1) GENETIC AND PHENOTYPIC LANDSCAPE OF PERIPARTUM CARDIOMYOPATHY

Abstract

Background:
Peripartum cardiomyopathy (PPCM) occurs in ≈1:2000 deliveries in the United States and worldwide. The genetic underpinnings of PPCM remain poorly defined. Approximately 10% of women with PPCM harbor truncating variants in TTN (TTNtv). Whether mutations in other genes can predispose to PPCM is not known. It is also not known if the presence of TTNtv predicts clinical presentation or outcomes. Nor is it known if the prevalence of TTNtv differs in women with PPCM and preeclampsia, the strongest risk factor for PPCM.

Methods:
Women with PPCM were retrospectively identified from several US and international academic centers, and clinical information and DNA samples were acquired. Next-generation sequencing was performed on 67 genes, including TTN, and evaluated for burden of truncating and missense variants. The impact of TTNtv on the severity of clinical presentation, and on clinical outcomes, was evaluated.

Results:
Four hundred sixty-nine women met inclusion criteria. Of the women with PPCM, 10.4% bore TTNtv (odds ratio=9.4 compared with 1.2% in the reference population; Bonferroni-corrected $P=1.2\times10^{-46}$). We additionally identified overrepresentation of truncating variants in FLNC (odds ratio=24.8, $P=7.0\times10^{-8}$), DSP (odds ratio=14.9, $P=1.0\times10^{-8}$), and BAG3 (odds ratio=53.1, $P=0.02$), genes not previously associated with PPCM. This profile is highly similar to that found in nonischemic dilated cardiomyopathy. Women with TTNtv had lower left ventricular ejection fraction on presentation than did women without TTNtv (23.5% versus 29%, $P=2.5\times10^{-4}$), but did not differ significantly in timing of presentation after delivery, in prevalence of preeclampsia, or in rates of clinical recovery.

Conclusions:
This study provides the first extensive genetic and phenotypic landscape of PPCM and demonstrates that predisposition to heart failure is an important risk factor for PPCM. The work reveals a degree of genetic similarity between PPCM and dilated cardiomyopathy, suggesting that gene-specific therapeutic approaches being developed for dilated cardiomyopathy may also apply to PPCM, and that approaches to genetic testing in PPCM should mirror those taken in dilated cardiomyopathy. Last, the clarification of genotype/phenotype associations has important implications for genetic counseling.

2) PEAK SBP DURING THE EXERCISE TEST: REFERENCE VALUES BY SEX AND AGE AND ASSOCIATION WITH MORTALITY
We sought to update norms for peak systolic blood pressure (SBP) on the graded exercise test and examine its prognostic value in patients without baseline cardiovascular disease. Mayo graded exercise test data (1993–2010) were reviewed for non-imaging tests using Bruce protocol, selecting Minnesota residents 30 to 79 years without baseline cardiovascular disease. We formed a pure cohort of patients without factors significantly affecting peak SBP to determine peak SBP percentile norms by age and sex. Then we divided the full cohort of patients into 5 groups based on peak SBP percentiles: low (<10th), borderline low (10th–25th), referent (25th–75th), borderline high (75th–90th), and high (>90th). The relationship between peak SBP and mortality was tested using Cox regression adjusting for age, sex, and comorbidities affecting peak SBP or mortality. We identified 20,760 eligible patients with 7,313 females (35%) and mean age 51.5±10.7 years. Our pure cohort included 7,810 patients. Over 12.5±5.0 years follow-up, there were 1,582 deaths, including 541 cardiovascular deaths. In the fully adjusted model, low-peak SBP was associated with increased total mortality (heart rate, 1.41 [1.19–1.66], P<0.0001) and cardiovascular mortality (heart rate, 1.54 [1.16–2.03], P=0.001), while borderline low-peak SBP was associated with increased cardiovascular mortality only (heart rate, 1.36 [1.02–1.81], P=0.027). High peak SBP was associated with increased total mortality only in the age-sex adjusted model (heart rate, 1.18 [1.02–1.36], P=0.026), not after full adjustment. We conclude that low exercise peak SBP is an independent predictor of higher total and cardiovascular mortality.

3) Strategies to Turn the Tide on Racial and Gender Inequity

Durand discussed additional ways to improve disparities of gender, race, and ethnicity. "It can all start with measuring the data," said Durand, also an assistant professor of pediatrics at Drexel University, Philadelphia. "This means looking at gender and race and ethnicity data by unit or section at your institution, as well as leadership positions." In 2017, authors led by Hilary Sanfey, MBChB, MBBCh, MHPE, FACS, published an article addressing strategies to identify and close the gender salary gap in surgery (J Am Coll Surg. 2017;225[2]:333–8). Their recommendations included changing policies, transparency, oversight of metrics, promoting women to senior leadership positions, and evaluating the organizational culture. "It goes back to culture, because it leads to accountability," Durand said. "Behavior change comes with accountability."

Part of holding people accountable within a culture change includes addressing microaggressions, or indirect expressions of prejudice. In 2016, authors led by Floyd Cheung, PhD, established a framework using the acronym A.C.T.I.O.N., which identifies a microaggression without being aggressive or evoking defensiveness towards the person communicating the microaggression. A.C.T.I.O.N. stands for Ask clarifying questions; Come from curiosity, not judgment; Tell what you observed in a factual manner; Impact exploration — discuss what the impact was; Own your own thoughts and feelings around the situation; and discuss Next steps.

"Granted, this might take a little time, but when we state microaggressions, most of us don’t realize that those statements could be hurtful or uncomfortable for the person receiving them," Durand said.

Another strategy to address disparities involves partially blinding the interview process for trainees. "You can do this by not giving any ‘cognitive information’ to your interviewers — such as United States Medical Licensing Examination Step scores — that may anchor their position prior to the interview taking place," she explained. "You can also standardize one or two questions that all interviewees have to answer, to have a more objective way to compare answers horizontally rather than vertically."

This complements the notion of the Association of American Medical Colleges' "holistic review," a principle that it describes as allowing admissions committees "to consider the ‘whole’ applicant, rather than disproportionately focusing on any one factor."

"The overall concept is to evaluate what are criteria of the position you are hiring for," Durand said. "Different criteria will have different levels of importance. You would take into consideration the values of the group or the institution and make sure those criteria are most important for selection, at the forefront."

Ganem and Durand have disclosed no financial relationships.
This MDEdge News article originally appeared on the-hospitalist.org. MDedge is part of the Medscape Professional Network.
Working to mitigate racial and gender inequity in hospital medicine may seem like a daunting task, but every physician can play a role in turning the tide toward equity, according to Jorge Ganem, MD, FAAP.

"Talking about bias, racism, sexism, gender inequity, and health disparities is difficult," Ganem, associate professor of pediatrics at the University of Texas at Austin and director of pediatric hospital medicine at Dell Children's Medical Center in Austin, said May 5 at SHM Converge, the annual conference of the Society of Hospital Medicine. "There certainly comes a heavy weight and responsibility that we all feel. But I believe that we should approach gender inequities and racial disparities through a quality and patient safety lens, and looking through that lens."

Ganem — along with Vanessa Durand, DO, FAAP, of St. Christopher’s Hospital for Children in Philadelphia, and Yemisi O. Jones, MD, FAAP, FHM, of Cincinnati Children’s Hospital — devised the concept of "functional allyship" as one way to improve representation in hospital medicine. The approach consists of three categories: listeners, amplifiers, and champions. Listeners are "those who take the time to listen and give space to the voices who are oppressed and disadvantaged," Ganem said. "Action may not always be possible, but the space gives those who are marginalized validation to the feelings that the oppression produces."

He described amplifiers as those who use their position of privilege to spread the message by educating their colleagues and other peers. "This includes elevating those from marginalized communities to speak on their own behalf and giving them the spotlight, given their expertise," he said.

Champions are those who actively work to dismantle the oppression within systems. Ganem cited organizations such as ADVANCE PHM, FEMinEM and HeForShe as examples of national and global efforts, "but this also includes those working in committees that are addressing diversity and inclusion in their workplace and coming up with policies and procedures to increase equity," he said.

Finding opportunities to practice mentorship and sponsorship are also important. "Positive mentorship relationships are key in avoiding burnout and decreasing attrition," he said. "The development of successful mentorship programs are a must in order to retain women physicians and ‘underrepresented in medicine’ physicians in your organization." He described a "sponsor" as someone who is in a position of influence and power who actively supports the career of a "protégé" whom they have identified as having high potential. "The sponsor may advance a protégé’s career by nominating them for leadership opportunities and introducing them into career networks," he said.

4) WHEN SHOULD CARDIOVASCULAR PREVENTION BEGIN? THE IMPORTANCE OF ANTENATAL, PERINATAL AND PRIMORDIAL PREVENTION

Abstract

Cardiovascular diseases represent a major health problem, being one of the leading causes of morbidity and mortality worldwide. Therefore, in this scenario, cardiovascular prevention plays an essential role although it is difficult to establish when promoting and implementing preventive strategies. However, there is growing evidence that prevention should start even before birth, during pregnancy, aiming to avoid the onset of cardiovascular risk factors, since events that occur early in life have a great impact on the cardiovascular risk profile of an adult. The two pillars of this early preventive strategy are nutrition and physical exercise, together with prevention of cardio-metabolic diseases during pregnancy. This review attempts to gather the growing evidence of the benefits of antenatal, perinatal and primordial prevention, discussing also the possibility to reverse or to mitigate the cardiovascular profile developed in the initial stages of life. This could pave the way for future research, investigating the optimal time and duration of these preventing measures, their duration and maintenance in adulthood, and the most effective interventions according to the different age and guiding in the next years, the best clinical practice and the political strategies to cope with cardiovascular disease.

5) ANTENATAL, PERINATAL, AND PRIMORDIAL CARDIOVASCULAR PREVENTION: WHAT IS KNOWN, WHAT IS HAPPENING, AND FUTURE DIRECTIONS

Although there has been substantial improvement in atherosclerotic cardiovascular disease
(ASCVD) outcomes in recent decades, ASCVD remains the leading cause of mortality and morbidity globally.  

Primary and secondary prevention in adults represent milestones in order to improve the health status of a population. An increasing number of cardiovascular health factors have been associated with the prevalence and incidence of several diseases: ASCVD events, heart failure, atrial fibrillation, cancers, depression, and cognitive impairment. Therefore, moving individuals toward ideal cardiovascular health is important for the prevention of many important health conditions.

Few information is available and there is low attention regard primordial cardiovascular prevention, as well as prevention in the antenatal and perinatal periods.

The paper by D’Ascenzi et al. focuses on these very important topics, providing a complete review of the contributions available in the field.

In this commentary, starting with the paper by D’Ascenzi et al., after a summary of the available knowledge in this area, an analysis of the gap between what we are doing and what we should do will be provided.

The knowledge

An increasing number of chronic diseases have been observed, especially metabolic disorders such as diabetes mellitus and obesity, as having a very important role in ASCVD risk. This phenomenon does not only involve adults and the elderly, but, day by day, it is also playing a major role among adolescents and young adults.

It is important to stress that ASCVD factors are able to negatively impact each stage in life. Correctly, D’Ascenzi et al. state that ASCVD prevention should start as soon as possible.

The American Heart Association defined a new model of “ideal cardiovascular health” based on seven health metrics, for both children and adults, referred as “Life’s Simple 7”: four healthy behavioural items, such as non-smoking, having a normal body mass index, being physically active, and healthy eating; and three health factors, including blood pressure, cholesterol, and plasma glucose level.

It has been reported that reducing the number of these metrics during childhood and adolescence reduces the incidence of arterial hypertension, metabolic syndrome, and dyslipidaemia; moreover, an inverse correlation exists between the number of metrics and carotid intima media thickness and arterial stiffness.

The individual ASCVD risk profile is influenced by the genetic patrimony, which cannot be directly manipulated. Nevertheless, D’Ascenzi et al. correctly state that healthy behaviour in the family is very important also in this field, since a tight relation between genetics and environment exists, with a reciprocal influence.

Evidence is available: dietary counselling, sodium restriction, and physical activity in children have beneficial effects on plasma lipid profile, blood pressure levels, and abdominal fat; also, insulin sensitivity and arterial stiffness are improved. Sharing these favourable effects with parents, with a virtuous diffusion of a healthy lifestyle, is a specific feature of family-based interventions.

Nutrition and physical activity are also milestones in these stages of the life; in their review, D’Ascenzi et al. underline some interesting data regarding their beneficial effects on endothelial function and retinal microcirculation.
Concerning the intrauterine life, pregnancy-related hypertensive disorders might significantly influence the ASCVD risk profile of the offspring; moreover, intrauterine exposure to a diabetic environment may have an impact on biventricular geometry and function later in the life. An appropriate method of management of these pregnancy-related disorders may play a relevant role as a preventive measure.

Finally, the increasing number of preterm births represents an epidemiologically relevant issue, involving around 15 million babies each year, worldwide. Preterms present a typical cardiac remodelling: left ventricular mass is increased, both ventricles show a reduced volume, and a reduced apical displacement is present. Left ventricular ejection fraction is preserved during rest, but a reduction during exercise has been demonstrated. A possible association between the risk of developing heart failure in young adults and the degree of prematurity has been hypothesized. In preterms, an association with a higher risk of future systemic hypertension and stroke exists, as compared to full-term newborns; this risk is independent from the cardiac alterations—increased arterial stiffness, reduced cutaneous capillary density, and endothelial function may play a role as drivers of this unfavourable evolution.

However, these pathophysiological substrates are not entirely understood and future studies are needed to investigate the impact of negative cardiac remodelling observed in preterms on the future ASCVD risk profile.

What is happening in the field?

After an alarming rise in mortality from ASCVD in the 1950s in most industrialized countries, the ASCVD epidemic levelled off and an impressive decline started. That decline has occurred in most European countries, commencing earlier in some compared to others. However, the epidemic is still very dynamic in different parts of the world and changes may again occur in the wrong direction.

There is clear evidence that traditional ASCVD risk factors, including elevated blood pressure, blood cholesterol, and blood glucose, have their origins in childhood and adolescence. Nevertheless, there is low cardiovascular disease awareness among young people.

In a recent paper, Gooding et al. assessed awareness of ASCVD and prevention efforts among 331 young women aged 15 to 24 years from the American Heart Association National Women’s Health Study survey. Responses from this cohort were compared to the 2012 American Heart Association online survey of 1227 women aged 25 years and older. The results are rather disturbing: only 10% of the young women correctly identified ASCVD as the leading cause of death in women, a proportion which is significantly lower than that found among all adult women in 2012 (64.0%) and women aged 25 to 34 years (53.6%) (P < 0.01 for both). Many (43.5%) young women said they were not at all informed about ASCVD; most worried little (39.2%) or not at all (38%) about ASCVD.

Therefore, the most important barrier to engaging in prevention behaviours is the lack of knowledge about the “killing power” of ASCVD, and, as a consequence, not considering oneself at risk.

As D’Ascenzi et al. correctly underline, the current situation in Europe regarding the adoption of proper measures for a healthy lifestyle is also unfavourable. Considering healthy eating and physical exercise, compliance to the current recommendations varies considerably according to gender and country: from 2% in Cyprus to 14.7% in Sweden for girls, from 9.5% in Italy to 34.1% in Belgium for boys. Paradoxically, a low adherence to the Mediterranean diet among children living in Mediterranean countries has been demonstrated.
More should be invested in the earliest possible prevention of ASCVD from childhood onwards. This can be achieved by aiming for a non-smoking generation of adolescents who keep physically active throughout life, preventing the development of overweight and obesity.

The authors correctly stress that medical doctors, nurses, scientific communities, and politicians should promote the most appropriate preventive measures since the youngest ages.\(^3\) Since ASCVD risk factors begin to accumulate risk early in life, the promotion of cardiovascular health and heart disease awareness among young people is essential to reduce the burden of ASCVD worldwide.

Future studies should explore effective strategies for linking heart health promotion with issues that matter to young people, as well as health communication channels most likely to reach childhood and adolescents. These strategies should also involve the whole family and not only the child, in order to be beneficial for all members of the family.

Finally, as the authors correctly underline, ante- and perinatal ASCVD prevention is still developing, with few data available.\(^3\) Thus, more research is needed to better study the role of ASCVD prevention during pregnancy and in premature babies.

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6) EXPERTS URGE ACTION TO REDUCE GLOBAL BURDEN OF CVD IN WOMEN

Urgent action is needed to improve care and prevention, fill knowledge gaps, and increase awareness about cardiovascular disease in women, according to a new report from the Lancet Commission. The first-ever global report on women and cardiovascular disease was published May 16 in The Lancet and presented during ACC.21.

Authored by 17 leading female experts from 11 countries, the report outlines 10 recommendations to tackle inequities in diagnosis, treatment, and prevention to reduce cardiovascular disease in women by 2030 – in line with the United Nations’ broader Sustainable Development Goals (SDGs) to reduce premature deaths from noncommunicable diseases. The recommendations include educating health care providers and patients on early detection to prevent cardiovascular disease in women; scaling up heart health programs in highly populated and underdeveloped regions; and prioritizing sex-specific research on cardiovascular disease in women and intervention strategies.

"Cardiovascular disease in women remains understudied, under-recognized, under-diagnosed, and under-treated globally," said Roxana Mehran, MD, FACC, one of the authors. "Achieving the important target set by the United Nations requires bold, distinct strategies to not only target factors contributing to cardiovascular disease but also to identify sex-specific biological mechanisms in women. Making permanent improvements to the worldwide care of women with cardiovascular disease requires coordinated efforts and partnerships involving policymakers, clinicians, researchers, and the wider community."

The Commission report is based on data from the 2019 Global Burden of Disease Study, which showed approximately 275 million women around the world with cardiovascular disease in 2019 alone, with global age standardized prevalence estimated at 6,402 cases per 100,000. The leading cause of death in women worldwide was ischemic heart disease (47% of cardiovascular disease deaths), followed by stroke (36% of cardiovascular disease deaths).

The data also underscored considerable geographical differences in cardiovascular disease, with the highest age-standardized prevalence in Egypt, Iran, Iraq, Libya, Morocco and United Arab Emirates, while the countries with lowest prevalence were Bolivia, Peru,
Colombia, Ecuador and Venezuela. Although globally the prevalence of cardiovascular disease in women has been declining, with an overall decrease of 4.3% since 1990, some of the world’s most populous nations have seen an increase in cardiovascular disease, including China (10% increase), Indonesia (7% increase), and India (3% increase). The highest cardiovascular disease mortality rates were in Central Asia, Eastern Europe, North Africa, and the Middle East, Oceania and Central Sub-Saharan Africa, where age-standardized mortality exceeded 300 deaths per 100,000 women. High-income Asia Pacific, Australasia, Western Europe, Andean Latin America and High-income North America recorded the lowest rates.

The evidence of important regional trends suggests a need for improved data collection at local and regional levels to effectively prevent, recognize, and treat cardiovascular disease in women, the authors said. They also note the importance of addressing established risk factors like hypertension, body mass index and high LDL cholesterol, but also said sex-specific risk factors such as premature menopause and pregnancy related-disorders must be more widely recognized and prioritized as part of treatment and prevention efforts worldwide. They also stress the importance of paying attention to socioeconomic and cultural factors, as well as mental health, in prevention and management of cardiovascular disease.

"While some risk factors for cardiovascular disease are similar for women and men, women are more likely to suffer from health disparities due to cultural, political or socioeconomic factors," said C. Noel Bairey Merz, MD, FACC, another author of the report. "For instance, some social or religious norms – such as restrictions on participation in sport and physical activities – can contribute to cardiovascular disease in women, highlighting an urgent need for culturally appropriate initiatives that are tailored to different regions and populations."

The Commission also highlights the need to increase awareness of cardiovascular disease risk in women among physicians, scientists, and health care providers. The authors point out the unmet need for cardiovascular disease prediction models that include sex-specific risk factors, as well as greater inclusion of women in clinical trials. Tailored interventions for the most vulnerable populations globally, including women from minority or indigenous populations and those whose roles in society are strongly defined by traditional or religious norms, as well as those not typically viewed as being at high risk, such as young women, are also important.

In a related editorial, Ana Olga Mocumbi, MD, of the Mozambique National Institute of Health, writes: "In the midst of the COVID-19 pandemic, values of human dignity, solidarity, altruism, and social justice should guide our communities to ensure equitable share of wealth and leveraging of efforts towards the reduction of cardiovascular disease burden in women worldwide. The Commission’s recommendations on additional funding for women’s cardiovascular health programs, prioritization of integrated care programs, including combined cardiac and obstetric care, and strengthening of the health systems accords with efforts to bridge the gap for the world’s worst off. Such a shift in women’s cardiovascular care would be a major step towards equity, social justice, and sustainable development."

7) Serial CMR Strain Measurements to Identify Cardiotoxicity in Breast Cancer

Abstract

Objectives

This study sought to compare the prognostic value of cardiovascular magnetic resonance (CMR) and 2-dimensional echocardiography (2DE) derived left ventricular (LV) strain, volumes, and ejection fraction for cancer therapy–related cardiac dysfunction (CTRCD) in women with early stage breast cancer.

Background
There are limited comparative data on the association of CMR and 2DE derived strain, volumes, and LVEF with CTRCD.

Methods

A total of 125 prospectively recruited women with HER2+ early stage breast cancer receiving sequential anthracycline/trastuzumab underwent 5 serial CMR and 6 of 2DE studies before and during treatment. CMR LV volumes, left ventricular ejection fraction tagged-CMR, and feature-tracking (FT) derived global systolic longitudinal (GLS) and global circumferential strain (GCS) and 2DE-based LV volumes, function, GLS, and GCS were measured. CTRCD was defined by the cardiac review and evaluation committee criteria.

Results

Twenty-eight percent of patients developed CTRCD by CMR and 22% by 2DE. A 15% relative reduction in 2DE-GLS increased the CTRCD odds by 133% at subsequent follow-up, compared with 47%/50% by tagged-CMR GLS/GCS and 87% by FT-GCS. CMR and 2DE-LVEF and indexed left ventricular end-systolic volume (LVESVi) were also associated with subsequent CTRCD. The prognostic threshold change in CMR-left ventricular ejection fraction and FT strain for subsequent CTRCD was similar to the known minimum-detectable difference for these measures, whereas for tagged-CMR strain it was lower than the minimum-detectable difference; for 2DE, only the prognostic threshold for GLS was greater than the minimum-detectable difference. Of all strain methods, 2DE-GLS provided the highest increase in discriminatory value over baseline clinical risk factors for subsequent CTRCD. The combination of 2DE-left ventricular ejection fraction or LVESVi and strain provided greater increase in the area under the curve for subsequent CTRCD over clinical risk factors than CMR left ventricular ejection fraction or LVESVi and strain (18% to 22% vs. 9% to 14%).

Conclusions

In women with HER2+ early stage breast cancer, changes in CMR and 2DE strain, left ventricular ejection fraction, and LVESVi were prognostic for subsequent CTRCD. When LVEF can be measured precisely by CMR, FT strain may function as an additional confirmatory prognostic measure, but with 2DE, GLS is the optimal prognostic measure. (Evaluation of Myocardial Changes During BReast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI [EMBRACE-MRI]; NCT02306538)