA-IR, hcy, hs-CRP in patients with previous Cardiovascular Disease</td>
<td>Significant inc. of NO (85.1 ± 11.54 vs 75.8 ± 10.7 μmol/l, P = 0.011); Significant dec. of ADMA (802.6 ± 60.9 vs 837.6 ± 51.0 μmol/l, P = 0.034); Insignificant dec. of MDA (3.2 ± 0.7 vs 3.6 ± 1.1 μmol/l, P = 0.329); Significant inc. of VEGF (228.1 ± 27.1 vs 222.7 ± 22.9 pg/ml, P = 0.122); Significant dec. of TG (176±56 vs 148± 52 mg/dl, P = 0.018), TC (186±43 vs 175± 35 mg/dl, P = 0.062), TC/HDL-C ratio (4.76±1.52 vs 4.01±1.49, P &lt; 0.001); Significant inc. of HDL-C (40±14 vs 46±13 mg/dl, P = 0.001); No significant change in FBS (112±42 vs 118± 38 mg/dl, P = 0.091), TC (186±43 vs 175± 35 mg/dl, P = 0.062) and LDL-C (115±31 vs 109± 39 mg/dl, P = 0.11)</td>
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<td>Yousefi et al.[25]</td>
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<td>Iran</td>
<td>21</td>
<td>NO,ADMA,VEGF,MDA,TG,HDLC,LDL-C,TC, HDL-C, FBS, TC, LDL in patients with previous cardiovascular disease</td>
<td>Significant inc. of NO (85.1 ± 11.54 vs 75.8 ± 10.7 μmol/l, P = 0.011); Significant dec. of ADMA (802.6 ± 60.9 vs 837.6 ± 51.0 μmol/l, P = 0.034); Insignificant dec. of MDA (3.2 ± 0.7 vs 3.6 ± 1.1 μmol/l, P = 0.329); Significant inc. of VEGF (228.1 ± 27.1 vs 222.7 ± 22.9 pg/ml, P = 0.122); Significant dec. of TG (176±56 vs 148± 52 mg/dl, P = 0.018), TC (186±43 vs 175± 35 mg/dl, P = 0.062), TC/HDL-C ratio (4.76±1.52 vs 4.01±1.49, P &lt; 0.001); Significant inc. of HDL-C (40±14 vs 46±13 mg/dl, P = 0.001); No significant change in FBS (112±42 vs 118± 38 mg/dl, P = 0.091), TC (186±43 vs 175± 35 mg/dl, P = 0.062) and LDL-C (115±31 vs 109± 39 mg/dl, P = 0.11)</td>
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difference in sample size, whereby the large sample size (1928 patients with CAD) in the study reported by Salam et al. might bring higher statistical reliability and generalizability. These three studies did not directly assess whether a participant did fast or not, but relied on the cultural norm of their respective societies that most participants would have fasted. This could be a limitation in the methodology of these studies since the exposure under study was not measured accurately but estimated. Only Khafaji et al reported a deterioration in lipid profile during Ramadan (decrease in HDL and increase in LDL).[26] An elevation in LDL and a decrease in HDL; a characteristic of hypercholesterolemia is an important risk factor for atherosclerosis in CAD. However, Salim et al attributed this to the timing of blood sample extraction which was at closer to the time of the last meal in Ramadan than that in non-fasting months.

[33] Some studies in healthy individuals show amelioration or no significant changes of lipid profiles in Ramadan. These studies also report elevation in HDL levels.[34-36] Other studies indicated an increase in LDL and TC levels.[37, 38] The results of studies regarding lipid profiles are thus contradictory, and are based on small sample sizes which could limit their reliability. Part of the contradiction can be due to the difference in dietary composition, eating habits, and physical activity between different populations and countries. According to the specific culture patients belong to, high fat diets might be common at the breaking of fast meals. Thus, patients with CAD are advised as a precaution to decrease cholesterol and saturated fatty acid (SFA) intake in their diet, as high levels of SFA are associated with increased TC and LDL levels. They are also advised to increase consumption of monounsaturated fatty acids (MUFA) found mostly in vegetable oils. MUFA are known to decrease the risk of CAD as evident by the decrease of CAD in Mediterranean cultures.[34] These patients are also advised to strictly abide by medications controlling their lipid profiles, hypertension or hyperglycemia. They are also advised to achieve the highest possible health benefits of Ramadan fasting and avoiding any risks.

Though Salam et al. studied hospitalization for atrial fibrillation patients with previous myocardial infarction,[23] the literature is lacking with studies on patients with arrhythmias during Ramadan fasting. In our search, no study included arrhythmic patients except the case report on a patient with diagnosed Brugada syndrome.[14]

Studies on cardiac risk factors in cardiac patients during Ramadan showed that fasting does not increase the risk of complications. As tabulated above, some showed no significant change in risk factors while others showed amelioration in cardiac risk factors. C-reactive protein (CRP) has been correlated with acute coronary events. Leptin has a vasoactive and prothrombic role, and it can increase with acute myocardial infarction.[26] High homocysteine levels are risk factors for cardiovascular disease and affect the vascular wall and the coagulation system.[35] Nitric oxide (NO) mediates the functions of vascular endothelial growth factor (VEGF), which in turn stimulates angiogenesis, vasodilatation, and vascular permeability. Asymmetric dimethylarginine (ADMA) reduces NO production and is thus an important risk factor for cardiovascular disease. Plasma malondialdehyde (MDA) is a determinant of oxidative stress and is shown to increase in level in cardiovascular disease.[25] These studies remain small studies with small sample sizes. Larger studies are needed to establish a clearer relation.

Studies on HF patients are scarce. Salam et al. reported no significant change in hospitalization in patients with previous HF during the month of Ramadan.[23] Though one other study showed no significant change in CHF incidence during Ramadan, precautions have to be undertaken by patients with previous heart failure to minimize the risk of recurrence during Ramadan due to harsh fasting conditions, and possible change in eating habits. [16] Controlling hypertension and dyslipidemia is important especially in the setting of CAD. Patients with hypertension on a twice per day regimen will require rescheduling the medications from the morning and evening to the Iftar and Suhur.

Studies regarding Ramadan fasting and cardiovascular disease are relatively scarce. Also different findings between populations are expected because of the differences in geography, climate, fasting and breaking fast traditions, health, activity and fitness levels of the study populations. Though many show amelioration or no significant effect of Ramadan fasting on cardiovascular health, cardiac patients should be closely monitored during Ramadan. Since there cannot be conclusive generalized evidence from the studies present at hand regarding any adverse effects Ramadan fasting could have on health cardiac patients, some precautions should be taken. Patients must frequently visit their doctors to check for any signs of complication. They must strictly adhere to any medication prescribed though its schedule is shifted. This medication should also be evaluated for any effects that might lead to hypoglycemia, dehydration, or hypotension as no food nor drink is consumed for long hours that can reach up to 18 hours depending on location and season. Medication or diet could be changed as an adaptation for the change of lifestyle. All cardiac patients are also advised to drink

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<td>Mousavi et al.</td>
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<td>Khafaji et al.</td>
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<td>Yousefi et al.</td>
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lots of fluid during non-fasting times, and adhere to a strict low fat, low cholesterol diet. Physical activity is also strongly advised but within the limit of personal physical ability.

Special attention should be made to diabetic patients, specifically those with previous stroke incidences, as they should be closely monitored during the fast. They should strictly follow a diet and exercise regime.[33] High blood pressure, smoking, abdominal obesity, diet and lack of physical activity are risk factors that may increase the recurrence of stroke.[39] Uncontrolled FBS may also lead to cardiac disease complications in diabetic patients. Diet is important in these patients to improve glycaemia stability and reduce atherogenic risk. These patients are also advised to monitor their blood pressure, adhere to prescribed hypertensive medication, monitor their diet and engage in physical exercise.

Well-controlled patients with diabetes mellitus (DM) treated with lifestyle therapy, metformin, acarbose, sulfonylurea, thiazolidinediones, incretin-based therapies and/or short-acting insulin secretagogues, and that are otherwise healthy, can fast in Ramadan.[40] Patients with diabetes on oral hypoglycemic will require adjustments of the doses: the metformin dose that is given three times daily should be changed to twice daily with two-thirds of the dose at the sunset meal and one third of the dose at the predawn meal. If a sulfonylurea is given twice a day, half of the usual morning dose is given at the predawn meal and the usual dose at the sunset meal. No change is needed for thiazolidinedione, alpha-glucosidase inhibitor or incretin-based therapies dosages. If patients are having premixed or intermediate-acting insulin twice daily, the regimen should be changed to long-acting or intermediate insulin in the evening with short or rapid-acting insulin with meals (usual dose at sunset and half usual dose at predawn meal).[40] The Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed increased hypoglycemia in patients with type 1 DM (4.7 fold) and type 2 DM (7.5 fold).[41] However, the Ramadan Education and Awareness in Diabetes (READ) study showed that hypoglycemic episodes during Ramadan in patients with type 2 Diabetes Mellitus was associated with no Ramadan-focused diabetes education.[42] Diabetic patients with a HbA1c of more than 10%, recurrent hypoglycemic episodes, acute illness, type 1 diabetes, or who engage in intense physical labor or are pregnant, are advised not to fast. [43]

One limitation of this review is the exclusive search for studies published in the literature. If any investigators did not publish negative results, their studies would have been missed by the search strategy for this review. The inclusion of results from articles that were not the main outcomes of their respective studies protects against this bias.

Conclusions

Patients with stable controlled cardiac disease may fast during the month of Ramadan since most studies show no significant adverse effect of fasting on these patients. Physician consultation and monitoring is highly advised in these patients before and during the fast. Adhering to prescribed medications, a strict diet, drinking fluids and increasing physical activity is highly advised. Diabetic and hypertensive patients with stable cardiac disease must be monitored closely and must commit to controlling glycaemia, blood pressure, and lipid levels during the fast.

Declarations of interest

The authors declare no conflict of interest.

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The authors state that they abide by the authors’ responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal [44].

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Acute Interventional Management of Spontaneous Coronary Artery Dissection: Case Series and Literature Review.

Enrico Cerrato¹, Ilaria Meynet², Giorgio Quadri¹, Federico Giacobbe⁴, Cristina Rolfo¹, Francesco Tomassini¹, Fabio Ferrari¹, Fabio Mariani¹, Luca Lo Savio², Matteo Bianco³, Paola Desteфанis³, Alessia Luciano³, Carol Gravinese⁴, Emanuele Tizzani², Sara Giolitto², Antonella Corleto², Fabrizio D’Ascenzo⁴, Umberto Barbero⁵, Fernando Macaya⁶, Javier Escaned⁶, Roberto Pozzi³, Ferdinando Varbella¹

1. Interventional Cardiology, San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Turin, Italy
2. Division of Cardiology, Rivoli Infermi Hospital, Rivoli, (Turin), Italy
3. Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Italy
4. University of Turin, Città della Salute e della Scienze di Torino⁴, Division of Cardiology, Turin, Italy
5. Division of Cardiology, SS. Annunziata Savigliano - ASL CN1, Savigliano (CN), Italy
6. Interventional Cardiology, Hospital Clinico San Carlos, Madrid, Spain

Corresponding author:
Enrico Cerrato,
Interventional Cardiology
San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Turin, Italy.
E-mail: enrico.cerrato@gmail.com

Abstract

Spontaneous coronary artery dissection (SCAD) treatment is currently a matter of debate as scarce data are available for the interventional cardiologists. In the present review we introduce four representative clinical scenarios in which different interventional strategies were carried out. Subsequently, we discuss different tools and useful techniques for the treatment of SCAD, presenting the advantages and drawbacks of the conservative approach versus percutaneous coronary intervention (PCI) with Drug Eluting Stent (DES) or bioresorbable scaffolds implantation, and/or cutting balloon angioplasty.

Keywords: Interventional cardiology; Coronary artery disease; Vascular disease; Spontaneous coronary artery dissection; Drug Eluting Stent; Bio-resorbable scaffolds.

Citation:

Introduction

Spontaneous Coronary Artery Dissection (SCAD) is an acute spontaneous separation between the layers of the coronary artery wall, causing the formation of a false lumen with or without intimal rupture. By definition, this should not be related to external trauma, direct instrumentation (iatrogenesis) nor complicated atherosclerosis[1,2]. The dissection can both act as an obstacle for the blood flow and as a path for clot activation.

SCAD is an important cause of myocardial infarction, though probably under-diagnosed. The incidence of SCAD in consecutive angiographic case series ranges between 0.07 and 0.2%[1,2] and rises up to 2-4%[2,3] in the coronary angiographies performed during acute coronary syndromes. Importantly, it has been reported to underlie 35% of myocardial infarctions in young female populations[3]. Generally, patients suffering SCAD show a smaller burden of coronary risk factors and are younger in age than the typical patients affected by atherosclerotic acute coronary syndromes[4,5].

There is still lack of consensus concerning the best treatment for SCAD; a couple of studies have reported outcomes of patients conservatively managed, treated with coronary angioplasty or with surgical coronary by-pass graft. However, no randomized trial is available, and the predictors of success for each of the therapeutic approaches are currently under investigation.

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* Corresponding author. E-mail: enrico.cerrato@gmail.com
In the present review we reported the experience with four SCAD cases treated with different approaches that illustrate the array of strategies that are currently available.

**A case conservatively managed**

A 45-year-old woman with no cardiovascular risk factors and a familial history of Ehler-Danlos syndrome was admitted for chest pain with transient Electrocardiogram (EKG) inferior ST-Elevation. Coronary angiogram showed a severe and long narrowing from the proximal to the mid-distal segments of the right coronary artery (RCA), compatible with an angiographic type 2b SCAD pattern (according to the latest classification proposed[1], with TIMI 3 FLOW (Figure 1, Panel A). Given her clinical stability, she was deemed suitable for conservative management. The patient developed EKG and echocardiographic signs of limited inferior necrosis, but was asymptomatic and had preserved a normal Ejection Fraction (EF). A surveillance scheduled coronary angiogram performed 1 week later showed a normal coronary artery suggesting the complete reabsorption of intramural haematoma (Figure 1, Panel B). Single antiplatelet therapy with acetylsalicylic acid was prescribed. Patient remains asymptomatic after more than 2 years of clinical follow-up.

**A case treated with drug eluting stents.**

A 42-year-old woman on estrogenic hormonal therapy and a history of multiple sclerosis treated with interferon presented with anterior ST-elevation myocardial infarction (STEMI). Emergent coronary angiogram showed spontaneous dissection of distal left anterior descending (LAD) (Figure 2, Panel A, left), which was subsequently complicated by a superimposed iatrogenic dissection of left main, proximal LAD and proximal Cx artery with severe hemodynamic impairment (Figure 2, Panel A, right). Percutaneous coronary intervention (PCI) was performed with implantation of 6 drug eluting stents (total stent length = 140mm) involving Left Main (LM), LAD and proximal Circumflex (LCX) (Figure 2, Panel B). The patient was discharged asymptomatic, with a moderate reduction of EF. After few months a myocardial Single-Photon Emission Computed Tomography (SPECT) demonstrated no inducible ischemia. Three years later, the patient was hospitalized with a diagnosis of non ST-Elevation Myocardial Infarction (NSTEMI) due to a diffuse spontaneous dissection of LCX and obtuse marginal (OM) branch downstream from the previous stenting (Figure 2, Panel C). The patient was stable and therefore was conservatively managed. Long-term dual antiplatelet therapy (DAPT) was prescribed and interrupted 2 years after because of menorrhagia, metrorrhagia causing anaemia. She is to date asymptomatic after approximately 3 years from the latest dissection.

**A case treated with bio-reabsorbable scaffolds.**

A 45-year-old hypertensive woman was admitted for NSTEMI. The coronary angiography showed type 2-3 spontaneous coronary dissection in mid-LAD with TIMI flow grade 3 (Figure 3, Panel A). Although an initial conservative approach was adopted, the patient experienced recurrent chest pain and developed EKG signs of acute asymptomatic anterior ischemia in the fifth day of hospitalisation. Coronary angiography was repeated, showing significant worsening of the LAD narrowing, causing sub-occlusion of true lumen (Figure 3, Panel B). PCI was performed under Optical Coherence Tomography (OCT) imaging guidance with successful implantation of two overlapped magnesium-made bio-reabsorbable scaffold (Figure 3, Panel C). After a few days asymptomatic, the patient was discharged and prescribed at least three years of DAPT. Surveillance angiogram showed a good angiographic and imaging outcome.
A case treated with cutting balloon.

A 50-year-old woman with no cardiovascular risk factors was admitted with an anterior STEMI. The coronary angiography showed spontaneous dissection of distal LAD. After successfully wiring the distal vessel, several dilatations with a 3.0/10mm cutting balloon at 12 atmospheres were performed (Figure 4, Panel A). Because of the absence of symptoms and TIMI 3 flow after dilatation, the operator opted to avoid stenting. The good result achieved in the acute phase (persistence of dissection flap but preserved flow) was confirmed with elective coronary angiography after both one week and one year (Figure 4, Panel B). The patient was discharged with EF 40% and with indication for one year of Dual Antiplatelet Therapy DAPT.

Treatment options in SCAD management

Conservative strategy

No randomized trials comparing conservative versus interventional strategies have ever been carried out so far in SCAD. The challenge of conducting such studies is due to the low incidence of the disease plus the varied severity of clinical presentations.

Today the available literature shows that the therapeutic strategy is conditioned by clinical presentation and stability, coupled with angiographic characteristics (site and extension of dissection or TIMI flow)[6]. The fact that PCI in SCAD is burdened with a high complication rate favours a conservative approach over a revascularisation strategy (either PCI or Coronary Artery Bypass Grafting) whenever clinically possible (i.e. stable patient without ongoing ischaemia).

Furthermore, there is a general understanding that, with a conservative treatment, dissections tend to heal completely over a certain period of time: with angiographic evidence from about 1 month after the acute episode[2,3,7]. Therefore, when revascularization is not required (i.e. in hemodynamically stable patient) the conservative management should be the first choice for these patients.

As mentioned above, revascularization is associated with high rates of failure and complications, likely due to an exaggerated vessel fragility[1,2,8]. This includes the risk of catheter-induced iatrogenic dissection of proximal-ostial locations, which may lead to serious clinical consequences and complex interventions (Figure 5).

Additionally, patients receiving a conservative strategy showed better in-hospital outcomes compared to the ones receiving revascularization, though similar long-term outcomes [4,6]. Distal location of the dissection and TIMI flow II or III may be considered predictive factors to favour the adoption of a conservative approach[6].

Nevertheless, our group recently highlighted the unpredictability of SCAD and the importance of a close clinical surveillance following an initial conservative strategy. In this case series[8], among four patients with similar angiographic and clinical presentation, two cases experienced a malignant evolution with need of emergent PCI and extensive stenting (including left main) while in the other two cases complete angiographic healing was demonstrated in follow-up angiograms.

Revascularisation should be reserved for high-risk patients with ongoing ischemia, left main artery dissection, ventricular arrhythmias or hemodynamic instability

Percutaneous Coronary Intervention

Procedural success of PCI in SCAD is dramatically low compared to that in the atherosclerotic population. The main studies assessing the role of PCI have shown a high rate of complications and unfavourable outcomes[10]. For an optimal procedural planification, careful assessment of the involved segment (proximal vs distal), lesion length and vessel sizing is mandatory in order to consider all potential challenges and feasibility.
Since SCAD is a disease related to the weakening of the arterial wall, entering the true lumen with a guidewire is quite challenging. Consequently, PCI may easily lead to iatrogenic dissection or may provoke propagation of the existing one. Furthermore, even when true lumen is appropriately wired, the subsequent implantation of stent may determine the “squeezing” of the intramural hematoma (with possible extension of the dissection itself) and increase the risk of in-stent restenosis and stent thrombosis.

In an Italian series of 134 SCAD patients where successful PCI was achieved in 72.5%, patients treated conservatively had lower in-hospital major cardiac adverse events (MACEs) compared with those treated with revascularization (3.8% vs. 16.1%)[6]. Likewise, in the Mayo Clinic series of 189 patients, PCI failure occurred in 53%, and emergency CABG was required in 13%[8,10].

Wiring of the true lumen distal to the dissection site is probably the most challenging part of the procedure. As a first-line approach, we suggest using floppy non-plastic wires to navigate in the true lumen compressed by the intramural hematoma. If the wire fails to advance into the true lumen, especially in the case of complete occlusion of the vessel, hydrophilic wires could be used in order to facilitate distal re-entry in the true lumen. A distal tip microcatheter injection is often necessary to confirm correct position in the true lumen before any balloon dilation (Figure 6). IVUS guidance may be employed to identify the false lumen and ensure correct wire placement within the true lumen. Likewise, IVUS will be useful for stent sizing. In fact, choosing the right length and dimension of the stent represents the next challenge. The distal coronary segments are the most frequently affected and these may be too small for stenting. Moreover, haematoma resorption could lead to late stent malapposition (stent under-sizing).

Drug Eluting Stents

Today Drug Eluting Stents (DES) are considered the standard of care for the invasive treatment of the atherosclerotic disease. However, in the past years, doubts about DES use in patients with SCAD were raised[11]. As a matter of fact, DES reduce the risk of neointimal growth, but on the other side they may potentially delay the healing of the dissected vessel. Recently, a large observational study compared the use of DES against Bare Metal Stent (BMS) and demonstrated the same advantages of DES observed in atherosclerotic disease over BMS even in patients with SCAD [12].

In any case, when a stent is to be implanted, less conventional interventional approaches can be considered to reduce the number of adverse outcomes[1–3,13]:

- Extended stent lengths to cover the intramural haematoma (IMH) borders to reduce the chances of proximal or distal propagation. Some authors[2] suggested to exceed at least 5 mm the dissection edges
- Sealing firstly the proximal and distal extremes of the affected segments with short stents to constrain haematoma before stenting the middle segment (sandwich technique)[14].
- Targeting an intimal tear for focal stenting or stenting just the proximal segment of the dissection to prevent proximal propagation.
- High-pressure dilation or post-dilation pursuing optimal stent deployment should be avoided to prevent iatrogenic propagation
- In cases of highly-compressive IMH, consider the use of cutting balloon prior to stent deployment (hybrid PCI)
- Consider optimising stent implantation in a staged procedure (allowing vessel remodelling/healing)

Bio-resorbable Scaffolds

When approaching a long dissected segment, operators usually prefer to implant long/multiple overlapped stents in order to cover the entire dissected segment. However, this exposes these generally young patients to the lifelong risk of restenosis and thrombosis[15].

For this reason, Bio-resorbable scaffolds (BRS) were proposed for the treatment of SCAD[16,17] in several case series in which biodegradable Absorb™ device was used[18,19] (Abbott Vascular, Abbott Park, Illinois). Recently, the first case of use of BRS Magnesium Made Magmaris (BIOTRONIK, Buelach, Switzerland) Scaffold for SCAD treatment was also reported by our group[20,21].

The use of biodegradable coronary scaffolds could be advantageous as there is general evidence that the temporary presence of the scaffold could reduce the risk of late maladjustment and thrombosis after resorption of IMH[20]. BRS provide a temporary support to seal the dissection and would potentially allow complete vessel healing over time. Coronary arteries affected by spontaneous dissection are usually free from hard plaque or heavy calcification which makes easier a full expansion of the scaffold avoiding the need for aggressive pre- and post-dilation, strongly recommended for BRS in atherosclerotic vessels. Moreover, BRS compared to permanent metallic DES could potentially reduce the risk of malapposition after IMH reabsorption. BRS are also useful when a long scaffolding is demanding, especially considering the young age of these patients.

Nevertheless, some drawbacks must be underscored. Firstly, the initial enthusiasm kept on these devices has been tempered by clinical trials showing an increased risk of target lesion failure, both early and late after implantation of first-generation Absorb™ in comparison to DES[22]. Newer generation of scaffolds with faster reabsorption process and improved platforms will probably overcome these issues in the future even avoiding the risk of...
prolonging DAPT over time in such patients. Moreover, most of the failure burden of BRS derives from the use of it in small-calibre vessels (2.5mm)[23]. As a matter of fact, such vessels are usually managed conservatively in SCAD. Finally, intracoronary imaging meticulous guidance should be central in any BRS implantation to achieve a satisfactory deployment and avoid complications.

Cutting Balloon
An alternative to deploy a stent/scaffold is to use cutting balloon only leaving the vessel prosthesis-free. The experience with such device is still limited to case reports, but the concept is very intriguing[24]. The basis derives from the potential to fenestrate the intimal-medial layer and depressurize the false lumen, restoring flow and alleviating acute ischaemia. Conversely, there is a theoretical potential risk of coronary rupture, thus the use of an undersized balloon is probably a reasonable option.

Less conventional interventional approaches
Among other specific devices, a rationale for the use of self-expandable stent (SES) has been recently proposed. Basically, SES could potentially overcome the risk of late malapposition of the struts (due to the underestimation of the vessel caliber) finalizing the expansion of the stent once the IMH reabsorption is completed. However the role of SES is limited to the best of our knowledge to a single case report[25].

Role of intravascular imaging in SCAD treatment
Use of intravascular imaging techniques (IntraVascular Ultra Sound (IVUS) or Optical Coherent Tomography (OCT)) plays a relevant role in confirming SCAD diagnosis when angiographic appearance is ambiguous. But more importantly, it probably should be an essential tool to guide PCI[2]. As discussed previously, imaging is helpful to prove the correct position of the intracoronary wire; to accurately size the lumen in order to choose the right dimensions of the stent; to verify the complete stent apposition and the whole coverage of the disease and potentially to show coexistent atherosclerosis or other vascular disorder. On the other hand, extraordinary costs and availability may limit the use of intravascular imaging techniques. Moreover, requirement of anticoagulation could provoke haematoma extension. Last but not least, vessel instrumentation can produce iatrogenic damage and superimposed dissections, as a consequence of the wire, the guiding catheter or the contrast infusion in case of OCT. In a single-centre study, some degree of iatrogenic damage was seen in a fifth of the cases where intracoronary imaging was used for diagnosing SCAD, which led to unplanned PCI in most of them[26].

Conclusions
SCAD represents today a coronary condition with unique pathophysiological characteristics clearly different from the common atherosclerosis. Therefore, when a PCI strategy is preferred, a tailored approach is required taking advantages from extensive use of imaging whenever it is feasible. Finally new technologies answer generations of scaffold has to keep in mind in order to avoid a permanent extensive stenting of an artery usually free from atherosclerosis and with a good chance of complete healing over time. However, dedicated trial should be conducted to define their safety and effectiveness in long term.

Definitions of interest
Enrico Cerrato received speaker fee in educational events supported by BIOTRONIK, ABBOTT, VOLCANO and a research grant from AstraZeneca.
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Fabio Ferrari and Fabio Mariani received speaker fee in educational events supported by BIOTRONIK and BAYER.
Javier Escaned received speaker fee at educational events and a consultant for BOSTON SCIENTIFIC, PHILIPS VOLCANO.
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Bibliometric Analysis of Cardiovascular Disease Research Activity in the Arab World

Hussein H. Khachfe¹, Marwan Refaat²

1. Faculty of Medicine, American University of Beirut
2. Department of Internal Medicine (Cardiology Division), American University of Beirut Medical Center, Beirut, Lebanon, mr48@aub.edu.lb.

Corresponding author:
Marwan Refaat,
Department of Internal Medicine (Cardiology Division), American University of Beirut Medical Center, Beirut, Lebanon
Email: mr48@aub.edu.lb

Abstract

Background and Objectives
There is an increased number of non-communicable diseases i.e. chronic disease such as cancer, chronic respiratory diseases, diabetes and cardiovascular diseases in the Arab World. In this article, we will be aiming to measure the activity of cardiovascular disease (CVD) research via publications that have been released in the Arab World over the last 15 years.

Methods
Search using Medline (via Ovid and PubMed) and EMBASE was used for this study. Publications related to cardiology/cardiovascular disease according to author origin/affiliation were collected from the 22 Arab countries between 2002 and 2016 (inclusive).

Results
The Arab world only produced 1% of the total percentage of CVD publications over the interval of our study. There was however, an increase in the number of publications in recent years. Qatar and Lebanon had the highest ratio for CVD to Non-CVD publications released. Qatar had the highest number of publications per million persons. Tunisia had the highest number of publications per GDP (in US Billion Dollars).

Conclusions
Overall, the Arab countries still lag behind other parts of the world in terms of CVD research activity. Five countries are responsible for the majority of publications.

Keywords: Cardiovascular disease, Cardiology, bibliometrics, Arab world, Medline, PubMed, Ovid, EMBASE

Citation:

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Introduction
The Arab world is comprised of 22 countries spread over the span of the Middle East and different parts of Africa [1]. As is the case globally, cardiovascular diseases (CVDs) are the leading causes of death in the Arab world. Approximately 17.7 million people died from cardiovascular related incidents in 2015, representing 31% of all global deaths [2]. Of these deaths, around 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. From 17 million deaths of people under 70 years of age (premature deaths) due to chronic diseases in 2015, 37% are caused by cardiovascular diseases [3].

In the Arab world, cardiovascular diseases are increasing at an accelerated rate due to the unhealthy lifestyles people in the Arab countries are leading. Excessive use of tobacco, unhealthy diets, lack of exercise, damaging consumption of alcohol and obesity are the main causes of these cardiovascular diseases [4].

Of all the Arab countries, the gulf region in general and the children there in specific are the most prone to developing CVDs according the World Heart Federation [5]. This is because of the rapid urbanization that has and is still occurring in the Gulf region which is causing packed living conditions for citizens, limitations on green spaces, increased water and air pollution, growing use of tobacco and narcotics and increased consumption of alcohol and fast-food, all of which increase the risk of cardiovascular diseases. Another critical risk factor for developing cardiovascular diseases is malnutrition. Yemen for example is recording the second highest rate of chronic malnutrition among children in...
the world lagging just behind Afghanistan. Also, 6.8% of children under five years of age are malnourished in Egypt [6].

The Institute for Health Metrics and Evaluation (IHME) has showed that the top leading cause of the death in the Arab world is CVDs [7]. Therefore, research in the Arab world concerning this topic is a top priority. In this article, we will be aiming to examine the activity of published cardiology and cardiovascular diseases related research in the Arab world. In particular, we will be dissecting the number of publications released on CVDs per country by checking the author location according to institutional affiliation.

Methods

The PubMed database of the National Center for Biotechnology Information (NCBI), Ovid and EMBASE databases were used to find the publications related to this study. Publications were identified by searching for the terms “Cardiovascular diseases” and “Cardiovascular” in the search field using MeSH (Medical Subject Headings) in PubMed and similar filters in Ovid and EMBASE.

In PubMed, papers from countries were then identified by using the Boolean operator (AND, OR and NOT) to find and exclude articles related to cardiovascular diseases and country of origin. To do so, we searched for publications with “cardiovascular diseases” as a heading and added the country of affiliation by using the operator “[ad]”. For example, to find publications on cardiovascular diseases in Algeria we inputted “Cardiovascular diseases [mesh] AND Algeria[ad]” into the search box of PubMed. To find all publications from Algeria disregarding cardiovascular disease related ones we used “Algeria[ad] NOT Cardiovascular diseases[mesh]”. Our search was filtered from 2002 to 2016 (inclusive) to find publications about CVDs specifically and all biomedical research in general from the past 15 years.

A similar process was performed in Ovid and EMBASE to extract publications from the two databases. The publications were imported to EndNote where they were filtered to avoid any occurrence of duplicates.

To find the number of publications per gross domestic product we divided the number of publications by the GDP in USD [8]. To find the ratio of publications per population size, we divided the number of publications by the population size in million persons [9].

Results

The population estimates and gross domestic products (GDP) of the 22 Arab countries are shown in table 1. In the selected year period of our study (2002-2016) 1,032,862 publications on cardiovascular diseases were released on the three databases. Of those, 10,496 publications were from the Arab world comprising only 1%. The ratios of CVD related to Non-CVD publications ranged from 0.031 (Algeria) and 0.033 (Palestine/West Bank) to 0.125 (Qatar and Lebanon).

Saudi Arabia ranked first in the number of publications on cardiovascular diseases (Table 1) with 2678, while Somalia and Mauritania ranked last with only 4 and 3 publications respectively (Table 1).

To avoid overlap of publications from Lebanon (Arab country found in MENA region) and Lebanon County from Pennsylvania, search terms were refined to “Beirut”, “Tripoli Lebanon”, “Saida”, “Nabatieh” and “Zahlé”.

To avoid another type of bias which would be related to population size, we found the number of publications per million persons (PMP). This showed that Qatar (253) and Kuwait (187) ranked first and second, followed by Lebanon with 139 publications per million persons (Figure 1). Somalia with 0.03 ranked last (Figure 1).

As for bias regarding the GDP of each country, that was accounted for by finding the number of cardiovascular disease related publications per GDP (in US Billion Dollars). Tunisia (22) ranked first, followed by Lebanon 18 publications per billion US dollars (Figure 2). Somalia ranked last with 0.64 (Figure 2).

Discussion and Limitations

Our results showed that the Arab world only produced 10,496 out of a total of 1,032,862 publications on cardiovascular diseases globally over the past 15 years. This is equivalent to only 1% of the total percentage of CVD related publications released on PubMed, OVID and EMBASE. The trend of the publications released shows an increase in the number of publications over the past 15 years in the Arab world. These results are similar to another study that showed a 36% increase in global CVD publications from 1998 to 2008 [10].

Despite these results the Arab world still lags greatly behind other regions of the world. There may be a great number of factors that are causing this underrepresentation of cardiovascular disease publications from Arab countries.

Figure 1
Cardiovascular disease related publications per million persons per country.

Figure 2
Cardiovascular disease related publications per Average GDP (US Billion Dollars) per country.
First, we could start off with the orientation of schools and universities in the region to molding physicians into purely clinical professionals with no regard to academia (research). Such orientation from the educational system is decreasing medical students’ interest in conducting research, which is decreasing the number of publications compared to the Western world where research is regarded as a priority [11].

Another factor would be the lack of funding in most Arab countries. Disregarding countries of the Gulf Cooperation Council (GCC), there is an extreme lack of funds present for research and this is causing a huge decline in the research activity of the Arab world [12,13].

The lack of proper research facilities is also a problem Arab countries face [14]. To solve this, we would need collaboration between the Arab countries as we have a diversity in resources. Some funding agencies run by wealthy Arab countries could help research facilities to pave way for more research activity in other parts of the Arab world. Another source of this underrepresentation could be bias from some journals towards the publishing of local research publications rather than international ones.

Also, with the great deal of political instabilities present in the Arab world, clinical research faced a great number of obstacles [15]. From political uprisings, such as the Arab Spring earlier in 2011, to the Syrian Civil War in 2011, and events such as those present in Yemen, Bahrain and Palestine, the Arab world is facing a great deal of brain drain from the West as well as a lack of funds because of these political feuds that are occurring, decreasing the amount of funds available for research [16-20].

With cardiovascular diseases being the number one cause mortality worldwide, it becomes very clear that further research in this field must be done. Increased awareness about the amount of deaths and different types complications occurring because of cardiovascular diseases would cause a greater allocation of funds dedicated for academic research concerning cardiovascular disease.

It is still extremely encouraging and impressive to see that in light of all these reasons mentioned above, there is still a growth in cardiovascular disease research in the Arab World.

<table>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>846,687</td>
<td>1,727,000,000(2015)</td>
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<tr>
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<td>39</td>
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<td>920</td>
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Note: The above numbers were retrieved from PubMed, Ovid and EMBASE.
*GDP is in current USD.
**Numbers from 2011 i.e. Beginning of Syrian War of 2011
Note: Population estimates were retrieved from CIA World Factbook and GDPs were retrieved from World Bank.
There are some limitations in our study. First, although we made use of three of the biggest medical databases (PubMed, Ovid, EMBASE) there still might be publications that were not in our scope. Second, we were dependent on the indexing operators of the databases used, as is the case in any other bibliometric study. Third, since we could not pinpoint the real geographical location of the corresponding author, we were limited with the institutional affiliation ([ad] function on PubMed or author affiliation filter on Ovid and EMBASE) to find the publications from each country. Fourth, in our search we only used the terms “cardiovascular disease” and “cardiovascular”, maybe more results could have appeared if we had used the search items “heart disease”, “coronary artery disease”, “myocardial infarction”, “cardiac death”, “valve disease” for example.

The final limitation we faced is that all the publications we gathered were in the English language. A great deal of publications from the Arab world are released in French and Arabic, especially in the Middle East and Northern African (MENA) region. This could have caused an underestimation of the number of publications released by each country and consequently the total number of CVD publications from the Arab world.

Conclusions
This the first bibliometric analysis of cardiovascular disease research activity in the Arab world. Although we are witnessing an increase of CVD publications in recent years, Arab countries are still lagging far behind in CVD research compared to the Western and other regions of the world. Knowing that CVDs are the main cause of deaths globally and in the Arab world specifically, it would be expected that research activity must increase with time. Five out of twenty-two Arab countries are mostly responsible for the majority of publications in the Arab world. These countries are Egypt, Lebanon, Qatar, Saudi Arabia, and Tunisia. With the increase of funding being allocated to research, especially in the Gulf area and the shift in orientation towards clinical research, it is expected that the research activity in the Arab world should increase and yield more high-quality publications. Specifically, the Gulf will see noteworthy research productivity in the years to come.

Declarations of interest
The authors declare no conflict of interest.

Acknowledgments
The authors state that they abide by the authors’ responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal. [21]

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Association Between ApoE Polymorphism in Obesity Markers in Healthy Adults Who Follow the Greek Orthodox Fasting Rules

Alexandra A. Koulouri1, Sousana K. Papadopoulou1, Dimitrios Loukovitis2, Nikolaos Rodopaios1, Eleni Vasara3, Maria Hassapidou1, Fani Biskanaki4, Dimitrios Tasoulas, Dimitrios5, Elias Tassoulas6, Andrew J.S. Coats7, Anthony Kafatos8

1. Department of Nutrition and Dietetics, Alexander Technological and Educational Institute of Thessaloniki, Thessaloniki, Greece
2. Department of Animal Production, School of Agricultural Technology, Technological Educational Institute of Thessaloniki, Thessaloniki, Greece
3. Laboratory of Animal Physiology, Department of Zoology, School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece
4. First Gymnasium of Arta, Greece
5. Internal Medicine Department of Arta General Hospital, Greece
6 3 Philippou Manolaki Street, Arta GR 47132, Greece
7. IRCCS, San Raffaele Pisana, Rome, Italy
8. Department of Social Medicine, Preventive Medicine and Nutrition Clinic, Medical School, University of Crete, Heraklion, Crete, Greece

Corresponding author:
Dr. Elias Tassoulas
3 Philippou Manolaki Street, Arta GR 47132, Greece.
Email: eltassou@otenet.gr

Abstract

Aim
Apolipoprotein E (ApoE) is one of the major triglyceride-rich lipoproteins, which acts as a genetic determinate of cardiovascular disease (CVD). A common polymorphism in this gene codes for 3 isoforms E2, E3 and E4 with equivalent allele ε2, ε3 and ε4, located on chromosome 19. Three alleles of apoE gene, e2, e3, and e4, are responsible for the major ApoE isoforms: ApoE2, ApoE3, and ApoE4. The ApoE phenotype has been reported to be the strongest genetic factor that affects serum lipid and lipoprotein concentrations, as well as influencing anthropometric parameters including obesity risk.

Methods
This case control study of randomly selected, free living individuals from North Greece investigated whether traditional Greek Orthodox dietary practices could affect obesity markers independent of genetic influences, by examining the association between ApoE genetic polymorphisms and BMI. Waist circumference (WC), waist hip ratio (WHR) and % fat mass (% FM), were measured in healthy adults who follow the rules of Greek Orthodox fasting compared to those who did not. 382 subjects (246 women and 136 men) were included in the analysis, 161 fasters and 220 non-fasters as a control group.

Results
Age affected obesity markers in all participants with more obesity in the older subjects. ApoE alleles did not differ between fasting and controls. When fasters where classified as obese and non-obese, there was no association with age (p>0.077). In the control group, BMI and WC were associated with age and gender and WHR with apoE alleles (p<0.001). In the fasting group these correlations are not observed (p=0.545 and p=0.365 respectively). In addition two-way ANOVA, including multiple comparison testing, demonstrated interactions between independent variables (sex, age apoE alleles and fasting status) and their influence on BMI, %BF and WHR. ApoE alleles and age significantly influence WHR (p=0.014). Between the three alleles statistically significant differences in WHR is observed only in the young participants; mean±SD is 0.82±0.08, 0.86±0.1 and 0.81±0.09 in E2, E3 and E4 carrier, respectively (p=0.04). Possibly Apo E4 showed a protective role against the increase of WHR, but age counterbalanced this effect.
Introduction

Obesity is a significant problem and is considered to have epidemic dimensions worldwide. Obesity constitutes a central risk factor for atherosclerotic CVD development and progression because of its association with many other cardiovascular risk factors [1,2]. According to the IDEA study, waist circumference is a strong predictor of CVD, stronger than BMI [3] and independently of the relationship that BMI has with CVD risk [4]. For that reason it is important to understand the pathogenesis of adiposity and its relationship with metabolic risk and cardiovascular disease. Apolipoprotein E (ApoE) is one of major triglyceride-rich lipoproteins. It is a 34 kDa circulating protein which associates with chylomicron remnants, very low density lipoproteins and high density lipoproteins. ApoE is the main ligand for the binding to their receptors [5].

ApoE is a foundational component of all lipoprotein particles apart from LDL and it works as a high-affinity ligand for lipoprotein receptors. It seems to be a genetic determinant of CVD since it influences factors which are related to obesity and lipid profiles [6]. ApoE4 is a risk factor for Alzheimer’s and cardiovascular disease [7]. ApoE alleles determine the risk of Alzheimer disease, atherosclerosis and the efficiency of dyslipidaemia therapy [8].

Apolipoprotein E genes are of critical importance in cholesterol and TG metabolism. A common polymorphism in this gene codes for 3 isoforms E2, E3 and E4 with equivalent allele ε2, ε3 and ε4, located on chromosome 19. Numerous studies have found that ε4 is associated with a higher risk of CVD in males and females. Three alleles of apoE gene, ε2, ε3, and ε4, are responsible for the major ApoE isoforms: ApoE2, ApoE3, and ApoE4, with respective allele frequencies of 10, 75, and 15% [8]. ApoE3 is the most common one in the Caucasian population [9,6,7].

The effect of genetic polymorphism in the ApoE gene has shown to have effects on lipid profiles and cardiovascular risk in adults [10]. The ApoE phenotype has been reported to be the strongest genetic factor that affects serum lipid and lipoprotein concentrations. It has been estimated to account for 16% of the genetic variation in serum LDL-cholesterol levels [11].

It has been shown that ApoE polymorphism also influences anthropometric parameters [12] such as adiposity in all genotypes, and it has variable effects in different ethnic groups [13], but it is more definite in ε2 homozygote patients [14]. Other researchers state that there is a certain point of fat accumulation where ApoE plays a role in adipose functionality [5].

Materials and methods

2.1. Study population

This is a case control study. All participants were randomly selected, free living individuals from North Greece. They were all healthy and free of any thyroid or metabolic disorders requiring treatment such as hypothyroidism, diabetes, hypertension, severe dyslipidemia, and coronary heart disease. Each participant was interviewed by a Registered Dietician in order to ensure that fasting rules according to COC was followed [15]. They were
DNA amplification was performed on a 2720 thermal cycler through dilution with distilled water and arrayed into 96-well plates. The DNA concentration of each sample was adjusted to 20 ng/μl using a NanoDrop 1000 Spectrophotometer (Thermo Scientific). The quality and quantity of DNA were checked using the PureLink Genomic DNA Mini Kit (Invitrogen by Life Technologies). Each patient underwent anthropometric measurements, and biochemical examinations on the same day. Height was measured to the nearest 0.5 cm with a stadiometer, with an accuracy of 0.5 cm (SECA 220, Seca Corporation, Columbia, USA). Body weight was measured using a regular calibrated digital scale with an accuracy of ±100g (Seca 707, Seca Corporation, Columbia, USA). Body mass index (BMI) was defined as the individual's body mass divided by the square of height (kg/m2).

Waist circumference (WC) was measured between the top of the iliac crest and the bottom of the rib margin, at the end of gentle expiration. Hip circumference (HC) was measured over the maximum posterior extension of the trochanters. Circumferences were measured with a tape to the nearest 0.1 cm over the naked skin. The Waist to Hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm).

Blood samples were drawn after a minimum 8-hour overnight fast, collected in EDTA-containing tubes, and centrifuged at 3,000 rpm for 20 minutes (Hanil Science Industrial Co., Ltd, Seoul, Korea). All samples were stored at -80°C.

2.2 Ethics Statement
The study protocol was approved by the Committee of the Technological institution of Thessaloniki. At the beginning of the study all subjects gave written informed consent for participation.

2.3 Body composition
Body composition was determined by Dual energy X-ray Absorptiometry (DXA). Fat mass (FM) and fat-free mass (FFM) were calculated with Lunar DPX Bravo equations, using a Lunar Prodigy Full Oracle (GE Healthcare, enCore software version 13.2). Body composition (fat mass, fat-free soft tissue mass) was obtained according to standard procedures, by trained personnel. All participants were scanned in light clothing lying at on their back and with arms by their sides. The two discrete energies X-rays that the scanner detects is 140 keV and 70 keV. This allows two components to be distinguished in those pixels that do not contain bone, fat and fat-free tissue [19]. Fat mass and fat-free mass were expressed in kilograms.

2.4 DNA extraction and genotyping
Genomic DNA was isolated from frozen whole blood, using the PureLink Genomic DNA Mini Kit (Invitrogen by Life Technologies). The quality and quantity of DNA were checked using a NanoDrop 1000 Spectrophotometer (Thermo Scientific). The DNA concentration of each sample was adjusted to 20 ng/μl through dilution with distilled water and arrayed into 96-well PCR plates.

DNA amplification was performed on a 2720 thermal cycler (Applied Biosystems) using the AmpliTaq Gold® 360 Master Mix (Applied Biosystems) with the following primers: P3-apoE: 5′-CTCGGGATGGCGCTGAGG and P5-apoE: 5′-CGGGCACGCGCTGCAAGG. PCR (total volume 25 μl) cycling conditions were as follows: 5 minutes at 95°C for DNA denaturation, 35 cycles (60 sec at 95°C (denaturation), 45 sec at 65°C (annealing), and 120 sec at 72°C (extension)), and finally 10 minutes at 72°C. Using the aforementioned primer combination, a 270 bp fragment of the Apo E gene was amplified, which encompasses the codons 112 and 158 containing the polymorphic sites. Post-PCR samples were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) on an ABI 3500 Genetic Analyzer (Applied Biosystems). Two SNPs, a C→T at codon 112 and a C→T at codon 158, were genotyped to identify the E2, E3 and E4 alleles in each sample.

2.5 Data analysis
Continuous variables (BMI, %BF, WC and WHR) are expressed as mean±SD. The normality of the distribution of continuous variables was tested by the Kolmogorov-Smirnov test. Categorical variables are expressed as percentage. ApoE alleles frequencies were calculated from genotype frequencies. Hardy-Weinberg equilibrium was assessed using the χ2 test.

World Health Organization standards were used for BMI categorization: normal weight: <25 kg/m2, overweight: 25 - 29.9 kg/m2 and obese: >30 kg/m2. Abdominal obesity was described as waist circumference more than 102 cm in men and 88 cm in women. WHR values above 0.9 for men and 0.8 for women, respectively, defined also abdominal obesity. Body fat status was evaluated according to age and sex of the participants [20,21].

Chi square2 tests were used in order to assess association among categorical variables concerning BMI, %BF, WC, WHR and the independent variables (age, sex, mode of nutrition, ApoE alleles). In order to further analyse the possibility of associations, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) binary or multinomial logistic regression models were used.

T-test and analysis of variance tests were used to compare the mean values of continuous variables between two groups or across groups, respectively. In order to assess if there is any interaction between the independent variables (sex, age, mode of nutrition, ApoE alleles) on obesity indices (BMI, %BF, WC, WHR), two-way Anova with Bonferroni multiple comparison tests were used.

For all comparisons p-value<0.05 was considered to be statistically significant. Statistical analysis was performed with SPSS statistical software package version 20, IBM (SPSS Inc. Chicago, IL, USA).

Results
ApoE genotypes were clustered into three groups: ApoE2 (carriers of the E2/2 and the E2/3 genotype), ApoE3 (carriers of the E3/3 genotype) and ApoE4 (carriers of the E3/4 and the E4/4 genotype). The E2/2 combination was found only in one sample (0.3%) and it was excluded. As it was expected, the most frequent allele was ApoE3, followed by ApoE4 and ApoE2 (Table 1).
Table 2 shows, no significant difference between the sexes (p=0.379) (using Pearson Chi Square test) regarding the allelic distribution. The genotype distribution was in Hardy-Weinberg equilibrium (x²=5.77; p=0.05).

Table 3 shows the baseline characteristics of the population. BF is higher while WC and WHR are lower in women compared to men independent of fasting status. However BMI values are smaller in women compared to men only in the controls. BMI did not differ significantly between sexes in the fasting group.

Age affected obesity markers in all participants. In both fasters and controls, mean values of all studied obesity indexes are significant lower in younger than in older participants (p<0.001). The comparison of mean values of indexes across carriers of the different ApoE alleles didn’t show any significant difference in both fastings and controls.

χ² analysis identified that according to WC when the participants where classified as obese and non obese, there was no association with age (p>0.077). On the other hand in the control group, χ² analysis showed that all indexes were related to age while BMI and WC were also associated with sex (p=0.006 &p=0.01, respectively) and WHR with apoE alleles (p<0.001). In the fasters group these correlations are not observed (p=0.545 and p=0.365 respectively).

Table 4 shows the multiple logistic regressions evaluating the contribution between independent variables (sex, age, nutritional model, ApoE polymorphism) and obesity markers. In both groups participants ≤35 years old are less likely to be obese, according to their BMI (p<0.001 fasters καp<0.001 control) and according to their %BF (p<0.007 καp<0.008 respectively). In the control group, women compared to men were more likely to be normal weight rather than obese (p=0.001) according to BMI but, according to WC are more likely to have over normal values. In the fasting group, sex and age did not appear to have any influence (p=0.542, p=0.081 respectively). WHR in the young, fasters and non-fasters (p=0.645), in women fasters seem to have significantly higher %BF compared to the controls (p=0.002). ApoE alleles and age significantly influence WHR (p=0.014). Between the three alleles statistically significant differences in WHR is observed only in the young participants; mean±SD is 0.82±0.08, 0.86±0.1 and 0.81±0.09 in E2, E3 and E4 carrier, respectively (p=0.04). Possibly Apo E4 showed a protective role against the increase of WHR, but age counterbalanced this effect.

Discussion

In our study, the allelic frequencies were 9.5%, 78.8% and 11.8% respectively, for the APOE2, E3, and E4 allele. The distribution of ApoE genotypes in our study resembles the findings of the only previous study in Greek population [22]. Similarly, Caucasian populations had similar values (8%, 77% and 15%), while a Chinese population study showed values of 8.4%, 85.2% and 6.4% and a Japanese study showed 3.5%, 85.1% and 11.2% respectively [23]. Accordingly, in a Chinese population, the e2, e3, and e4 allelic frequencies were 8.3%, 83.4% and 8.3% for men and 8.7%, 82.9%, and 8.4% for women, respectively [24]. In an urban Tehran (Iran) population, frequencies of E2, E3, and E4 alleles were 9.7%, 73%, and 14.6%, respectively

Table 3. Anthropometric status of participants according to sex and fasting status.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N=136</td>
<td>Fasters N=56</td>
<td>Control N=80</td>
<td>Total N=136</td>
<td>Fasters N=105</td>
</tr>
<tr>
<td>BMI</td>
<td>27.30±s.18</td>
<td>27.17±s.46</td>
<td>27.40±s.39</td>
<td>26.29±5.00</td>
<td>26.72±4.64</td>
</tr>
<tr>
<td>%BF</td>
<td>28.41±s.68</td>
<td>28.02±s.45</td>
<td>28.69±s.15</td>
<td>40.69±s.25</td>
<td>42.62±s.99</td>
</tr>
<tr>
<td>WC</td>
<td>90.69±12.25</td>
<td>90.78±14.22</td>
<td>90.63±10.82</td>
<td>79.69±12.65</td>
<td>80.90±12.05</td>
</tr>
<tr>
<td>WHR</td>
<td>0.95±0.11</td>
<td>0.95±0.11</td>
<td>0.95±0.11</td>
<td>0.88±0.12</td>
<td>0.89±0.12</td>
</tr>
</tbody>
</table>

Table 1. Distribution of ApoE genotypes.

<table>
<thead>
<tr>
<th></th>
<th>Total sample N=382 (%)</th>
<th>Males N=146 (%)</th>
<th>Females N=236 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2/3</td>
<td>9.2 9.8 8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3/3</td>
<td>78.8 78.0 80.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3/4</td>
<td>11.5 12.2 10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2/2</td>
<td>0.3 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4/4</td>
<td>0.3 0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Distribution of ApoE alleles

<table>
<thead>
<tr>
<th></th>
<th>Total sample N=382 (%)</th>
<th>Males N=146 (%)</th>
<th>Females N=236 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>9.4 9.8 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td>78.8 78.0 80.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td>11.8 12.2 11.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Higher values for APOE4 presented in French-Canadians, where contribution of the APOE2, E3, and E4 allele found to be 6.9%, 69.1%, and 24.0%, respectively [25]. It is remarkable that frequency of the ApoE4 phenotype varies markedly around the world, but Finland has one of the highest prevalences [26]. As a result, Finnish men were 6.2% APOE2 carriers, 60.1% APOE3 carriers and 33.8% APOE4 carriers [27].

In our study population, the obesity and overweight rates (according to BMI classification) were very high (66.9% men and 55.3% women). Based on WHR, those at risk for abdominal obesity were found to be 73.5% of men and 73.4% of women. Based on WC, abdominal obese and at risk were 42.4% of men and 44.9% of women. Those with an above-normal body fat level included 61% of men and 61.2% of women. Age affected obesity markers in all participants. In both fasters and controls, the mean values of all the measured obesity indexes were significant lower in younger compared to older participants (p<0.001).

Similarly, in a previous survey of 17,341 Greek men and women, the overweight prevalence was 35.2% (41.0% in men, 29.8% in women), the obesity prevalence was 22.3% (25.8% in men, 18.4% in women), and that for abdominal obesity 26.4% in men and 35.9% in women [28]. Accordingly, the prevalence of overweight and obesity in the present study was also similar to WHO [29] estimates for the Greek population and a bit higher than the results of the Eurostat 2014 report [30].

To our knowledge there has been no other study estimating the association of genotypes and Greek Orthodox fasting in obesity. BF is higher, while WC and WHR are lower in women compared to men, independent of fasting status. However BMI values are smaller in women compared to men only in the controls. BMI did not differ significantly between the sexes in the fasting group; thus BMI is significantly higher in fasting women compared to non-fasting ones. This can be attributed to the fact that orthodox women who follow the rules of their church in terms both of living and eating, may have paid less attention to their physical appearance or dieting outside of the religious dietary restrictions, perhaps related to a preferential focus on spiritual concerns.

In the present study we found that the effect of ApoE alleles on

| Table 4. Logistic regression model for BMI, %BF, WC and WHR in study population |
|-------------------------------|----------------|----------------|
| **Test variable** | **Predictor variable** | **Total sample** | **Fasters** | **Control** |
| BMI | Age | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p |
| Normal | Young | 8.786 | (4.787, 16.126) | <0.001 | 7.583 | (2.927, 19.646) | <0.001 | 9.682 | (4.398, 21.314) | <0.001 |
| overweight | Young | 1.606 | (0.887,2.907) | 0.118 | 1.204 | (0.480, 3.021) | 0.693 | 2.045 | (0.937,4.465) | 0.072 |
| %BF | Age | non normal | Young | 0.439 | (0.288, 0.699) | <0.001 | 0.402 | (0.208, 0.778) | 0.007 | 0.474 | (0.274, 0.822) | 0.008 |
| WC | Age | Obese | Young | 0.396 | (0.227, 0.692) | 0.001 | 0.482 | (0.213, 1.094) | 0.081 | 0.349 | (0.162, 0.751) | 0.007 |
| | Women | 2.538 | (1.352, 4.762) | 0.004 | 1.290 | (0.565, 2.945) | 0.545 | 5.660 | (1.121, 16.679) | 0.002 |
| WHR | Age | at risk | Young | 0.086 | (0.047,0.160) | <0.001 | 0.148 | (0.066, 0.033) | <0.001 | 0.042 | (0.015, 0.123) | <0.001 |
| ApoE alleles | at risk | E2 | 2.187 | (0.856, 5.592) | 0.102 | 1.432 | (0.316, 4.942) | 0.642 | 2.872 | (0.861,9.575) | 0.086 |
| | E3 | 2.862 | (1.503, 5.450) | 0.001 | 2.012 | (0.718, 5.636) | 0.184 | 3.617 | (1.569, 8.340) | 0.003 |

Odds Ratios (OR) are unadjusted. Ref: Reference category. p: p-value for the binary logistic regression model. p*: p-value for the multinomial logistic regression model.
Adiposity was associated with age. Between the three alleles statistically significant differences in WHR were observed only in the younger participants. Possibly Apo E4 played a protective role against the increase of WHR, but age counterbalanced this effect. When we analyzed our population according to mean values we could not identify any effect of obesity markers in either group, fasters or control. When we sub-divided the population into normal or non-normal, ApoE4 showed a protective role against the increase of WHR and age in younger male group. This result warrants further investigation.

The protective effect of the ApoE allele on obesity status is controversial. Thus, Zarkesh et al [13] did not find any association between obesity related factors and Apo E polymorphism while Zeljko et al [31] reported a strong relation between the Apo E polymorphism and obesity status suggesting that it plays an important role in obesity development in a Roma population of Croatia.

Apo E plays a key role in lipid metabolism, and thus encoding this gene has been of great importance in order to find its effect on obesity and cardiometabolic disorders [13]. Obesity might contribute to heart failure through different effects such as increased cardiac output and total blood volume, hypertrophy and diastolic dysfunction of left ventricular, adipositas cordis [32] and alterations in cardiac metabolism [33]. It can lead to diabetes which subsequently adversely affects survival in established heart failure syndromes [34]. However, BMI cut-off points might be appropriate for defining overweight optimally in populations like Asian Indians that have higher percentage of body fat compared to whites [35].

Obesity and central obesity are associated with many cardiometabolic diseases [20]. A key reason for the accelerating CVD epidemics is changing in lifestyles such as unhealthy eating habits and diminished physical activity. These diseases can also impact economic growth due to healthcare expenditure and diminished productivity [9]. Cardiovascular diseases afflict both the affluent communities and poorer ones. Numerous studies have revealed that mutations in specific genes can cause the early development of CVD. A genetic analysis of hyperlipidemic patients found a correlation in the development of CVD due to interaction of hyperlipidemic genes and environmental factors such as unhealthy diet, stress, sedentary life style and smoking habit [36].

An early allelic discrimination can act as a prognostic procedure against health disorders. APOE genotyping can provide a rapid quantitative diagnosis of metabolic disturbances such as dysbetalipoproteinemia, Alzheimer disease and in population screening for CHD risk factors [8]. MetS is also increased in a dose-dependent manner when carrying APOE4 alleles. So, considering that health disturbances can be prevented and reverted more effectively if detected early, the characterisation of an individual’s APOE genotype may be helpful for identifying at-risk overweight persons [37], and may help in determining who may benefit from traditional health promoting practices such as Yoga [38].

In conclusion, even if genetic risks factor influence the susceptibility to obesity and cardiometabolic disorders, we should always bear in mind that the environmental conditions play an important essential role in the development of disease. Thus, a healthy lifestyle, including both balanced nutrition and physical activity, taking into account the culture, the religion and the ethics of each population should be promoted through intervention programs such as those described recently that have suffered from sub-optimal implementation [39]. Government and international policies, food and beverage industries, educational institutions, local communities should work towards lifestyle changes that reinforce well-being [9].

Declarations of interest
The authors declare no conflicts of interest.

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The authors state that they abide by the authors’ responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal [40].

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Elevated LVEDP, Chronic Pulmonary Oedema and Valve Disease

Prithwish Banerjee, MD, FRCP, FESC

1. Consultant cardiologist and Lead of Heart Failure Services, Department of Cardiology University Hospitals Coventry & Warwickshire

Corresponding author:
Professor Prithwish Banerjee
Clifford Bridge Road, Coventry
CV2 2DX, United Kingdom.
Honorary Professor
Coventry University, United Kingdom
Honorary Associate Professor
University of Warwick Medical School, United Kingdom.
Tel: 44 2476 965670,
Fax: 44 2476 965657
E-mail: Prithwish.Banerjee@uhcw.nhs.uk

Introduction
Elevated left ventricular end diastolic pressure (LVEDP) is one of the main features in the diagnostic algorithm of heart failure with preserved ejection fraction (HFpEF) [1]. It is also a feature in those with pure left ventricular diastolic dysfunction (LVDD), (and preserved ejection fraction), who have never developed heart failure [2]. In fact, it has been proposed that left ventricular diastolic dysfunction may progress through stages with increasing LVEDP from a stage of asymptomatic pre-clinical diastolic dysfunction to a pre-HFpEF stage and finally to the HFpEF stage [2]. With the population of elderly people rising, increased LVEDP appears to be a common finding on echocardiography and during left ventricular angiography [2, 3]. An important cause of this may be increased vascular resistance associated with ageing coupled with common comorbidities present in the elderly such as hypertension, diabetes mellitus or chronic kidney disease [4] but other causes such as coronary artery disease [5] may also play a role. It has been speculated that in many cases the elevated LVEDP may be the end result of the increased effort that the LV muscle undertakes to force blood into a high resistance vascular circuit [4]. This world of elevated LVEDP related to HFpEF and left ventricular diastolic dysfunction appears to be bringing in some unique challenges that are worth highlighting. I would like to briefly describe a patient of mine to make my case.

Case Report
A 77 year old lady presented with recurrent pulmonary oedema, the cause of which was initially unclear. She had a background history of hypertension, Type 2 diabetes mellitus, chronic renal impairment and moderate aortic stenosis (AS) with mild to moderate aortic regurgitation (AR). None of these were clinically important at that stage. On echocardiography, her LV systolic function was well preserved but the E/e was elevated at >15 suggesting an elevated LVEDP but aortic valve Dopplers indicated moderate aortic stenosis (peak velocity 3.3m/s, peak aortic valve gradient 42.4 mm Hg and mean gradient 24.9 mm Hg) with mild moderate AR. Left and right heart catheterisation showed non obstructive coronary atheroma with an elevated LVEDP of 20mm Hg and a mean instantaneous gradient across the aortic valve (using a Langston catheter) of 25 mm Hg suggesting moderate AS. There was no evidence of a left to right shunt on oximetry but pulmonary artery mean pressure was mildly elevated.
at 31mm Hg in keeping with mild post capillary pulmonary hypertension. The main problem appeared to be left ventricular diastolic dysfunction leading to elevated LVEDP and after other investigations I felt that the recurrent pulmonary oedema was being triggered by paroxysmal atrial fibrillation; I was luckily able to control this with oral amiodarone. My thinking here was that the AF was easily triggering the pulmonary oedema since the LVEDP was chronically elevated due to LVDD. Interestingly, this lady was also persistently hypoxic with an oxygen saturation of 90% on air and a PO2 of between 8-9kPa. The cause of the hypoxia remained unclear as lung function testing and a respiratory assessment did not find any abnormalities. Chest X rays showed frank pulmonary oedema during admissions with acute worsening of breathlessness but at other times simply suggested mild pulmonary venous congestion (figure 1). A high resolution CT scan of the thorax did provide some clues showing no lung parenchymal abnormalities of significance but there was mild perihilar and lower zone ground glass changes seen on the CT suggestive of chronic pulmonary oedema at a time when the patient was clinically stable and living at home with NYHA class III to IV exertional breathlessness (not in acute heart failure).

My feeling about this was that she was suffering from chronic interstitial pulmonary oedema due to the persistently grossly elevated LVEDP. I would have liked to reduce her LVEDP with drugs like diuretics but I found it difficult to treat. High doses of diuretics affected her renal function markedly; her blood pressure was already well controlled and she was now in sinus rhythm, so there was no AF to cardiovert. I restricted her fluid intake and arranged home oxygen for her which did help. Despite this, she was subsequently admitted with congestive cardiac failure a few times. I looked carefully to find another cause for her breathlessness (including an opinion from a colleague in respiratory medicine) but couldn’t find anything of significance. Over the next 4 years she remained very symptomatic with limiting breathlessness and her gradient across the aortic valve slowly climbed but the aortic stenosis remained in the moderate range until right at the end of this period.

**Discussion**

Now here is a dilemma in such cases with moderate valve disease and pre-existing marked elevation of LVEDP due to LVDD: should we consider valve surgery early even when the valve disease is moderate rather than severe? The argument would be that moderate AS in this case would be very likely to be contributing to the high LVEDP that almost invariably is the reason for her chronic pulmonary oedema and her disabling symptoms (as her aortic valve gradient climbed in the next few years this became more likely and more relevant). Correcting the valve problem may well help symptoms by reducing the chronically elevated LVEDP. She is not my only patient with this problem (another one has moderate mitral regurgitation with pre-existing high LVEDP of >20 mm Hg) and I am sure that many other cardiologists are asking this question. If we think that the question is valid then we might need to review the indications for valve intervention in the light of HFPEF as well as in those with pre-existing high LVEDP due to LVDD. In fact, my lady described above, eventually developed severe aortic stenosis (peak velocity 4.2m/s, peak gradient 69mm Hg, mean gradient 41mm Hg, and valve area 1 square cm with moderate to severe AR on echocardiography) for which she underwent a TAVI (Transcatheter Aortic Valve Implantation) procedure. This helped both her hypoxia and her symptoms quite dramatically and rapidly post procedure making me wonder why I had to wait that long to intervene on her valve disease!

**Conclusion**

Ground glass changes on chest CT scans (in non acute pulmonary oedema patients) have been described mainly in patients with Pulmonary Hypertension due to left heart disease (WHO Group 2 Pulmonary Hypertension) [6, 7]. Bilateral septal thickening often accompanies patchy ground glass changes predominantly in the dependant lower lobes, sometimes accompanied by small
unilateral or bilateral pleural effusions. However, the changes can be subtle and intermittent and recognition that this represents chronic interstitial pulmonary oedema leading to hypoxia in HFPEF/LVDD patients is limited, often leading to an intensive hunt for other (mainly respiratory) causes of hypoxia without success, causing confusion. With an ever increasing burden of LV diastolic dysfunction, HFPEF and pulmonary hypertension secondary to HFPEF, being familiar with all the expected clinical presentations (including the unusual ones) of this syndrome will help to arrive at a diagnosis early and to intervene in a timely and appropriate manner. As for chronic pulmonary oedema related to HFPEF/LVDD the mainstay remains diuretics but a common sense treatment approach for HFPEF [8]

Declarations of Interest
The author declares no conflict of interest.

Acknowledgements
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