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Original Article

Addressing the Enduring Primary Care Physician Shortage in the United States: The Direct and Indirect Effects of Gender on the Medical Specialty Decision-Making Process

Kelly Rhea MacArthur,[1] Emily Royer,[2] Daniel N. Hawkins.[1]

Abstract

Background: There has been an enduring primary care (PC) physician shortage in the United States (U.S.) for decades, which is projected to worsen. With women entering PC at significantly higher rates than men, the aim of this study was to explore various pathways through which gender may affect the medical specialty decision-making process. **Methods:** Using data from the National Survey of Attitudes and Choices in Medical Education and Training (ACMET) II on a sample of 492 medical residents, this study employed structural equation modeling (SEM) to explore how gender shaped residents' preferences for future practice and their perceptions of PC, and how their experiences with faculty affected the medical specialty decision-making process. **Results:** As expected, women were significantly more likely than men to report choosing PC. This study also found that there were several indirect pathways through which gender affects specialty choice, including through negative perceptions about PC and the time spent with PC faculty in medical school. **Conclusion:** Given the multiple pathways through which gender affects the medical specialty decision-making process, this study highlights a need for gender-specific interventions when addressing the enduring PC physician shortage in the U.S. Specifically, the results of this study suggest that increasing the time that male medical students spend in PC through structural changes in medical education might mitigate negative perceptions about PC and encourage males to enter PC at higher rates. Future research should assess the effectiveness of such gender-specific interventions.

Key Words: Medical Education; Primary Health Care; Medical Specialty; Gender Identity; Physician Shortage Area (MeSH Terms).

Introduction

The Primary Care Physician Shortage in the United States & Gender

Primary Care (PC) physicians, or general practitioners, are doctors on the front-lines of medicine with the responsibility of monitoring patients' overall well-being by providing preventative care, treating most common ailments, and serving as gatekeepers for access to specialists. Family medicine doctors, general internists, general pediatricians, geriatricians, and obstetrician-gynecologists fulfill the vital role of providing the holistic and cost-effective care that characterizes PC specialties.[1] Despite the well-documented crucial role that PC doctors play for producing better and more equitable health outcomes, generalists only constitute approximately one third of doctors in the United States.[2] This enduring PC physician shortage dates back at least five decades and is far more severe in America than in many other developed countries.[3-5]

The extent of and reasons for the PC physician shortage have fluctuated over time, with the percentage of medical students matching to a generalist residency reaching a height of 53.2 percent in 1998 and then steadily declining thereafter.[5] Reasons for the PC shortage have also varied alongside socio-political trends, including: the growing and aging population; the growing income gap between generalists and specialists; the rise of physician assistants and nurse practitioners; socioeconomic deprivation in rural areas; declining income and job satisfaction among PC doctors; and the passage of the Affordable Care Act (ACA) of 2010 that mandated health insurance and increased access to health care for an estimated 34 million Americans.[1,5-6] One study estimates that the U.S. will require an additional 52,000 PC doctors by 2025 to keep up with demand, and another study by the American Association of Medical Colleges (AAMC) projects a shortage of approximately 124,000 physicians.[1,7] Regardless of the future of the ACA, the PC physician shortage is expected to endure and scholars generally agree that by 2025 the demand for PC doctors will far exceed the supply.

The PC physician shortage would be even more dire if not for women's increased rates of entry into PC, which partially compensated for declining rates among men.[8] Past research has established that gender is perhaps the most powerful predictor of specialty choice, with women entering PC specialties at significantly higher rates compared to men. More than a third of PC physicians are women, with women comprising the majority of some PC specialties such as family medicine and pediatrics.[9] Moreover, approximately half of female physicians are PC doctors compared to about 32% of male doctors.[8-9] While this gender segregation is well-documented, the current study contributes to the area by examining how gender affects the ultimate outcome of specialty choice not just directly, but also indirectly through various pathways in the specialty choice decision-making process.[8] Using the only publicly available, nationally representative data on medical specialty choice, this study seeks to explore how gender might be an effective focal point for the development of strategies to address the increasingly problematic PC physician shortage in the United States.

Factors Affecting Medical Specialty Choice: The Role of Gender

Scholars have devoted considerable attention to identifying the factors that affect the process through which medical students choose a specialty. Several meta-analyses indicate that among the factors associated with medical specialty choice are: socio-demographic

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characteristics, such as age and marital status; individuals' values and needs, such as a desire for higher income; individuals' perceptions of a specialty; and the medical school curriculum and institutional culture, such as time spent in PC clerkships and with PC role models/mentors.[6,10] While there are some influences that both men and women cite as important in choosing a specialty, all the aforementioned factors likely vary by gender and affect the medical specialty decision-making process.[11]

Research suggests that there are many reasons why women prefer PC more than men. Unappealing characteristics of PC—both real and perceived—may disproportionately deter men from entering PC. Some of the perceived practice characteristics of PC that may be especially unappealing to men are beliefs that PC is more interpersonally arduous, yet less academically rigorous, and that PC yields lower income and prestige than specialties. Many American residents begin their careers with over $100,000 of medical school debt and PC offers less salary than other specialties to compensate for this debt, so it is not surprising that degree of debt is related to PC specialty choice.[12-13] However, one study shows that even after controlling for debt, women are still more likely to choose PC, suggesting that debt is just one factor in the medical specialty decision-making process and does not explain gender differences. PC also tends to offer less flexibility in terms of time.[14] As a result, PC may largely be low among men because it does not allow for a "controllable lifestyle" compared to other sub-specialties.[15-16]

Conversely, certain specialties such as surgery may be unappealing to many women, due to the overwhelming male predominance that creates male-centric cultures, values, and behaviors, as well as difficulty in finding female mentors.[14] On average, men tend to prefer medical practices that are characterized by the antithesis of PC, such as high pay, unlimited autonomy, and working with fewer disadvantaged patient populations. Since the decline of PC is inversely associated with the rise of specialties, understanding the PC physician shortage involves examining both why women are drawn to PC and deterred from specialties, as well as why men are deterred from PC and attracted to specialties.[7]

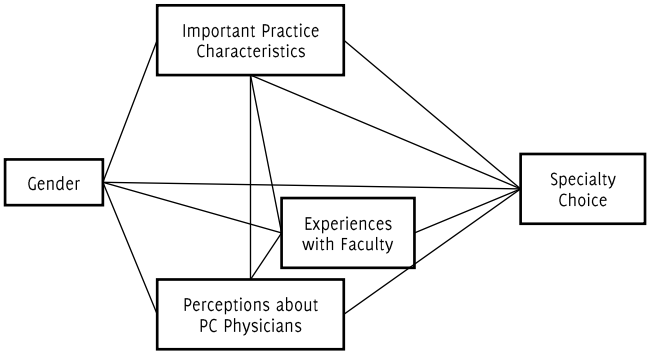
Individuals enter medical school with certain preferences for their future medical practices and research shows that these preferences are gendered in that women more than men tend to prefer the characteristics that depict PC.[14] For example, women tend to want to work with disadvantaged patient populations more so than men and PC work allows for more communicative and relationship-focused patient care.[14] Conversely, males entering medical school report more frequently than women that they desire things like higher income and more autonomy, which accompany specialties more readily than in PC.[14] Although students have preferences upon entering medical school, research suggests that they often choose a different specialty from the one they declared upon entering medical school.[17] Thus, it can be inferred that women and men's different experiences in medical school account for a large portion of gender segregation in medical specialties. These gendered experiences may change perceptions about PC and preferences for future practice.

There are several experiences during medical school that could change one's original specialty choice to or from PC. For example, research shows that women are more likely to work with underserved populations in clinics and complete a PC clerkship.[18] Additionally, the significance of PC physicians serving as positive role models in specialty choice is well-established and this presents a challenge to increasing PC physicians.[19] As long as negative perceptions of PC prevail, it is unlikely that PC physicians will implicitly or explicitly encourage medical students to enter PC. The time that is spent in PC during clerkships and faculty's encouragement of PC are two other aspects of the medical specialty decision-making process that may also be gendered and affect perceptions about PC.

The Current Study: Conceptual Model for the Effects of Gender on the Medical Specialty Decision Making Process

Gender appears to directly affect not only specialty choice, but also the many aspects of the medical specialty decision-making process. Thus, this study addresses the research question: What are the direct and indirect ways in which gender shapes the medical specialty decision-making process? Specifically, how are individual attributes, personal preferences for practicing medicine, perceptions toward PC versus specialties, and experiences during medical school related to each other and in turn affect specialty choice? Based on the literature, the current study tests the conceptual model shown in **Figure 1** in which gender will have both direct and indirect effects on PC specialty choice with all of the determinants of specialty choice being related to each other. Specifically, it is hypothesized that there will be a direct effect on PC specialty choice with women reporting significantly higher rates of PC specialty choice than men. It is also hypothesized that women more so than men will 1) desire practice characteristics more specific to PC than other specialties (e.g., wanting to work with underserved populations); 2) have more positive attitudes toward PC; and 3) spend more time with PC physicians who encourage them to enter PC. In turn, the conceptual model predicts that these gendered perceptions, experiences, and preferences account for women's greater likelihood to go into PC. If all these factors are related to each other in the hypothesized manner, then any one of the gendered factors in the medical specialty decision-making process can be targeted for gender specific interventions to increase PC choice for both men and women.

Figure 1. Conceptual Model for Specialty Choice Decision-Making Process



Methods

Sample

The data were drawn from the National Survey of Attitudes and Choices in Medical Education and Training (ACMET) II, 1997, which is a nationally representative cross-sectional survey of students, residents, and faculty.[20] This stratified probability sample includes a variety of variables regarding attitudes toward PC. The current analyses were on a subsample of only the residents, for which there are 492. Although the data are older, to our knowledge, a nationally-representative data set with a comprehensive set of factors affecting specialty choice and a sufficient sample size of medical residents that is publically available has not been collected more recently. All study procedures were approved by the Institutional Review Board (IRB). The study was approved by Nebraska's Health Science Center Office of Regulatory Affairs Institutional Review Board (IRB) (Approval #698-16-EX).

Measures

Dependent Variable: PC Specialty Choice is a dichotomous variable coded 0=specialty choice and 1=primary care or mixed primary/specialty.

Socio-demographics: All the socio-demographic variables/controls are binary categorical variables coded as gender (1=female), race/ethnicity

(1=white), marital status (1=married or living with partner), and age group (1=35 and older).

Important Characteristics of Future Practice: Respondents were asked "Now I will mention several aspects of practicing medicine in the real world…. As you think about each in the context of your practice choice, I would like you to rate its importance on a scale from 0 to 10. 0 means completely unimportant and 10 is as important as an item can be." Residents rated the importance in practicing medicine of: 1) job security, 2) income, 3) autonomy, 4) limiting time spent on the business side of medicine, and 5) devoting a portion of their time to "needy" populations.

Perceptions about PC Physicians: Residents were asked about their perceptions concerning PC physicians' quality of clinical research and clinical teaching compared to specialists', ranging from 1= PC physicians are worse than specialists, 2=about the same, and 3=PC physicians are better than specialists.

Experiences with Faculty: Two items measure residents' experiences with faculty. The first asked whether or not faculty encouraged them to go into PC (1=strongly toward the specialties to 4=strongly toward PC). The second asks about the percentage of time during residency that was spent with PC versus specialist faculty, ranging from 0-100%.

Plan of Analysis

To address the main research question and the conceptual model shown in ***Figure 1*** regarding the direct and indirect ways in which gender is associated with the specialty choice decision-making process, this study employs Structural Equation Modeling (SEM), using Maximum Likelihood Estimation (MLE). SEM is a superior method for testing hypotheses compared to similar linear techniques, such as multiple regression, because it simultaneously examines relationships between all variables (i.e., the overall model fit), as well as the existence and strength of indirect effects and direct relationships with multiple dependent variables. To assess model fit of the structural model, the Tucker Lewis Index (TLI), Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR) are reported. All analyses were conducted using the statistical modeling program Mplus 7.31 and uses Maximum Likelihood Estimation (MLE), the standard for SEM models because it produces robust estimates even when assumptions of normality are violated.[21,22] For all analyses, p values of equal to or less than .05 are considered statistically significant.

Results

Descriptive Results: Gender Differences in Predictors of Specialty Choice

Table 1 shows descriptive statistics (means, standard deviations, ranges) and results for independent samples t-tests by gender (t value, significance) for all variables included in this study. The sample of 494 residents was 43.7% female and about 76% white. The majority of residents were under the age of 35 and married/living with a partner, with men being significantly more likely than women to be married. Two hundred and five residents (42.7%) reported intent to go into PC, with women significantly more likely than men to choose PC.

Of the five preferred practice characteristics assessed, both women and men reported that autonomy was the most important, followed by job security. Residents reported that income was the least important out of the 5 'importance' variables. Results of the independent sample t-tests indicated that women wanted to limit their time spent on the business side of medicine (7.54±1.87, t=-2.29, p<.05) and have a practice in which a portion of time is devoted to disadvantaged populations (7.12±2.65, t=-3.23, p<.001) significantly more so than men did (7.13±2.12 and 6.48±2.17, respectively). There were no gender differences in residents' ratings of importance of job security, autonomy or income

Table 1. Descriptive Statistics for Key Analytic Variables by Gender (N=492).

Dependent Variable	Women (n=215) n (%)	Men (n=277) n (%)	*t*-Test Value	Range
Specialty Choice	116 (55.24)	89 (33.21)	-4.91***	1=PC specialty choice
Socio-demographics				
Race/ethnicity	153 (71.8)	217 (78.3)	1.64	1=white
Marital Status	125 (58.4)	203 (73.6)	3.52***	1= married
Age	36 (16.7)	38 (13.8)	-0.90	1= 35 and older
Important Practice Characteristics	**Mean±SD**	**Mean±SD**		
Job Security	8.47±1.52	8.49±1.51	0.20	0=completely unimportant to 10=as important as an item can be
Income	6.73±1.57	6.97±1.47	1.72	Idem
Autonomy	8.51±1.32	8.71±1.24	1.62	Idem
Limited time spent on business side	7.54±1.87	7.13±2.12	-2.29*	Idem
Practice devoted to dis-advantaged populations	7.12±2.65	6.48±2.17	-3.23***	Idem
Perceptions about PC Physicians				
Perceived research competency	1.67±0.55	1.49±0.55	-3.59***	1= PCs worse to 3= PCs better than specialists
Perceived teaching competency	2.15±0.50	2.05±0.56	-2.00*	idem
Experiences with Faculty				
Faculty encouraged PC	2.73±1.07	2.58±1.04	-1.49	1=strongly toward the specialties to 4=strongly toward PC
Percentage of time spent with PC faculty	34.87±30.46	22.13±27.31	-4.81***	0-100%

Legend: *p< 0.05, **p< 0.01, ***p< 0.001. PC: Primary care; SD: Standard deviation.

(t= 0.20, 1.62, and 1.72, respectively). Men had significantly more negative perceptions about PC physicians (research: 1.49±0.55, t=-3.59, p≤0.001; teaching: 2.05±0.56, t=-2.00, p≤0.05) than did women; women perceived PC physicians to be more competent than specialists in both clinical research (1.67±0.55) and clinical teaching (2.15±0.50). Women also estimated the time they spent with PC faculty throughout their training to be significantly more (34.87±30.46, t=-4.81, p< 0.001) than

the time men reported (22.13±27.31), but there were no gender differences in whether faculty encouraged PC (t=-1.49).

Direct Effects on PC Specialty Choice

As can be seen in ***Figure 2***, the structural model fit the data well ($X^2_{(df=30)}$ = 50.83, CFI: 0.97, RMSEA: 0.04, SRMR: 0.03). The model fit indices and the R^2 value (0.569) suggest that the process of choosing PC generally functioned as depicted in ***Figure 1***, with 56.9% of the variation in specialty choice explained by the tested model. The final model in ***Figure 2*** displayed standardized coefficients for significant relationships only (correlations also not shown). One of the goals of this study was to confirm that gender has a direct effect on medical specialty choice. As expected, women were significantly more likely than men to report that they wanted to go into PC rather than a specialty (β=0.07, p< 0.05). Without the mediators in the model, this effect of gender on specialty choice would have been substantially stronger (β=0.23, p< 0.001).

Although not one of the main research questions, since the goal of this study is to identify the factors that affect the medical specialty decision-making process, it is worth noting the direct effects of the predictor variables that affected specialty choice independent of gender. Of the five characteristics of future medical practice on which residents were asked to rate their importance, none of them were directly associated with specialty choice. Residents' perceptions about whether the quality of PC physicians' clinical teaching compared to specialists' had a direct effect on PC specialty choice. Specifically, those who believed that PC doctors' teaching is 'better' than specialists were more likely to choose to go into PC than a specialty. Respondents' experiences with faculty members during their residencies also had direct associations with choice of specialty. The more that faculty encouraged residents to go into PC, the more likely residents reported that they intended to do so (β=0.16, p< 0.001). Additionally, the more time residents spent with PC faculty, the more likely they were to have chosen PC (β=0.63, p< 0.001). Thus, in addition to gender, only two of the four types of predictors measured here had direct associations with PC specialty choice.

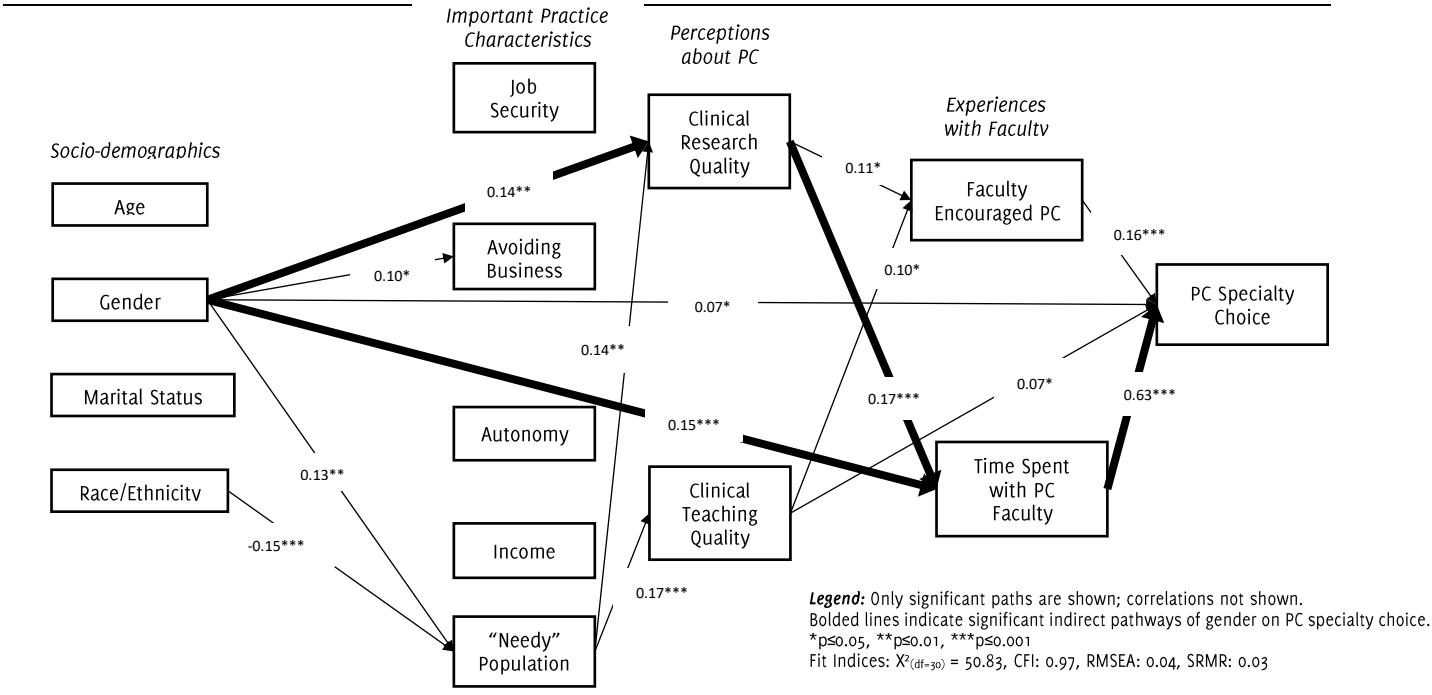
Indirect Effects on PC Specialty Choice

As denoted by bolded lines in ***Figure 2***, there were several statistically significant indirect pathways through which gender affected specialty choice (total indirect effects of gender: β=0.16, p< 0.001). Gender was indirectly associated with choosing PC through the time spent with PC faculty and perceived research quality. That is, women spent significantly more time with PC faculty, which in turn increased the likelihood of choosing PC. Women also reported significantly more favorable attitudes toward the quality of clinical research that PC physicians do compared to specialists, which had a positive association with time spent with PC faculty, in turn significantly increasing the likelihood of PC specialty choice. The indirect effect of time spent with PC faculty (β=0.01, p< 0.000), as well as the indirect effect of perceptions toward research quality (β=0.06, p<_0.05), were both statistically significant. Additionally, even with these partial mediators in the model, the main effect of gender on specialty choice remained (direct effect: β=0.07, p< 0.05).

Contrary to hypotheses in the conceptual model tested here, there were also indirect effects on specialty choice that did not operate through gender. Of the important practice characteristics variables, wanting one's future practice to have a portion of it dedicated to serving disadvantaged populations was indirectly related to PC specialty choice through its positive associations with time spent with PC faculty and perceived research quality. Thus, both experiences with faculty and perceptions about PC doctors explained the effect of disadvantaged populations on specialty choice (total indirect effects: β= 0.09, p< 0.01, direct effect: β=0.02, p=0.54).

Residents' perceptions about the quality of PC faculty's clinical research and teaching was partially mediated by the experiences they had with faculty during their internships/residencies (total indirect effects: β=0.12, p< 0.001). Perceiving that the quality of PC doctors' clinical research was better than specialists' was indirectly associated with specialty choice through both their positive associations with how strongly faculty encouraged residents to go into PC and the time they spent with PC faculty. The effects of perceptions of PC physicians' research was mediated by the experiences that residents had with faculty. While the total indirect effects of perceived teaching quality on specialty choice was statistically significant (β=0.06, p< 0.05), no single item significantly mediated this relationship.

Figure 2. Standardized Coefficients for the Direct and Indirect Effects of Gender on Specialty Choice Decision-Making Process (N=488).



Discussion

Summary of Findings

The purpose of this study was to identify the direct and indirect ways in which gender affects the medical specialty decision-making process, and how those factors are related to each other. As hypothesized and supported by the t-tests, women in this study chose PC at higher rates than men did. Women also placed higher importance than men did on practice characteristics that are perceived to define PC compared to specialties (i.e., more time spent with underserved patients), although there were no gender differences in the desire for autonomy, income, or job security. Women also had more favorable perceptions of PC faculties' competency in research and teaching than men did and, during their residencies, women reported spending a greater proportion of time with PC faculty than men. The structural model also shows that gender was directly associated with PC specialty choice, as well as indirectly related through several paths, including through the time spent with PC faculty and perceived research quality of PC physicians. Taken together, these findings suggest that the medical specialty decision-making process generally functions as hypothesized in the conceptual model depicted in ***Figure 1***, with gender affecting each part of the process.

Breaking the Gendered Cycle

This study shows that one of the key factors that deters medical students, and in particular men, from entering PC is the negative perception that the quality of research by PC faculty is poor. The specific variable employed in this study likely reflects negative perceptions of PC more broadly, as the devaluation of female dominated fields that leads men to flee is common.[17] In addition to the gender composition of PC in which more women choose PC than men, the nature of PC practice itself (e.g., the focus on the interpersonal relationship between doctor and patient, the social-psychological aspects of care in PC), is thought of as more feminine, and thus less intellectually demanding than the more technical specialties.[14] This is an important consideration for graduating medical students, as one study found that the most common reason for choosing their specialty was the perceived intellectual challenge of that field.[23]

Findings showed that men tend to have less favorable attitudes about the quality of PC physicians' clinical research compared to specialists and this is one of the factors that leads them to enter PC at lower rates than women. Therefore, one possible intervention is to attempt to change male's perceptions about PC. However, the increasingly large numbers of women entering medicine, with approximately half of them expected to choose PC, may exacerbate the already-established cycle in which PC physicians—both women and men— are more likely to promote and model positive PC to female medical students. To break this cycle and improve men's attitudes toward PC, this study's implications are in alignment with other studies that argue two possible ways to change negative perceptions and increase PC specialty choice: 1) curriculum changes that mandate more time spent in PC and 2) formalized mentorship programs.[19,24]

This study shows that the proportion of time spent with PC versus specialist faculty is an important factor in understanding why more women than men choose PC, as gender was directly and indirectly related to this variable that, in turn, significantly increased the likelihood of choosing PC. Additionally, time spent with faculty was positively associated with perceptions about the quality of PC research, suggesting that negative perceptions about PC are unfounded and do not reflect actual discrepancies in the degree of intellectual rigor of PC compared to specialties. That is, this study suggests that spending more time with PC faculty can change negative perceptions. Increased time spent with PC faculty could be incorporated directly into the medical education curriculum through more required PC clerkships and this would in effect target men to go into PC, since as this study shows men report less time spent with PC faculty than do women.

The finding that time spent with PC faculty was related to perceptions about PC and likelihood of choosing PC supports past research showing that more time in PC through increased required clerkships increases entry into PC.[25] Women, who already have an increased interest in PC than men, may be attracted to schools that have a greater focus on PC and thus require more PC clerkships. There is some evidence that, when choosing which medical school to attend, women more so than men consider a school's curriculum and they rate PC clerkships as more important than men do.[18] Especially since women are more likely to complete a primary care clerkship, one possible way to systematically increase time spent in PC would be to make PC clerkships compulsory in more medical schools, which one meta-analysis showed that mandatory clerkships improve attitudes toward PC and increase PC specialty choice, particularly in family medicine.[18,22] Furthermore, research shows curricula changes over time, such as mandatory PC courses added to the curriculum or entire programs dedicated to PC, might produce the most significant increases in rates of PC specialty choice.[25] Since this study shows that women are already self-selecting themselves into more time spent with PC, such changes to the medical education curriculum would in effect be targeting men who would not otherwise choose a PC clerkship or take multiple PC courses— or attend a school that focused on PC in the first place.

Some of the gender difference in the variable employed here about "contact time" with PC faculty may be attributable to informal time spent with PC faculty because women who are already more interested in PC specialties may be more likely to seek out, and subsequently form relationships with, PC faculty. Since ethical considerations would preclude the development of gender-specific curriculum requirements, a more feasible point of intervention would be to focus on potential PC faculty role-models. Prior research has established the importance of mentors, in a variety of role-modeling capacities, in the medical specialty decision-making process, although there is some evidence that early role models are more influential in choosing PC for men, while personal factors such as family responsibilities are more influential for women.[19,26-29] Since role models can also be a negative influence on PC specialty choice, it is important to more formally institutionalize mentorship programs designed specifically to increase PC specialty choice.[6]

Since there is no conclusive evidence that women PC faculty are more likely to suggest PC than are men PC faculty, to reverse the gendered cycle, more PC faculty need to explicitly encourage male medical students to enter PC. While most women and men PC faculty likely naturally encourage students to enter PC already, this study suggests that formalized mentorship programs, such as those in which students are assigned a faculty membership and participate in, for example, shadowing. Faculty could volunteer to participate in a mentorship program (and receive financial incentives to do so) to focus on identifying and encouraging male medical students into PC over the course of students' medical education. The findings of this study suggest that long-term curriculum changes and mentorship programs might be especially efficacious in recruiting men into PC and thus addressing the PC physician shortage.

Conclusion

Limitations

This study has several limitations, one of which is that this study could not determine causal order and so we cannot determine whether spending time with PC faculty differentially affects women's and men's specialty choices or if there is a selection effect in which women spend more time with PC faculty because they are more interested in PC in the first place. Similarly, we cannot establish the causal order between perceptions about PC physicians and time spent with PC faculty. However, given the multiple pathways to PC specialty choice and the

correlations among the various factors, this study suggests that changing one of the predictor variables is likely to affect the others.

Another limitation is that this study does not include several important factors known to be related to medical specialty choice and that differ by gender, such as a desire for specialties that allow for a "controllable lifestyle," meaning those specialties that allow for greater balance between domestic and work duties.[11,27] While it was beyond the scope and intent of this study to examine all possible factors in the medical specialty decision-making process, this study nonetheless demonstrates that gender affects this process through a multitude of pathways of which any of them can be targeted to encourage either or both women and/or men to enter PC and decrease the enduring PC physician shortage in the U.S.

The most notable limitation of this study is that the data were collected in 1997 and there have been major changes in the American health care system since then that have conceivably affected the ways in which gender affects the medical specialty decision-making process. However, medical education tends to be a self-reproducing institution that produces stability over time in the gendered medical specialty decision-making process.[17] Furthermore, many of the gendered patterns in specialty choice are a reflection of gendered socialization in the larger society, which has likewise not drastically changed since the 1990s.[18] Therefore, there seems to be a "cycle" that has been largely unaffected throughout time of more women choosing PC than men perpetuating the perceived culture of PC as feminine and less academically rigorous and leading to more women— and less men— choosing PC.

In this paper, we argue that the importance of this study's focus on identifying gender differences in specialty choice lies within its implications for addressing the enduring primary care physician shortage in the U.S. PC specialty choice has been steadily decreasing since the time this data were collected, which was at the peak of PC specialty choice among medical students in the mid-1990s.[11] Thus, the older data employed here likely underestimates the extent of the PC physician shortage. Additionally, PC specialty choice among men continues to decline, while women have been relatively consistently about 1.5 times more likely to choose a PC specialty than men through the mid-2000s and now into the current era.[8,30] The increasing absolute number of women entering medical school has kept the primary care physician shortage from being even more problematic than it currently is. However, the likelihood of this pattern continuing is precarious.

As primary care becomes increasingly female-dominated, it is also likely that the salary gap—as well as the level of prestige—between PC and other specialties will continue to grow, as it has in other occupations with a growing percentage of women.[8,17] In turn, if women begin to gravitate even more to non-PC specialties, where the gender pay gap is smaller and not rife with negative perceptions due in part to its feminization, it will exacerbate the PC physician shortage.[8,14,17] In spite of the data collected around the historical height of PC, the gender differences identified in this study are likely to have remained stable and thus the curriculum changes of required PC clerkships/electives and formal mentorship programs are still relevant, and arguably increasingly applicable, in order to address gender differences in specialty choice.

Future research should continue to examine the conceptual frameworks and specific variables that affect medical specialty choice and how these factors vary by gender. In particular, researchers should seek to examine whether and how increased time spent in PC through structural changes in medical school (i.e., mandatory PC clerkships/courses and formalized mentorship programs) improve men's perceptions about PC. Furthermore, given that there are several pathways through which gender affects PC specialty choice, targeting any one of the factors in the conceptual model tested here is likely to affect the entire medical specialty decision-making process. Thus, this study contributes to the literature on primary care specialty choice by offering a conceptual model with gender as the focal point and one that points to structural changes in medical education as the solution as opposed to the gendered preferences and styles that women and men bring with them into medical school. Specifically, this study suggests that changing men's perceptions of PC by increasing their time spent with PC faculty in medical school has the most potential to positively address the enduring PC physician shortage in the U.S., which is increasingly critical in order to create a sustainable and cost-effective health care system that promotes a healthy population.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Assessment of Healthful Lifestyle Behaviors between Graduate Programs

Erik Vincek,[1] Dana Angelo White,[1] Richard Feinn.[1]

Abstract

Background: Heart disease is a condition with many etiologies, some of which include genetics, obesity, exercise, diet, smoking, and alcohol use. Studies show that increased years of education lead to better health outcomes, specifically lower rates of heart disease and obesity. Despite their high level of education, physicians have been shown to have a disproportionally higher rate of heart disease. Our objective was to determine whether there are particular lifestyle habits present among medical students that may lead to increased risk of heart disease as their academic and clinical futures progress. **Methods:** A total of 201 Quinnipiac University medical, law, and education graduate students were recruited to this survey study. Descriptive statistics were used to present the data. Chi-squared test and Kruskal-Wallis tests were used to test the significance and a p-value ‹0.05 was considered significant. **Results:** Medical students were able to answer health-related questions correctly more than their law and education student counterparts (p-value ‹.001), felt able to explain the terms saturated fat (p-value ‹.001) and trans fat (p-value ‹.001) and give an accurate estimate of personal BMI status better than their counterparts in the law and education programs, but did not significantly differ in meeting Dietary Approaches to Stop Hypertension (DASH) diet recommendations or American Heart Association (AHA) recommendations for physical activity. **Conclusion:** Increased health-related knowledge has little bearing on individual dietary and physical activity habits of graduate students. We found no evidence to show that increased medical knowledge leads individuals to pursue lifestyle habits that lower the risk of heart disease. The failure of medical students to meet or surpass their peers in levels of physical exercise and heart-healthy diet choices may contribute to their increased risk of heart disease as physicians.

Key Words: Medical Students; Cardiovascular Diseases; Heart Diseases; Health Behaviors; DASH Diet (Source: MeSH-NLM).

Introduction

In the United States, heart disease is the number one cause of death.[1] Obesity, history of smoking, lack of exercise, and poor diet are just a few of the factors that contribute to heart disease in the United States. According to a Health United States Report 2016 estimate, 70.7% of Americans aged 20 and over are overweight or obese, and in 2014 only half of American adults met the American Heart Association requirements for aerobic physical activity, based on self-report.[2-3] Additionally, about one third of coronary heart disease deaths are attributable to smoking or exposure to second-hand smoke.[3]

Various diets are known to be better for long-term heart health. It has been shown that diets using non-hydrogenated unsaturated fats instead of saturated fats, whole grains as the predominant source of carbohydrates, and inclusion of adequate fruits and vegetables can lower the risk of cardiovascular disease (CVD).[4-6] The Dietary Approaches to Stop Hypertension diet includes the incorporation of fat-free and low-fat dairy products, poultry and fish, beans, nuts, fruits and vegetables, and vegetable oils into the diet, while limiting the intake of sugar-sweetened products and sodium. The DASH diet has been shown to lower blood pressure and LDL cholesterol, and is endorsed by the AHA and National Heart, Lung, and Blood Institute. There is strong evidence that hypertension is a predominant contributor to CVD, thus population adherence to DASH diet recommendations is important to investigate.[7-8]

Studies have shown that increased socioeconomic status and years of education lead to better health outcomes, specifically lower rates of chronic heart disease, obesity rates, and smoking.[9-11] Some of this variation may be due to differences in diet and levels of physical activity. Physical activity is positively correlated with vascular health and reduces the lifetime risk of developing CVD.[12] Adopting a regular exercise routine can have immediate benefits, including weight loss, fat loss, increased cardio-respiratory fitness, and longevity.[13]

Despite the correlation between higher levels of education and greater long-term health, several studies have shown that physicians have a particularly increased risk for cardiovascular disease and are at greater risk for CVD than nurses working in the same healthcare setting.[14-16] Additionally, studies have shown higher rates of depression and suicidal ideation among physicians compared to the general population[17-19]. These findings are paradoxical to those that suggest that a greater level of education leads to greater health outcomes. To determine when and how these increased risks develop, it may prove important to investigate whether there are already changes in lifestyle behaviors during medical school which might facilitate unexpectedly higher risks of CVD later in physicians' careers.

Controlling for years of education, we sought to compare medical students to counterparts who were at an identical graduate level of education. First and second year Quinnipiac University law and education graduate students were compared to first and second year Quinnipiac University medical students to determine whether the three graduate programs showed similar trends in heart-healthful lifestyle behaviors. We assessed heart-healthful lifestyle choices via adherence to recommendations from the American Heart Association and the DASH diet.

Methods

A cross-sectional study was conducted during the 2017-2018 academic school year on Quinnipiac University medical students, law students,

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and School of Education graduate students using a self-administered questionnaire.

A paper questionnaire was designed by the authors, which included 29 questions, the content of which included questions regarding dieting habits, exercise levels, and general health knowledge (see Appendix). Four questions were considered general health questions, fifteen questions assessed dietary habits, three questions assessed physical activity levels, three questions assessed individuals' perceived knowledge, and four questions were used to establish a profile of the students that included age, height, weight, gender, and perceived BMI. The students were assured that survey responses would remain anonymous. A complete written informed consent form was received from each participant in the study upon acknowledgement that the survey responses would be used for research purposes only. No names were collected in this study. Each questionnaire was distributed in person to the subjects on the campus of Quinnipiac University. This study was approved by the Quinnipiac University IRB (approval no. 04418).

Collected data was tested using the program IBM SPSS Statistics 25. The students were placed into groups based on their graduate area of study (education, law, medicine). To compare significance among student groups, a Chi-squared test was used for nominal variables, Kruskal-Wallis tests were used for ordinal variables, and a one-way ANOVA for continuous variables. Continuous variables were checked for normality. A p-value of ‹0.05 was considered statistically significant.

Results

The participants in this study included 201 graduate students affiliated with Quinnipiac University. 50 (24.8%) were education students, 53 (26.4%) were law students, and 98 (48.76%) were medical students. The mean age of students in this study was 25.0 years. Mean ages and BMI of students in each program are shown in ***Table 1***. There was a significant difference in mean BMI between programs (p-value 0.008), of which medical students had the lowest score. Using a post-hoc Bonferroni comparison, the mean BMI between the law program and medical program was significantly different (p-value 0.006), but there was not a significant difference between the mean BMI of the education program and law program, or between the education program and medical program. No significant difference was found in smoking and alcoholic drinking habits between programs.

Table 1. Mean Age and BMI of Students in Each Program (N=201).

	Education	Law	Medicine	P-value
Mean Age	23.46±2.12[a]	24.57±3.38	26.03±2.78	‹0.001
Mean BMI	24.36±3.77	26.09±5.96	23.72±3.80	0.008

Legend: [a] Numbers in parenthesis specify standard deviation.

Three questions assessed students' perception of their own knowledge. A significant difference was found between programs in two of three of these questions. A significant difference existed in the proportion of students that felt they could explain the definition of a saturated fat (p-value ‹0.001) and a trans-fat (p-value ‹0.001). No significant difference existed in the proportion of students that felt they could explain the difference between natural and added sugar (P-value 0.132). These results are represented in ***Table 2.***

Four questions in the survey asked how often students think about limiting sugar intake, saturated fat, trans fat, and sodium intake. There was only a significant difference between programs in responses to "When making food choices, how often do you think about limiting your intake of trans fat?" (p-value ‹0.001). Results from this question

Table 2. Percentage of Students in Each Program Who Answered "Yes" to Each Perceived Knowledge Question.

Question	Education	Law	Medicine	P-value
Do you feel that you could accurately explain to a friend or colleague the definition of a saturated fat?	28.0%	24.5%	93.9%	‹0.001
Do you feel that you could accurately explain to a friend or colleague the definition of a trans-fat?	22.0%	26.4%	92.9%	‹0.001
Do you feel that you could accurately explain to a friend or colleague the difference between the terms "natural sugar" and "added sugar"?	72.0%	71.7%	83.7%	0.132

are shown in ***Table 3***. Of the questions related to dietary habits, only "On average, how many servings of nuts, seeds, or dry beans do you consume weekly?" yielded a significant difference between groups (p-value 0.002).

Table 3. Responses to "When Making Food Choices, How Often Do You Think about Limiting Your Intake of Trans Fat?"

Program	Never	Rarely	Sometimes	Most of the time	Always
Education	20.0%	30.0%	16.0%	28.0%	6.0%
Law	15.1%	13.2%	39.6%	20.8%	11.3%
Medicine	8.2%	14.3%	16.3%	36.7%	24.5%

There was no significant difference between groups meeting the overall AHA recommendation for physical activity. There was also no significant difference between the study groups meeting individual components of the AHA physical activity recommendation. ***Table 4*** shows the percentage of students in each group that met the AHA recommendation and percentage that met each component of the AHA recommendation.

Table 4. Percentage of Students in Each Program Who Met Individual Components and Overall AHA Recommendations for Physical Activity.

Program	Meet vigorous aerobics component	Meet moderate aerobics component	Meet muscle-strengthening component	Meets overall AHA requirement
Education	54.0%	12.0%	76.0%	64.0%
Law	52.8%	9.4%	79.3%	66.0%
Medicine	33.6%	17.4%	61.2%	52.0%

Four questions assessed general health knowledge of the participants. Each one of these questions was answered correctly by medical students significantly more than by students in the other groups. Medical students also answered a significantly higher total number of health-related questions correctly compared to the other two groups (p-value ‹0.001). ***Table 5*** show results from these questions.

Table 5. Percentage of Students Who Responded to Each Health-Related Question Correctly and Mean Number of Health-Related Questions Answered Correctly.

Question	Education	Law	Medicine	P-Value
"What is the number one killer of Americans?"	68.0%	88.7%	94.9%	<0.001
"What is the effect of increased sodium intake on blood pressure?"	98.0%	88.7%	100.0%	0.001
"How many milligrams of sodium are in one teaspoon of salt?"	40.0%	28.3%	49.0%	0.047
"A healthy daily intake of sodium (in milligrams) falls into which range?"	34.0%	39.6%	57.1%	0.014
Mean # of health-related questions answered correctly	2.40 (±0.904)	2.45 (±0.774)	3.01 (±0.780)	<0.001

Discussion

With heart disease's global impact on patients and health-care systems, it is well worth investigating the trends that may lead certain populations to have less risk for cardiovascular disease. Studies have shown that a higher level of education leads to greater health outcomes, including lower rates of heart disease.[9-11] The authors believed that an important reason for this trend was greater access and adherence to healthy diets and fitness regimens as well as increased knowledge of healthy lifestyle habits. This study revealed several characteristics of the physical activity level, dietary habits, and general health-knowledge between Quinnipiac University graduate students.

Despite a curriculum that strongly emphasizes the importance of healthy eating and exercise in terms of heart and overall health, Quinnipiac University medical students failed to surpass their peers in either category. Medical students answered significantly more health-related questions correctly, yet it seemed to have little bearing on their dietary habits. There was no significant difference in any of the dietary habits between the programs, except for the number of servings of nuts, seeds, and dry beans consumed weekly. This is one of several findings that may seem hypocritical of medical students and is a recurring theme of this study: medical students that are expected to become the primary source of health management for countless of patients fail to incorporate into their own lives what they are taught in medical school. If medical students and physicians are unable to follow their own advice, it seems unfair that we should expect patients to follow such advice. It might not be a stretch to suggest that improving medical student and physician adherence to healthy lifestyle behaviors may increase their patients' likelihood to do so as well.

Despite the findings regarding dietary habits, medical students had a lower BMI than both other groups. Although studies have shown that lower BMI is correlated with lower rates of coronary heart disease, high variability in body structure and composition among individuals continues to make BMI an uncertain predictor of heart health, and thus this finding was not used as a primary indicator of heart health in this study.[20]

Medical students were more likely to feel they could explain the definition of a saturated fat and trans-fat, but were similar in thinking about limiting saturated fat intake. Medical students were also able to answer correctly the range of the healthy amount of daily sodium intake and the range of the amount of sodium in one teaspoon of salt more than individuals from the other programs, but there was no difference in thinking about limiting sodium intake, despite the well-known negative consequences of a high sodium diet on heart health of which is heavily reinforced in the medical school curriculum. Knowing about daily sodium intake recommendations has been shown to increase the likelihood of individuals using nutrition labels to make healthier food choices[21]. The authors' reasoning for this finding is that even with more health knowledge, medical students may not have sufficient time or money to cook healthy meals during a demanding curriculum and constricted budget. High stress levels, common in medical students, have been shown to be associated with unhealthy eating and obesity and may be impacting their dietary choices negatively. [22-24] These results suggest that education itself is not the sole factor facilitating healthy dietary and physical activity habits.

There was no significant difference in meeting the AHA recommendations for physical activity. Worth mentioning however is that the proportion of medical students who met the AHA recommendation for vigorous aerobics and that for muscle strengthening activity, as well as the overall AHA requirement for physical activity, was lower in medical students than in both other groups. A potential reason for this finding could be a difference between the medical student and law or education student schedule; however, individual schedules outside of required curriculum are variable and cannot be assumed.

Although it would be expected that medical students would practice healthier lifestyle habits due to their greater health knowledge, our results suggest otherwise and point to the previous research that shows that physicians are not healthier than the general public. We would expect that medical students and physicians who devote their careers to improving the health of others would have the willingness and ability to improve their own health, but for undetermined reasons they fail to do so. To help up-and-coming physicians improve their own health, research is required to determine why physicians in particular are experiencing increased CVD risk and if it may be due to habits that are already present in the cradle of their medical careers.

The primary limitation of this study was that the findings were based on an anonymous survey and thus self-report bias may have existed.[25] This study was a representation of the students at a single point in time and only included students from one university. Future studies with more students and that involve more universities could provide more information on the dietary and physical exercise habits of graduate students.

Even though there was potential for self-report bias, the anonymity provided by the survey may have allowed the students to give more accurate responses about personal information such as their lifestyle habits. Future studies may also benefit from including survey questions regarding stress levels, number of hours spent in mandatory classroom events, and number of hours spent studying outside of mandatory classroom events.

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Author Contributions

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Review

How does the Extracellular Matrix Change in the Setting of Heart Failure?

Amerikos Argyriou.[1]

Abstract

The Extracellular Matrix is a dynamic entity, showing constant degradation and deposition while providing the framework for the cardiomyocytes and interstitial proteins to lie on. Its function is important for the proper myocyte alignment within the heart and for internal communication from cell to matrix. Dysregulation of the remodeling process resulting in the breakdown of collagen by matrix metalloproteinases is a hallmark of heart failure pathophysiology and produces functional changes encompassing all matrix proteins. Several etiologies with distinct mechanisms ultimately bring about signs of heart exhaustion such as reduced ejection fraction, reduced compliance and ventricular dilatation. Discussed in this paper is the role of inflammation, collagen cross-linking and of myofibroblasts in matrix dysfunction and the mechanisms with which these changes occur in heart failure. Understanding extracellular protein roles within this context would allow for specific drug targeting and thus prevention of heart failure in the early stages of the disease. More studies must be conducted to discover the specific matrix proteins and cytokines that modulate the pathological remodeling process. Serum biomarkers of extracellular degradation products, selective metalloproteinase inhibitors and a personalized treatment approach with a revisal of the current classification of heart failure are topics requiring further exploration.

Key Words: Heart; Heart Failure; Extracellular Matrix; Cardiomyocytes; Matrix Metalloproteinases (Source: MeSH-NLM).

Introduction

Heart Failure is a global problem that is on the rise in the developed world. Worldwide, 38 million people are living with this disease, with a 50% increase within the last 15 years alone.[1] With medical advances improving outcomes from myocardial infarctions (MI) and congenital cardiac conditions, the same advances have also inadvertently brought about a steep increase in the prevalence of chronic heart failure.[2] For the elderly in England and Wales prognosis can be worse than most cancers, with a 10% 30-day mortality following admission, highlighting the need to improve our understanding and treatment of this progressive disease.[3] The extracellular matrix (ECM) is a scaffold including extracellular proteins, in which cardiac cells and cardiac vessels are arranged. We are now aware that the ECM is not a static structure but is actively broken down and reformed by an array of chemical and physical signaling within the heart.[4] Changes in the myocardial matrix even encompass the cardiomyocytes, the resident cells of the myocardium that respond with a state of pathological hypertrophy.[5] With heart failure, we see changes to the ECM that may differ in etiology, but all progressively results in an impaired contractility, fibrosis and eventual cavity dilatation.[6] This review describes the ECM environment, identifies key modulators of its remodeling process in heart disease and finally mentions the clinical implications and future directions of this ever-growing field.

The Extracellular Enviroment

The ECM composition is vital for the heart's structure as it regulates the alignment and activity of the cardiomyocytes, which are the resident cardiac contractility, which require a stable interstitium to properly function.[7] Fibroblasts make up over 70% of cells in the myocardium and functionally secretes the most matrix proteins which is suggestive of the large quantities constantly being made in the interstitial space.[4] The tight space between the myocytes must be able to transfer signals from the matrix to cell and also convert the individual contracting myofibrils into a collective pump, via the Collagen-Integrin-Cytoskeleton-Myofibril relationship.[8-9] The ECM includes structural, adhesive and regulatory proteins that work together to maintain the heart's normal function.[10] It is vital that all these proteins within the ECM stay balanced as they hold important roles in the maintenance of tissue homeostasis.

Structural Proteins

Fibrillar Collagen: In the heart, we can find collagen types I, III, IV, V, VI and VIII of which types I and III dominate the matrix. Type I provides tensile strength and type III distensibility.[11-12] I, II, III, V and VI all have a common fibrillar structure and are not found on the basement membrane of cells.[11] They all contain one main triple helix chain of Glycine-X-Y repeats where X is usually proline and Y can be any amino acid. The collagen helix terminates into 2 globular side chains on either side, referred to as the N- and C- Propeptides and these help in the alignment of the collagen strands as they are secreted from the cell.[13] Upon maturation, the side-chains are cleaved by procollagen peptidases, releasing the Propeptides into the ECM and rendering the mature collagen insoluble.[14] Cross-links between collagen fibrils are formed via the copper-containing enzyme, lysyl oxidase.[15] This is a physiological occurrence that helps protect the collagen fibrils, both against the mechanical strains imposed on them as a result of the heart's dynamic function, but also to enzymatic proteolysis resulting in degradation. ***Figure 1*** shows the structure and cleavage site of a procollagen molecule. Collagen that has formed these cross-links is extremely stable and, pound for pound, is stronger than steel.[16] The collagen in the ECM is constantly being remodeled under the control of fibroblasts that communicate with this scaffold via Discoidin Domain Receptor 2 (DDR2) surface receptors. These receptors allow collagen synthesis and degradation to be finely monitored by fibroblasts.[17] The correct concentration of fibrillar collagen is vital for the heart's form and function, and an inappropriate amount of deposition is associated

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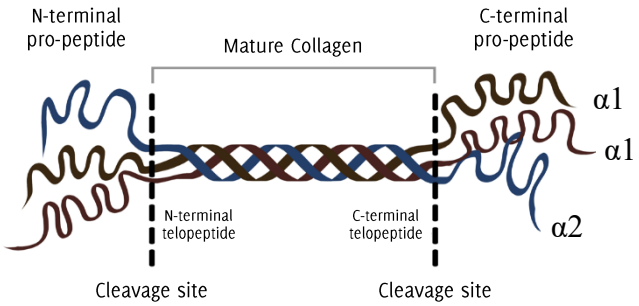
with cardiovascular disease and more specifically diastolic heart failure.[18]

Elastin: Elastin, unlike collagen, is not subject to a fixed turnover rate, and in a healthy myocardium can persist life-long.[19] Elastin is implanted within its own scaffold of glycoprotein microfibrils once synthesized by fibroblasts, cardiomyocytes or endothelial cells.[20] The stiffness of the collagen fibers is counteracted upon by the elastic recoil properties of elastin, being up to a thousand times more flexible than collagen.[9] This is what gives the heart the ability to rebound in diastole following a contraction. Elastin is also vulnerable to degradation in cardiac disease, either due to chronic stretch-recoil or due to increased protease activity of Matrix Metalloproteinases (MMP).[21]

Figure 1. Formation of Mature Collagen from its Pro-Collagen Precursor, Releasing the Pro-Peptides at the N- and C-Terminals and in this Way Becoming more Stable and Resistant to Degradation.



Adhesive Proteins

These include all the non-collagenous proteins and account for over 95% of all the molecules in the ECM.[22] They are vital for communication between cells and between the cell and the matrix.[23] Yonggang et al studied their function in the setting of cardiac injury and concluded that they have a part to play in the response to injury, but individual roles and functions have yet to be identified.[24] These proteins allow cardiomyocytes to monitor the myocardium and therefore modulate their behavior accordingly, through complex feedback loops.[25]

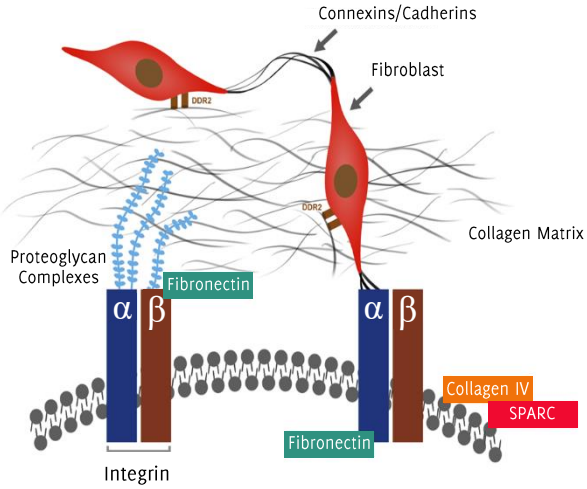
Collagen IV: This type of collagen is only found outside the membrane of cardiomyocytes where it folds into a sheet across the basal lamina.[26] Collagen IV connects the contractile myofibril within the cardiomyocytes with the ECM and is therefore vital for the transfer of force across the cardiac tissue.[27]

Integrin: This cell-interstitium linking protein is made up of an α and β transmembrane subunit, as shown in **Figure 2**, and is required for nearly all communication within the ECM.[28] Ross and Borg's review on integrin role and function concludes that they are not merely adhesive proteins but have an important role in cell transduction in health and disease.[29] Shed integrins have been found in heart failure by Ding et al, cleaved from distressed cardiomyocytes and dysregulating communication within the heart.[30] Targeting this molecule for treatment has not been successful as there is complex sub-specialization within the integrin family where certain heterodimers bind fibronectin (α5β1) while others bind to collagen and laminin (α3β1 and α5β1).[31]

Fibronectin: This molecule exists as 3 different subtypes and can exist intracellularly and within the ECM (seen in ***Figure 2***). It has been shown by Sharma et al to unfold itself and thus bind to integrin from within the cell's basal lamina. In this way it assists in cell migration and differentiation. It is also produced following an injury by fibroblasts, macrophages and endothelial cells to help link up the cells that form the scaffold in the injured area.[32]

SPARC (Osteonectin): SPARC stands for secreted protein acidic and rich in cysteine and is found in the basal lamina with many important functions. It stabilizes the collagen matrix by phosphorylation of the SMAD2 pathway with which it controls procollagen secretion out of the cell.[33] It also facilitates cytokine and growth-hormone efficacy, regulates MMP expression and can alter cell shape.[34-35] SPARC levels will markedly increase following cardiac injury, acute and chronic.[24]

Figure 2. The Complex Cytoskeletal-Matrix Interaction as well as the Role of the Fibroblast in Contact with the Collagen Matrix via Discoidin Domain Receptor 2 Receptors and with the Myocite via Integrins.[24,51,100] DDR2 is the Discoidin Domain Receptor 2.



Collagen Remodeling: Synthesis and Degradation

One of the most noticeable changes to the ECM in the setting of heart failure is the dysregulation of collagen deposition and degradation. This fine control is performed by Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs), two enzymes both formed within the fibroblast.[36] The former is a protease enzyme and the latter its endogenous inhibitor with both being controlled by fibroblasts within the ECM. MMPs and TIMPs keep a homeostatic control over the collagenous matrix of the ECM as well as over the rest of the matrix proteins. As a result, the ECM is a dynamic entity constantly being broken down and reformed, in both health and disease. What separates a physiological state from a pathological one is the balance of the same remodeling process.

Matrix Metalloproteinases

The matrix metalloproteinases are a family of over 24 zinc-containing endopeptidase enzymes. They are present in cardiovascular disease but can also be found in fibrosis and inflammation all over the body, as well as in tumor metastases.[37] There are 6 main subtypes of MMP, and their enzymatic action dictates their title. They are all mentioned in **Table 1** along with the substrate they degrade and the effects they produce. MMPs are released into the ECM as inactive zymogen molecules where they are activated by proteases such as plasmin or by another MMP.[38-39] Spinale states that the catalytic domain is similar across all subtypes, but the extracellular binding domain, the C-terminal, is specific and conveys to each MMP its independent properties.[40] In **Table 1** are shown MMP-2 and MMP-9, the Gelatinases, but can even break down Collagen types I, IV, V and the contractile apparatus from within a cell.[41] Another MMP of importance in heart failure is MMP-14 or otherwise Membrane Type-1 MMP (MT1-MMP). This class of protease, unlike the rest, exists only in an active form and can degrade all basement proteins as well as collagen.[42] Tyagi as well as Nagase have both written an extensive list on the cytokines and hormones that they believe activate each MMP and have linked increased MMP activity to a heightened risk of heart failure (shown in

Table 1). A factor that must be considered is the complex interaction between all the ECM components and how they are all intertwined. For example, it has been shown that MMP-3 might produce a shielding effect to disease, through an unclear downstream effect.[43] Some MMPs, such as MMP-2, have shown pro-fibrotic capabilities and may actually cause a net increase in collage deposition rather than what we would expect, most likely via the TGF-β pathway.[44] To conclude, MMPs perform a diverse set of functions. On one hand they are able to degrade collagen but on the other hand also function to activate fibroblasts and increase collagen deposition. Radauceanu et al have discovered that ECM turnover is an independent predictor of all-cause mortality and heart failure hospitalization, therefore a very important aspect in the pathophysiology of Heart Failure.[45] More studies into this field are necessary to more accurately elucidate individual MMP roles.

Tissue Inhibitor of Metalloproteinases

The TIMPs are folded disulphide-linked proteins that contain 2 domains: a C-terminal and an active N-terminal which binds to the active site of MMPs.[46-47] This binding occurs due to cysteine residues at the N-terminal that react with the Zinc ion within the MMP active site.[48] TIMP inhibition of MMPs has been shown to overpower MMP activity as certain studies of left ventricular hypertrophy and chronic heart failure where both MMP and TIMP levels were similarly increased resulted in fibrotic deposition and not degradation.[44] Perhaps this is a marker of TIMP efficacy being superior in the balance of MMPs and TIMPS. TIMP-4 is believed to be a key player in terms of fibrotic deposition in the heart by Li et al, Schultz et al and Graham et al.[49-51] Moore states that TIMP-2 and TIMP-3 are most abundant while TIMP-4 is not cardio-specific and only partly expressed by healthy cardiomyocytes.[46] These minor discrepancies in the results could reflect the fact that more studies are required in order to understand the exact roles and populations of these protease inhibitors.

ECM Turnover in Heart Failure

In a failing heart, many pathological events are occurring that have a large impact on the constituents of the heart's tissues. Both the ECM and the cells of the heart are affected by an increase in inflammatory mediators and an increased dynamic load.[52] We now know fibroblasts have the potential to signal pro-inflammatory mediators in the absence of infection or ischemia.[52] This signaling occurs as a result of the heart's inability to cope with mechanical demands and directly impacts the cardiac molecular environment.[53] It is now well documented that ECM remodeling is a distinguished feature of cardiac risk that will gradually lead to heart failure.[40] The key player we tend to focus on are the MMPs that have a direct functional role in the progression to heart failure by enzymatically breaking down the structure of the collagenous matrix.[54] The question that remains is why do we see fibrotic deposition in some cases while in others we see collagen degradation? An interpretation of these seemingly conflicting phenotypes is in line with Kim et al's transgenic mouse model. Mice given an active MMP-1 gene initially responded with myocyte hypertrophy, myofibroblast formation and increased collagen synthesis at 6-weeks. This matches the initial state of hypertrophy and fibrosis seen in early stage heart failure.[55] However, at 12-months the collagen content of the transgenic mice was far lower than the wild-type control mice.[56] The proposed mechanism is one of adapting to the stressor, this case the collagenase MMP-1, by synthesizing more collagen to the point of exhaustion. At this point we begin to see a destruction of the matrix and weakening of the heart wall, markers that we also see in human patients suffering from heart failure.[56] These matrix changes directly influence the heart's mechanical functioning and lead to the gradual signs and symptoms we associate with cardiac failure.

Inflammation mediates ECM Remodeling

As we know, the ECM is constantly active and subject to remodeling and as a result is exceptionally susceptible to any chemical or mechanical stressors that might affect it.[57] Inflammation due to increased cardiac stress induces cytokines such as TGF-β, IL-1β, FGF,

Table 1. Description of the Target and Effect of Each of the Main Matrix Metalloproteinases Implicated in Heart Failure.[46,54,101-102]

MMP	Enzyme Family	Substrate	Result of Activation
MMP-1	Collagenase	C-Terminal Collagen I	↑ Collagen breakdown
		Basement Membrane Proteins	↑ Myocardial Fibrosis
			Pro-Inflammatory
			Mesenchymal Cell Differentiation
MMP-2	Gelatinase	Chondroitin Sulphate Proteoglycan	Vasoconstrictor
		Angiostatin	Cell Apoptosis
		Collagen III	↑ TGF-β
			↑ Risk of Heart Failure
			↑ IGF-1
MMP-3	Stromelysin	Basement Membrane Proteins	Epithelial cell Apoptosis
		Plasminogen	↑ IGF-1
		E-cadherin	Pro-Inflammatory
		Perlecan	Anti-Inflammatory
MMP-7	Matrilysin	Fas Ligand	Adipocyte Differentiation
		Rank Ligand	Fas-mediated Apoptosis
		ECM proteins	Pro-Inflammatory
		Precursor of TNF-a	Chemoattractant
MMP-9	Gelatinase	Precursor of TGF-β	↑ TGF-β
		Citrate Synthase	↓ IL-2
		ECM proteins	↓ Mitochondrial Function
		Collagen IV	Pro-Inflammatory
		Plasminogen	↑ Fibroblast migration
MMP-12	Macrophage Elastase	ECM proteins	Pro-Inflammatory
		Plasminogen	↑ Fibroblast migration
		Elastin	↑ Endostatin-like fragment
MT1-MMP (MMP-14)	Stromelysin	ECM proteins	↑ Myocardial Fibrosis
		Collagen I	↑ Risk of Heart Failure

Legend: ↑ IGF-1 means an increase in IGF-1 as a result of that MMP being activated. ECM Proteins accounts for osteopontin, fibronectin, hyaluronan, tenascin-C and galectin-3 in these studies.

Angiotensin II and Endothelin-1, which upregulate MMP activity and increase the migration of myofibroblasts into the heart.[22,58-59] Damage associated molecular patterns (DAMPs) released from distressed cells promote further inflammation and were shown to activate fibroblasts in vitro.[60] Bradham et al looked at zymographic activity in failing canine cardiac tissue and discovered decreased MMP activity in tissue injected with a TNF-α blocker.[61] This suggests that TNF-α and potentially other cytokines and hormones do interact with ECM turnover and can worsen

the progression to heart failure by directly interfering with the MMP/TIMP control of the ECM. It should be stated that some attempts to tackle these mediators are being pursued in current specialized centres.[62] This inflammatory response is not limited to collagen but also affects fibronectin, osteonectin, elastin and laminin, which were all found to be increased in heart failure pathology by Hein et al.[63] Finally, inflammatory mediators can serve as transcription factor activators for MMPs, tipping the scale of collagen homeostasis by direct MMP upregulation.[64]

The role of the Myofibroblast

Myofibroblasts, which are commonly absent in healthy myocardium having been identified only in heart valve leaflets, are key drivers of ECM remodeling in disease (Progenitor populations shown in ***Figure 3***).[65-66] They perform all the functions of an active fibroblast to an even greater degree to cause and increase in matrix deposition and fibrosis.[65] They also exhibit a myocyte-like phenotype with contractile capabilities and the generation of a stress-fiber network.[67] The matrix deposited by these cells is also said to differ to that of fibroblast origin, with particularly increased amounts of Collagen I and Fibronectin.[68] All these features lead to a change in the normal environment both structurally and composition wise in the setting of heart failure. In the acute setting myofibroblasts are generated from cardiac pericytes, fibroblasts and smooth muscle cells. Long-term stressor persistence allows myofibroblasts to form from cardiac endothelial cells that transition into mesenchymal cells and also from cells derived from the hematopoietic stem cell line (***Figure 3***).[69] Myofibroblasts contribute to pathological hypertrophy, usually with accompanied diastolic dysfunction.[70] This dysfunction is a direct result of the fibrotic stiffness brought about by the myofibroblasts, as described above. Overall, the changes described result in a stiffer, less compliant myocardium that is less effective in its ability to pump blood around the body.[71] Myofibroblasts damage the cardiac environment in heart failure but in an MI can have beneficial properties and be necessary for wound healing.[72-74] Interestingly, several animal studies have been pursued in the beneficial treatment using myofibroblast differentiation from progenitor populations such as BMDCs in the response to acute ischemic damage post-MI.[75]

Collagen Cross-linking in Heart Failure

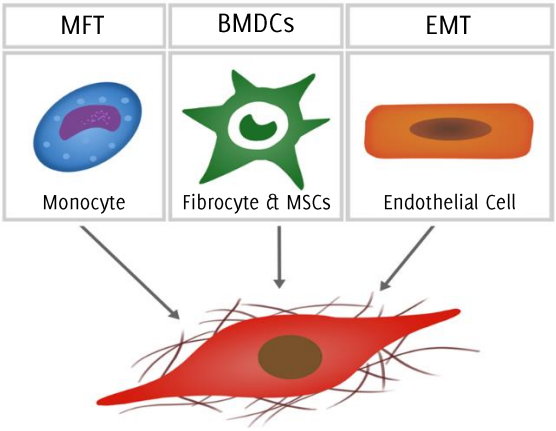
Collagen Cross-linking (CCL) is a feature of ECM remodeling in heart failure[16,76] and has been shown by Graham et al to be more indicative of a worsening prognosis than collagen type ratios in the ECM.[37] CCL occurs via two different mechanisms in the heart: an enzyme-mediated pathway and a pathological proteoglycation pathway.[37] The latter is most evident with aging and in diabetics, but can occur incidentally with other groups too.[77] The end result is an increased stiffness of the myocardium and ventricular dilatation, both increasing the risk of heart failure.[78] As previously described, collagen must be cross-linked to increase its strength and resistance to degradation, and a collagen matrix with decreased CCL is a weaker and more unstable structure. Gunja-Smith et al investigated the amount of pyridinoline CCL in human heart collagen directly post cadaveric transplant and found that even though collagen levels were quadrupled in some specimen, the overall CCL between that collagen was poor, resulting in dilatation and decreased compliance, both clinical features of heart disease.[79] This study is suggestive of the fact that even though a fibrotic state exists in heart failure (study in question looked at dilated cardiomyopathy), the collagen of these patients although plentiful is weak as a result of its poor cross-linking.

Future Directions of ECM Remodeling Research

ECM Plasma Profiling as a prognostic measure of Heart Failure

In current specialized centers, it is standard practice for multiple cardiac biomarkers to be monitored in patients with heart failure. Several biomarkers including BNP, NT-pro BNP, Troponins as well as proteins like Galectin-3 are screened for to help in disease prognosis.[80-81].

Figure 3. The Different Progenitor Populations that Differentiate into Myofibroblasts in the Setting of Injury and Mediate further Remodeling.[50, 55, 65].



Legend: MFT: Monocyte Fibroblast Transition, BMDC: Bone-Marrow Derived Cell, EMT: Endothelial-Mesenchymal Transition, MSC: Mesenchymal Stem Cell.

With the recent advances of cardiac matrix proteomics, ECM biomarkers may also be monitored. As previously described, collagen Propeptides are released into the ECM and are picked up in blood tests as a measure of collagen synthesis. Collagen telopeptides on the other hand should not be cleaved in the physiological state, therefore C- and N-telopeptides in serum can point at pathological collagen degradation.[82] These biomarkers are good indicators of what is going on in the ECM and are found in our bloodstream before any physical symptom of heart failure is apparent. Using these biomarkers in a day-to-day clinic for cardiac observation should be explored further as the N-terminal propeptide of Type I and the C-terminal of Type III Collagen have been shown to statistically correlate with myocardial fibrosis.[45,83-84] Furthermore, Kato et al highlighted the prognostic potential of using other ECM biomarkers in the clinic as osteopontin and MMP/TIMP ratios all decrease significantly post-LVAD (Left Ventricular Assist Device) implantation in patients with heart failure and were found to be consistently higher in those who suffered with right ventricular failure in the months following the surgery.[85] A final reason to further explore this area of research, as opposed to looking at the ECM under a microscope, are the barriers with attaining live cardiac biopsies which although proven relatively safe in practice, having them performed for research purposes is not ethically justifiable.[86] A Review written by Mr. R.J. van Kimmenade summarizes the novel biomarkers in Heart Failure.[87]

The Need to look for a Selective MMP Inhibitor

Since Weber et al linked the Renin-Angiotensin-Aldosterone-System (RAAS) with eventual myocardial fibrosis and stiffness in 1994 we have treated most forms of heart failure thus far with Diuretics, Anticoagulants, Digoxin, Beta-Blockers, ACE Inhibitors and Aldosterone Inhibitors.[88-90] We have recently discovered that inflammatory markers inducing MMP activation are in play even before the RAAS system is activated in heart failure.[39,91-92] Therefore, MMP inhibition could be considered as a potential early intervention strategy. Positive results depicting a decrease in collagen deposition have been recorded in animal trials yet the transfer to human trials has been slow due to the side-effects brought about by the many beneficial and vital functions of the MMPs.[93] Selectively identifying an MMP causing pathological remodeling without a concomitant role in health has proven difficult with limited efficacy in the former and significant musculoskeletal side-effects in the latter.[94] Nevertheless, the future of early treatment in patients with heart failure could very well lie in treating their specific matrix pathology, and not in purely treating the neurohormonal systemic symptoms, as is current practice.

Table 2. The Different Etiological Subtypes of Cardiomyopathy along with Their Mechanism, Biomarkers and Clinical Features.[46,103-105]

	Ischemic	Idiopathic	Hypertrophic	Hypertensive	Sources
Mechanism	Fibroblast Differentiation into Myofibroblasts	Genetic mutation of collagen turnover (reported hyperactive MMP-1)	TGF-B driven fibrosis	RAAS driven perivascular fibrosis	Tyagi, 1998
	Inflammatory Cascade				
Biomarkers	↑ MMP-1, ↑ MMP-2		↑ TGF-B, ↑ MMP-2	↑ TGF-B, ↑ Angiotensin II/Aldosterone	Vilahur el al, 2012
	↓ TIMP-1, ↓ TIMP-3, ↓ TIMP-4	↓ TIMP—4	↑ MMP-2, ↑ TIMP-1, ↑ TIMP~2	↑ MMP-2	Moore et al, 2011
Features	Dilatation in infarcted zone	Dilatation	Hypertrophy (matrix and myocytes)	↑ Collagen deposition	Vilahur et al. 2012
	Hypertrophy in non-infarcted zone	Hypertrophy	Fibrosis	Myocyte Hypertrophy	Bradford, 2007
	Collagen deposition	Systolic Failure	Diastolic Failure	Perivascular Collagen	

Legend: MMP – Matrix Metalloproteinase, TIMP – Tissue Inhibitor of Metalloproteinase.

Personalizing Heart Failure Treatment to each Patient

Miner and Miller suggested that the future of heart failure medicine will be tailoring treatment to each patient's specific condition and body.[57] As **Table 2** describes, there are many different routes to acquiring heart failure and they will all likely produce very different inflammatory responses to disease with differing amounts and type of collagen remodeling. As a result of relatively recent research, we now know that collagen consistency will widely differ amongst the population in the amount of cross-linked collagen fibers they will exhibit, affected by disease and age.[23,44] In a canine trial, Jugdutt showed that age affected an animal's response to heart failure medication post-MI.[95] Also, as **Table 3** will highlight, different causes of heart failure all vary in their exact mechanism and pathophysiology and therefore require specific and individual treatment.[96] Following a one-fits-all treatment plan might not be the most successful approach considering the vast amount of research that has been done on the cardiac ECM until now.

Conclusion

Heart Failure is a complex and progressive disease involving both the cells and ECM of the myocardium. A tip in the fine balance of ECM dynamic remodeling, mostly concerning MMPs and TIMPs, affects the heart's physiological properties immensely and can lead to the dysregulation that provides the basis for progression to heart failure in the future. These imbalances within the myocardium occur through distinct mechanisms of variable root cause, as shown in **Table 2**, with the final result remaining the breakdown of a stable matrix and the common pathophysiology that will ensue. The current research field requires further clarification into the key protein modulators that have an effect on the ECM in disease, other than the enzymatic MMPs and TIMPS. Although many discovered, it is yet unclear as to which changes are primary or secondary to the remodeling process. Zamilpa and Lindsey concluded with a similar view in the need for a catalogue on the specific changes that occur in the ECM with cardiac injury.[97] Many studies have pointed out Osteopontin, Galectin, Periostin and Integrin as potential modulators.[8,22,29,32,84,98-99] The near future will help us get an even clearer picture of the roles and importance of these non-collagenous proteins in heart failure. The field of the Cardiac ECM holds many academic and clinical applications and we have yet to realize its true potential in combatting the chronic issue of heart failure.

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Case Report

Dandy-Walker Malformation in an Asymptomatic 27-Year-Old Woman. A Case Report

Joyce Antonella Jiménez,[1] Daniel Francisco Landívar,[1] Fernando Xavier Posligua,[1] Jorge Rigoberto González.[1]

Abstract

Introduction: Dandy-Walker malformation (DWM) is a rare congenital disorder that involves the cerebellum and fourth ventricle. Incidentally detected asymptomatic DWM is sparsely reported in literature at extremes of age (from 1 to 75 years) in association with different diseases. We aim to report the case of a patient with an incidental finding of a DWM after a road traffic accident, reinforcing the importance of suspicion, investigation, diagnosis of clinical presentations. **The Case:** This case report describes a 27-year-old female patient who presented to the emergency room after a motor vehicle collision. She suffered a left kidney and spleen injury. The patient's brain CT scan revealed an enlarged cisterna magna with normal cerebellum, partial hypoplasia of the cerebellar vermis and enlargement of the fourth ventricle compatible with DWM. Neurological examination was unremarkable. An exploratory laparotomy was performed, and the left kidney and spleen showed hemorrhage, so a left nephrectomy and splenectomy was done. **Conclusions:** This case report aimed to characterize the DWM, which is a congenital malformation of the central nervous system. Asymptomatic patients do not require surgical treatment; however, these patients should be followed up once a year.

Keywords: Dandy-Walker Syndrome; Dandy-Walker Variant; Hydrocephalus; Cerebellar Vermis Hypoplasia (Source: MeSH-NLM).

Introduction

Dandy-Walker Malformation (DWM) is a congenital malformation that occurs during embryonic development of the cerebellum and 4th ventricle, and has a prevalence of 1 out of 25000-30000 live births.[1] The classic anatomic hallmarks of DWM are hypoplasia of the cerebellar vermis, anterior–posterior enlargement of the posterior fossa, upward displacement of the torcula and transverse sinuses, and cystic dilatation of the fourth ventricle.[2-3] In addition to the classic findings that define it, DWM is related to many other abnormalities and malformations in the central nervous system (CNS) including agenesis of corpus callosum, heterotopias, occipital meningocele, visual deficits, and epilepsy.[4]

The clinical presentation of DWM can be variable. Hydrocephalus is not uncommon prenatally or during the neonatal period, although this is a complication rather than part of the disease. Most cases are diagnosed during infancy. Infants may present with early signs such as somnolence, vomiting, convulsions, irritability, lack of muscle coordination and unsteadiness. Older patients might be asymptomatic with normal or near-normal neurological examinations. They usually present with neurological manifestations such as developmental delay, spasticity, poor head control and seizures.[5]

This report describes a 27-year-old female with incidental findings of hypoplasia of the inferior vermis and an enlargement of the cisterna magna after a motor vehicle collision. The patient never developed important symptoms and signs of cerebellar involvement.

The Case

This patient is a 27-year-old Latin American female who presented to the emergency room at the Teodoro Maldonado Carbo Hospital in Ecuador with cervical, posterior left-side thoracic and abdominal pain after a road traffic accident while her husband was driving. She was in the front passenger seat of the car when they were hit by a bus driver. She reported no relevant past medical history except for irritability, drowsiness and a caesarean section 4 years ago. She refers no allergies. Her family medical history includes a mother with a history of anxiety and hypertension. Her mother did not provide any history of medication during pregnancy. She was born at term and was the first child of non-consanguineous parents and the only affected case in the family. Her social history is important for occasional alcohol use. She lives with her husband and son, and is psychosocially independent.

At the time of the incident, the seat belt was not fastened and the patient reports that she lost consciousness for a few minutes.

Upon arrival to the emergency room (ER), the patient was pale and noted to be tachypneic with an oxygen saturation of 98% on room air. Glasgow Coma Scale was 15. Vital signs in the ER showed a blood pressure of 90/63 mmHg, heart rate of 112, respiratory rate of 23 and temperature of 97.5 °F. Blood sampling was done, and fluid and blood resuscitation were continued.

The patient's ER workup further revealed a creatinine of 0.72 mg/dL, urea of 23 mg/dL, sodium of 141 mEq/L, potassium of 4.10 mEq/L, INR of 1.04, Prothrombin Time of 12.6 s, Partial Thromboplastin Time of 26.7 s, white blood cells of 14.850 cells/mm^3, platelets of 120.000 cells/mm^3, hematocrit of 32.3% and hemoglobin of 10.3 g/dL.

Additionally, a FAST (Focused assessment with sonography for trauma) was performed which revealed echo-free space around the left kidney and the spleen (370 cc of free fluid). Contrast Computerized Tomography (CT) examination revealed bloody ascites around the left kidney and the spleen and we diagnosed intra-abdominal bleeding.

Figure 1. Sagittal (Top) and Axial (Bottom) CT Images Demonstrating Cystic Dilatation of IV Ventricle, a Giant Cisterna Magna and a Hypoplastic Cerebellum.

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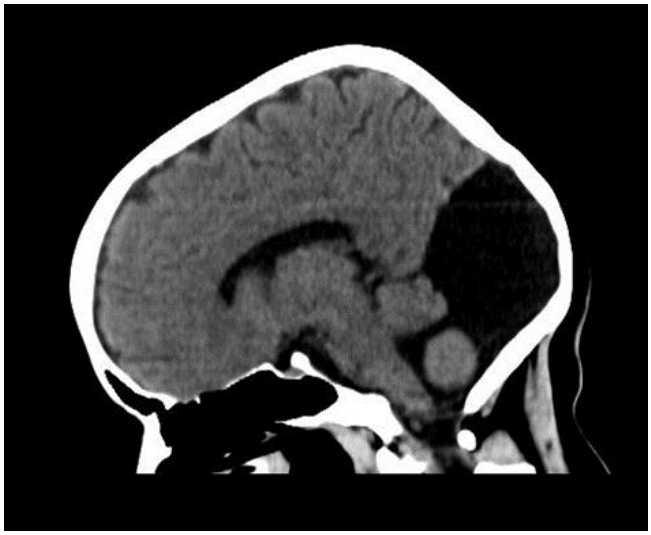

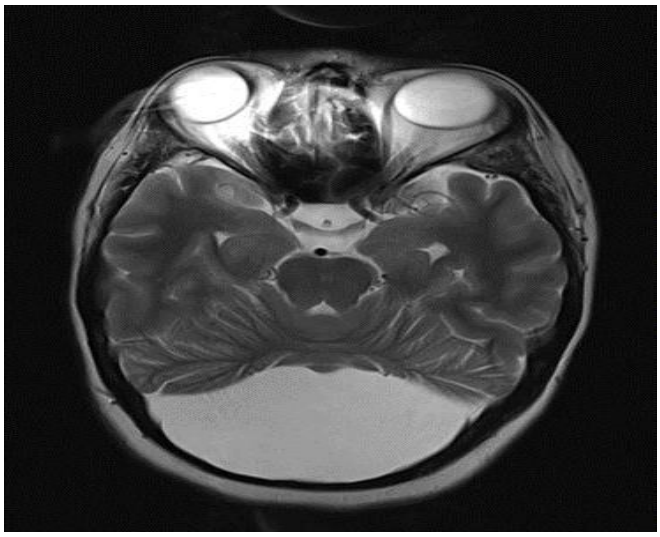

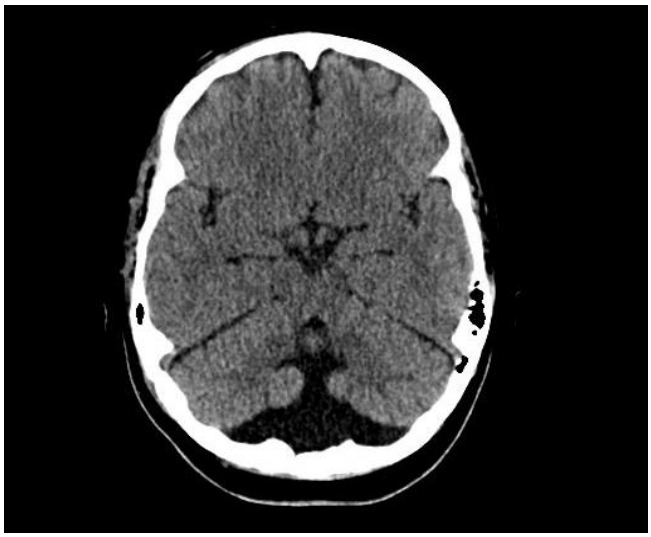

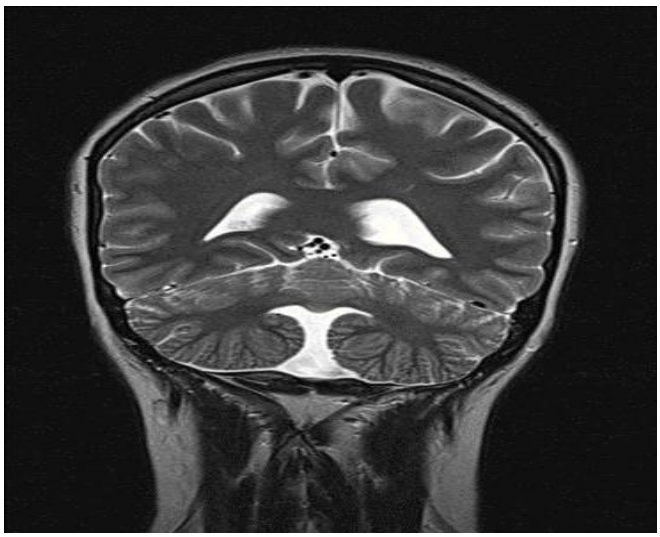

Her skull CT scan showed an enlarged cisterna magna, partial hypoplasia of the cerebellar vermis and enlargement of the fourth ventricle (***Figure 1***). The cerebral parenchyma appeared normal with no focal lesions or midline shifts. This suggested a mild form of Dandy-Walker syndrome.

Neurological examination and electroencephalogram (EEG) were unremarkable. Magnetic Resonance Imaging (MRI) to confirm these findings was suggestive for DWM (***Figure 2***). The patient was evaluated by the Neurosurgical team before the surgery and no intervention was recommended.

An exploratory laparotomy was performed with the left kidney and spleen showing signs of hemorrhaging. Subsequently, a left nephrectomy and splenectomy was carried out.

The patient had an uneventful post-operative recovery and went home on post-operative day 10. Further investigations with MRI were carried without detecting any anomaly related to DWM. The patient remained without signs of disease after one year of follow-up.

Figure 2. Axial (Top) and Coronal (Bottom) Brain MRI Showing a Large Fourth Ventricle and a Small Cerebellar Vermis in T2 Weighted Image.

Discussion

The patient described in this case conforms to what is defined in the literature regarding the imaging characteristics for the diagnosis of DWM. The radiological images show the classic triad formed by the cystic dilation of the fourth ventricle, complete or partial agenesis of the cerebellar vermis and an enlarged posterior fossa.[6] Many concomitant problems may be present, but the syndrome exists whenever these three features are found. Approximately 70%–90% of patients have hydrocephalus, which often develops postnatally. However, the patient in this case study did not present with this clinical feature. DWM may be associated with atresia of the foramen of Magendie and the foramen of Luschka.[7]

Depending on the time of onset and degree of hydrocephalus, the age at diagnosis varies from birth to older childhood. Presentation in adulthood has been reported but is infrequent. The feasible reason that may explain the mild or absence of clinical expression is the preserved cortical cytoarchitecture and the rarity of additional neuro-developmental changes in DWS adults, compared with DWS infants.[8]

The clinical manifestations in symptomatic individuals include psychomotor and growth retardation, strabismus, myopia, a short neck, brachycephaly, hypertelorism, microcephaly, hypotonia, antimongoloid

slant of palpebral fissures, large mouth with down turned corners, globulus large nose, poorly lobulated ears, high arch palate, cleft palate, small hands and feet, clinodactyly and the brachymesophalangy of the little fingers.[9-10]

The clinical spectrum of DWM is broad with a varying degree of neurological impairment. Dandy-Walker Variant (DWV) is a less severe form of the spectrum of DWM. Patients with DWV are more likely to present in adulthood than in infancy or childhood. The isolated DWV abnormality has the highest incidence of survival and there are reported cases of people who have had DWV their entire lives without any symptoms, such as the patient in this case study. Individuals with DWV are more likely to present in adulthood than in infancy or childhood, as presented in this case.[11-12]

The diagnosis of DWM can be made by ultrasonography as early as 14 weeks gestation.[13] Common ultrasonographic findings include the presence of a large posterior fossa cyst, absent cerebellar vermis and splayed cerebellar hemispheres.[14] Diagnostic tools after the infant is born differed from prenatal diagnostic tools for detecting DWM. Those tools included CT scans and MRI. In infants and adults, investigations for the diagnosis of these malformations are cranial CT and brain MRI. Brain MRI is the optimal exploration for the differentiation of DWM from other posterior fossa pathologies. Usually, the MRI investigation is required for better anatomic resolution prior to surgical intervention.[15]

For symptomatic patients, the most effective treatment incorporates the partial resection of the arachnoid membranes that constitute the "lining" of the cyst accompanied by the simultaneous insertion of a "shunt" to divert the CSF to the peritoneal cavity from where the fluid can be harmlessly reabsorbed. In this patient who was an asymptomatic DWM case, there is no extensive literature to review for their treatment. In our judgment, follow-up is the most important measure. Asymptomatic DWM patients who have been confirmed should be followed up once a year.[16]

The content of the follow-up should include, at least, the following three aspects: CT of the head to monitor the degree of hydrocephalus and to assess if hydrocephalus has increased; inspection of symptoms suggestive of increased intracranial pressure includes severe headaches, vomiting, and papilledema; and examination of cerebellum symptoms is also noteworthy. Cerebral trauma and intracranial infection may change the path of cerebrospinal fluid circulation in asymptomatic DWM patients.[17]

Conclusion

Although the DWM is rarely overlooked in early childhood, there are individuals who meet the criteria for diagnosis without clinical presentation throughout their lives. These cases should not receive pharmacological or surgical treatment, however, should be followed up due to the possibility of the onset of symptoms in later stages of life.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Case Report

Recurrent Painful Ophthalmoplegic Neuropathy Affecting Right Oculomotor Nerve in 10-Year-Old Male. Case Report

Sharmila Segar,[1] Chandni Duphare,[1] Osemelu Aburime.[1]

Abstract

Background: Recurrent painful ophthalmoplegic neuropathy (RPON), formerly known as ophthalmoplegic migraine (OM), is a poorly understood condition that presents with recurrent unilateral headaches and at least one ocular cranial nerve (CN) palsy, generally in childhood. There has been ongoing debate about whether the etiology of this disorder is neuropathic or related to migraines. **The Case:** We present a case about a 10-year-old male with his third presentation of RPON, repeatedly affecting his right oculomotor nerve. His treatment choices are discussed, along with associated outcomes. The patient was treated with topiramate with resolution of his symptoms occurred within one month. **Conclusion:** As the annual incidence of RPON is rare at fewer than 1 case per million people, clear documentation of observed cases with treatment failures and successes is key to building evidence for future management.

Key Words: Ophthalmoplegic Migraine; Cranial Nerve Diseases; Oculomotor Nerve (Source: MeSH-NLM).

Introduction

Recurrent painful ophthalmoplegic neuropathy (RPON) is a condition that can present with days to weeks of ocular cranial nerve palsies and debilitating headaches. The majority of cases of RPON are found in patients with a history of migraines, with the associated headache having migrainous features, including photophobia, phonophobia, nausea, and vomiting.[1] A headache lasting several days to a week is typically the first sign of RPON, with high intensity in the periorbital and/or retro-orbital region. Ophthalmoplegia tends to present during or after the headache. Based on 84 cases, median age of first attack is 8 years, with a range of 7 months to 50 years, while most cases start in childhood.[2] The condition is very rare, with a reported annual incidence of 0.7 per million based on a population of 615,000 studied over 10 years.[3] While this condition is rare, further understanding of the condition and treatment is warranted, as associated headaches and ocular impairments can result in lost productivity from missed school or work days, along with uncertainty about recurrence.

We encountered a pediatric patient with a history of migraines during his third case of RPON. He was treated with migraine prophylactic medications with an increase in his dose of topiramate and the continuation of his regularly scheduled dose of verapamil. The treatment of RPON is not standardized, and this case illustrates that the use of migraine medications without steroids may be efficacious. The pathophysiology of RPON is discussed below, with proposed etiologies including migrainous, neuropathic, and vasculopathic.

The Case

A 10-year-old Hispanic male presented with a history of right-sided frontal headache without aura lasting for 4 days. The patient reported vomiting and phonophobia on days 1-2. During days 3-4, the patient developed diplopia and ptosis of the right eye (OD). At the time of the clinic visit, the headache had subsided but the patient was still unable to open OD. He denied any eye pain, injection, discharge, blurry vision, numbness, or weakness. He denied fever, upper respiratory illness, sick contacts, recent vaccinations, or trauma.

Key Points:

- Recurrent painful ophthalmoplegic migraine is a condition defined as having 1) unilateral headache with ipsilateral paresis of at least 1 ocular cranial nerve; 2) at least two attacks; 3) exclusion of orbital, parasellar, or posterior fossa lesions; and 4) lack of more fitting headache diagnosis.
- While pathophysiology and treatment of RPON are unclear, steroids and migraine prophylaxis medications may improve symptoms.
- Larger scale studies are essential in determining which treatment regimens most definitively improve outcomes.

The patient was diagnosed with migraines at age 5 and had 2-3 severe migraine episodes per year. When he was 8 years old, he had his first presentation of ptosis OD following headache, which resolved after several weeks. When he was 9, he was hospitalized for one night for an episode of headache that lasted 4 days as well as ptosis OD and horizontal diplopia. He underwent appropriate investigations and was started on migraine prophylaxis. The patient was discharged with verapamil titrated up to 40 mg BID for 4 weeks and prednisone for 6 days. After his previous attacks, his current medications were topiramate (25 mg PO BID) and verapamil (40 mg PO daily). It's worth noting that the patient's family history did not include oculomotor palsy.

On ocular exam, visual acuity was symmetric at 20/25 in both eyes (OU). Extraocular movements (***Figure 1***) showed right eye exotropia in primary gaze, -4 adduction, -4 elevation, -3 depression and normal abduction. The left eye (OS) had full extraocular movements. The remainder of the ocular examination was within normal limits.

Complete blood count (CBC), comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), angiotensin converting enzyme (ACE), hemoglobin A1c (HbA1c), rheumatoid factor (RF), antinuclear antibody (ANA), lysozyme, and Quantiferon Gold were within normal limits. Lumbar puncture CSF studies were unremarkable, reducing suspicion for treatable infections, inflammatory or neoplastic etiologies.

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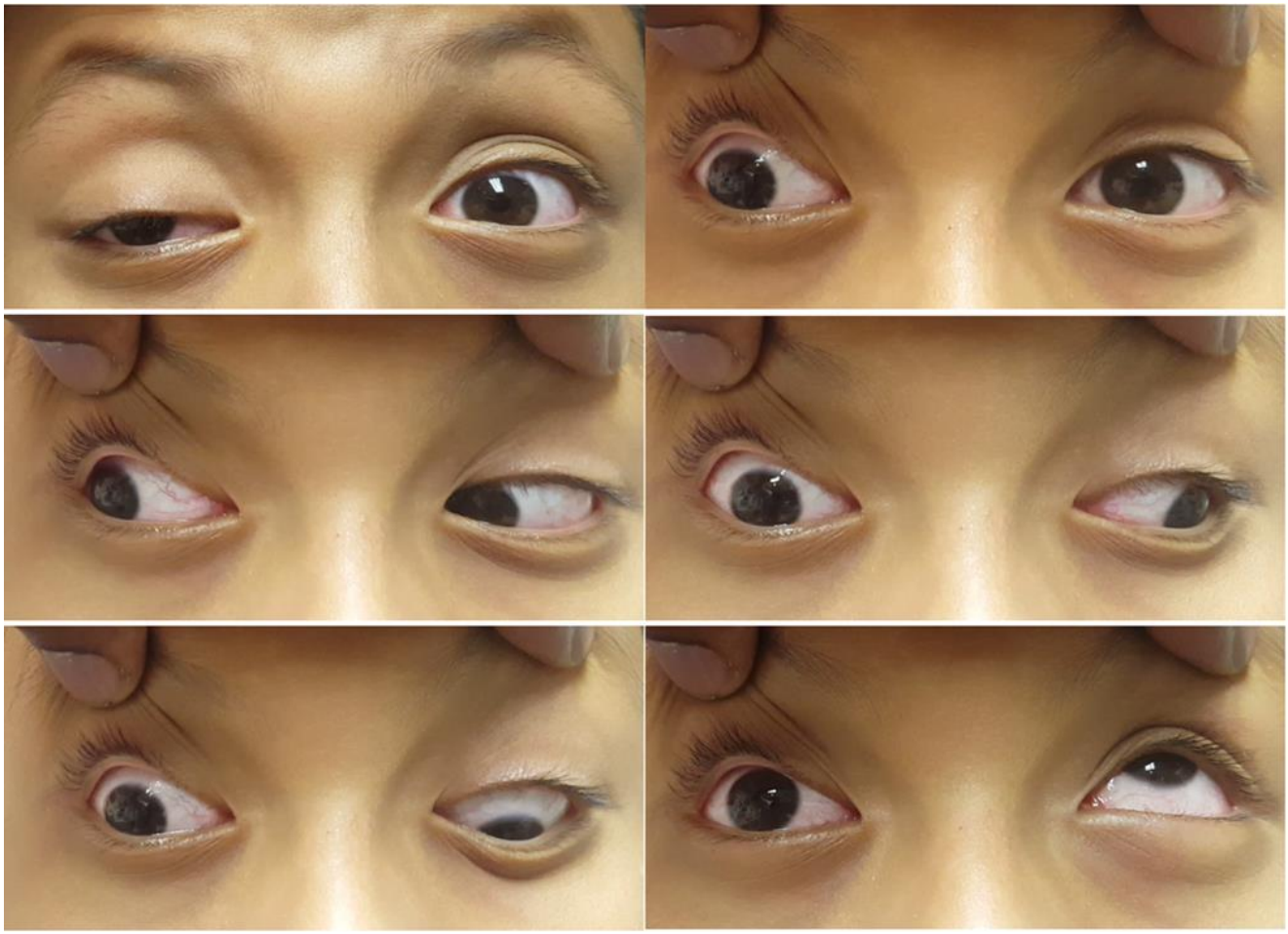
Figure 1. Extraocular Movements with Oculomotor Nerve Palsy.



Magnetic resonance imaging (MRI) of the brain with contrast (***Figure 2***) showed mild loss of volume and abnormal enhancement with the contrast of the cisternal portion of the right oculomotor nerve. The amount of abnormal enhancement and the degree of loss of volume appeared slightly decreased in comparison to the prior MRI from age 9. Otherwise, there were no changes in comparison to the prior MRI.

The patient was treated by increasing the dose of topiramate from 50 to 75 mg BID. The patient's parents were informed to contact the eye clinic if the condition worsened in order for steroids to be prescribed. One month after the current presentation, the patient had near full resolution of ptosis and impaired extraocular movements.

During the episode that resulted in hospitalization at age 9, patient was discharged with verapamil titrated up to 40 mg twice daily with a four-week supply, and a six-day prednisone course. The patient's mother reported that verapamil did not decrease the intensity of his headache, and that the ptosis did not resolve with the completion of prednisone. All three of the patient's ophthalmoplegic episodes resolved in approximately one month. He is being followed by pediatric neurology and ophthalmology.

Discussion

The name change from "ophthalmoplegic migraine" to "recurrent painful ophthalmoplegic neuropathy" highlights how the condition was previously thought to be a migraine variant, while it is now predominantly thought to arise from a recurrent demyelinating neuropathy. The change was first reported by the International Classification of Headache Disorders in its 3rd edition (published in 2013). The four diagnostic criteria include: 1) unilateral headache with ipsilateral paresis of at least 1 ocular cranial nerve; 2) having at least two attacks; 3) exclusion of orbital, parasellar, or posterior fossa lesions; and 4) lack of a more fitting headache diagnosis.[4] The third cranial nerve is most commonly involved.

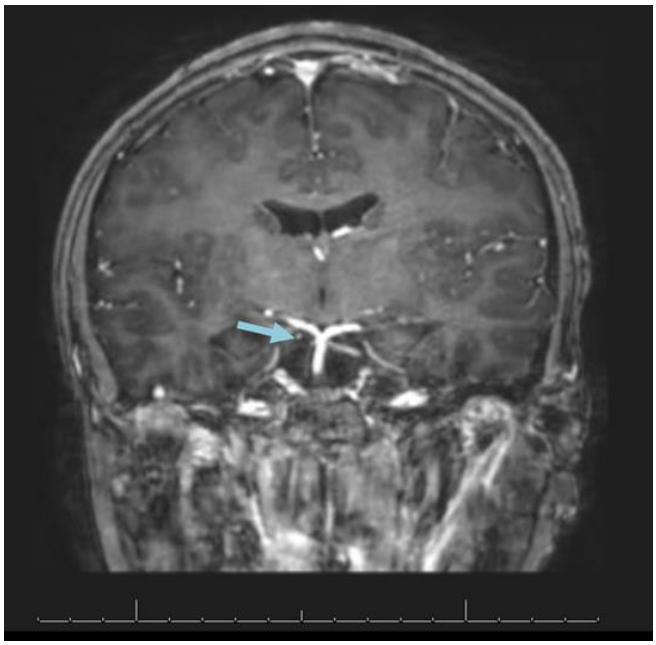
Pathophysiology

The pathophysiology of the RPON remains uncertain. Regarding a migraine-related etiology, swelling of the internal carotid or posterior cerebral artery vessel walls could lead to occlusion of branches supplying the cisternal portion of the oculomotor nerves, leading to vasogenic edema contributing to ophthalmoplegia and abnormal contrast enhancement on MRI.[1] Neuropeptides involved in migraines, including calcitonin-gene-related peptide may also contribute to inflammation at the blood brain barrier.[1, 5]

MRI findings associated with RPON are typically not present with migraines. The pain associated with migraines tend not to last for longer than 72 hours. Cranial nerve palsies can be associated with pain lasting for multiple days or weeks.[6] In a study of motor palsies, some were associated with diabetic neuropathy, with one-third of patients having pain preceding visual symptoms.[6]

It has also been proposed that RPON is the result of a vasculitis-type immunologic response in the nerve or a post-viral inflammatory condition.[7] In 2018, Huang C et al. suggested that a multifactorial etiology, including neuropathic and migrainous, should be maintained given the existing evidence.[8] Some even propose a microvascular, ischemic etiology to the disease.[9] In cases of patients with RPON, both

Figure 2. MRI with Contrast Showing Mild Loss of Volume and Abnormal Enhancement of the Cisternal Portion of the Right Oculomotor Nerve.



neuromuscular hamartoma and schwannoma have been found originating from the oculomotor nerve, which have been discussed as being primary pathologic factors or even mimickers of RPON.[10-13] Further research and evaluation of autopsy cases are required in order to understand how this condition arises.

Diagnosis

In order to differentiate between RPON and infectious, noninfectious inflammatory conditions, and malignancies, there is a need for clinical evaluation, blood tests, lumbar puncture, and imaging studies.[14] The first attack is generally incorrectly considered to be aneurysm, trauma, infection, or recent immunization, with no recurrent attack present to be included in diagnostic criteria of RPON.[15] Lab tests can include CBC, CMP, ESR, CRP, ACE, HbA1c, RF, ANA, lysozyme, human leukocyte antigen B27 (HLA-B27), and antineutrophil cytoplasmic antibody (ANCA). These tests tend to be negative in RPON.[2]

MRI with gadolinium contrast during both of the patient's episodes at ages 9 and 10 indicated abnormal enhancement and loss of volume of the cisternal portion of the right oculomotor nerve. The abnormal enhancement and degree of volume loss were similar in comparison to the first MRI. A study showed that contrast enhancement of the cisternal segment of the affected oculomotor nerve is a common finding during the acute phase of oculomotor RPON, which was found in all six participants.[14] Focal thickening at the exit of the nerve in the interpeduncular cistern was present in most patients, and whole nerve thickening was present in one patient. This enhancement was later found to be almost fully resolved 7 to 9 weeks later. A lack of significant MRI findings should not exclude RPON.[16] In our case, instead of focal or whole nerve thickening, the oculomotor nerve had a mild asymmetric loss of volume.

Treatment

Treatment for RPON is not clearly established. In one study of 26 patients, steroid use improved symptoms in over half of patients, with unclear benefit to the other patients with RPON.[2] One case reported resolution of painful ophthalmoplegia within 7 days of initiation of oral prednisone 2 mg/kg/day, followed by steroid taper and initiation of migraine prophylaxis.[15] These mixed results with steroids have been documented, with optimal prophylactic and acute medications not clearly established.[17] In a study with two steroid responsive patients, cyproheptadine hydrochloride was effectively used to prevent RPON by reducing vascular edema around the affected nerve.[18]

Medications used for migraine prophylaxis have not been well studied for use in RPON. In this case, the patient's first ophthalmoplegic event at 8 years was defined by ptosis OD with headache, resolving without any medication. At age 9, his second event presented with diplopia, ptosis OD, and headache, and he was prescribed six-day prednisone course as well as 40 mg verapamil BID for 4 weeks. His mother reported unclear benefit. For his third presentation at age 10, his regular dose of topiramate was increased from 50 to 75 mg BID. It is unclear whether his resolution occurring consistently at 1 month after initial presentation was because of the medications or the natural course of the disease.

Prognosis

While there is still great potential for further understanding of pathophysiology and treatment of RPON, the prognosis is excellent. Some deficits may persist after multiple attacks while this occurrence is unlikely after one attack.[17,19] In order to prevent events of RPON and long-term sequelae, further research is warranted.

Conclusion

RPON is a disease with an unclear pathophysiology and many proposed treatments. With a better understanding of the pathophysiology, the most efficacious treatment regimens may be elucidated. Considering the rare nature of the disease, documentation of cases of RPON is essential. Prospective research goals should include randomized clinical trials for specific therapeutic agents.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Incentive-based Strategy for Introducing Health Systems Perspective to Medical Students

Krit Pongpirul,[1,2] Seelwan Sathitratanacheewin.[2]

The Experience

Setting and Problem

Clinical practice is affected by factors beyond the doctor-patient level including healthcare systems. Since 2001, the introduction of Thailand's Universal Coverage Scheme has not only led to the successful expansion of population coverage and improvement of major health indicators but has also stressed the importance of health systems perspective in clinical practice. Thai medical students now have to understand how to offer optimal treatment choices to a patient that concur with the payment policy of the responsible health insurance schemes. Likewise, American medical students are expected to demonstrate competence in "system-based practice" by understanding cost containment, practicing cost-effective medicine and resource allocation, assisting patients in navigating the complexities of the health systems, and coordinating with other providers.[1] According to the World Health Organization, a health system consists of all organizations, people and actions whose primary interest is to promote, restore or maintain health.[2]

The current cohort of medical students is comprised mostly of the millennial generation (or Generation Y; born between 1980 and 1999) who are the generational demographic cohort following the Generation X (born between 1965 and 1979). Known for being self-reliant, inquisitive, and technologically advanced beyond any other age group[3], the millennial generation of medical students would not welcome the traditional approach to integrating a new perspective into the currently overwhelming medical curriculum. With collaborative efforts of key national authorities, the Medical Students for Health Systems and Services (MS-HSS) was launched as an innovative program to introduce health systems perspective to medical students in Thailand. This paper describes program characteristics, outcomes, and lessons learned from the first year of implementation with specific examples.

Intervention

The intervention was systematically developed to be an incentive-based program to help medical students understand and integrate health system perspectives into their basic science and clinical competencies. A budget for essential expenses for conducting projects relevant to health systems or health services and presenting the findings in international conferences was set aside. A committee was formed, consisting of faculty members nominated by students, to oversee the program and make decisions on budget allocation.

Medical students voluntarily participated in the program after they were informed through word of mouth about associated incentives, such as an opportunity to attend international conferences. A committee member was then assigned to be the student mentor. The responsible mentor conducted an initial discussion with each group of students to identify a potential health systems research topic that concurs with their current knowledge and career goal of medical training. Some class assignments were also used as a starting point. A few tailored lectures were conducted to fill in potential gaps of essential knowledge, such as conducting a literature review, data collection, data analysis, and abstract and manuscript preparation.

Outcomes to Date

Ten projects were launched in the first year. One student received the Prince Mahidol Award for a project on system-wide improvement of critical care, and one project on comparative analysis of medical licensing examination systems across Southeast Asian Nations was orally presented and won the Patil Award at AMEE 2013. Another national survey project exploring factors affecting the decision of newly graduated physicians in choosing potential practice areas was chosen, financially supported by the Second Global Symposium on Health Systems Research in Beijing. Both works were successfully published in international and domestic journals.[4-5]

Key principles that led to the program's success were voluntary participation and blending recruitment, tailored schedules and lectures, incentive systems, special financing mechanisms, and support by faculty members. As these components exist in any context, the generalization of our experience is possible; however, the following concerns should be addressed. Firstly, providing financial and non-financial support to this incentive-based extracurricular program is challenging in the absence of collaborative efforts between the understanding financing authority and the adaptive medical school management team. Secondly, identifying and recruiting the faculty members who are not only knowledgeable in health systems but also good mentors is critical. Finally, it is not known whether or not health systems perspectives are sustained and long-term and thus follow-up of this cohort of medical students is required.

Ethical Consideration

The nature of this voluntary, extracurricular activity for medical students is experience sharing rather than scientific research. While the names of participating medical students may be identifiable through online internet searches, the information is publicly available and does not incur additional risk to the medical students. The content of this work has not been published previously in whole or part; however, it was orally presented at the Third Global Symposium on Health Systems Research, September 30 – October 3, Cape Town, South Africa, to which the first author was awarded full support for registration, travel, and accommodation from the Symposium Secretariat.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

New Frontiers in Biomedical Research: A Medical Student Perspective

Ben Sayer.[1]

The Experience

When I was offered a placement in Professor Haniffa's world-leading immunology laboratory at Newcastle University, it was a one-time opportunity to gain an insight into a field that is rapidly developing. The focus of her group is mononuclear phagocytes, a family of immune cells including dendritic cells, monocytes and macrophages, in different contexts. A degree in Biomedical Sciences at St George's University of London had given me lab experience using techniques such as Western Blot, ELISA and confocal microscopy. I am now enrolled in a graduate medicine course and was keen to bring together my laboratory and clinical experience. I was particularly interested in exploring how new technologies are revolutionising biomedical research and clinical practice.

New advances in biomedical research

As part of my placement at Newcastle University's immunology lab led by Professor Haniffa, I was introduced to cutting-edge single cell technologies. I learned that high-dimensional analysis of single cells is providing new insights into biological processes and pathology. Past research has focused on morphology, physical properties and surface markers. However, this approach only facilitates study of limited cellular parameters, which introduces intrinsic bias and can lead to erroneous conclusions. Subsequent exploration of gene expression and function has been conducted on a population level, taking an average from a sample of many cells. This involved prior identification and isolation of cells using techniques such as flow cytometry, which is limited by a finite number of parameters. Study of the transcriptome (transcriptomics), which can be defined as the complete set of RNA transcripts in a cell under specific conditions, has opened up further avenues for single cell research. Single cell transcriptomics does not require *a priori* selection, enabling researchers to use the transcriptome of individual cells for their identification. Thus, single cell mRNA sequencing (scRNA-seq) data can be accrued to subsequently direct functional study with greater accuracy. As this approach considers many more parameters, it minimises bias within the experimental system.[1]

Bioinformatics

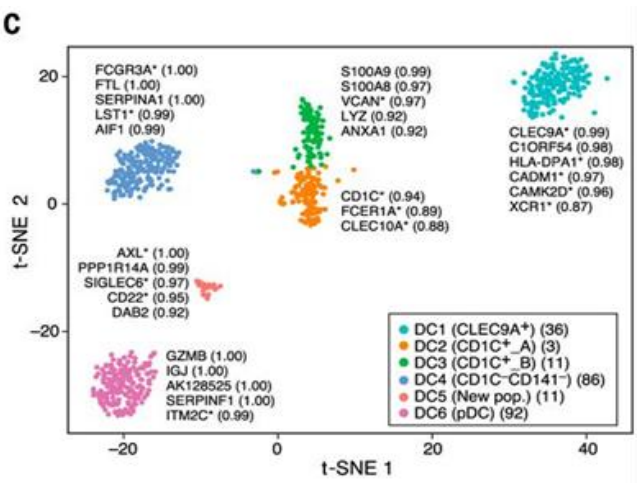
A key requirement to maximise the benefits of this new research is robust bioinformatics capabilities. Bioinformatics utilises computation to convert biological data into interpretable information. Genomics is producing increasing quantities of data which need to be stored, processed, interpreted and visualised. A suite of analysis programmes is available which are statistically-based and often incorporate machine learning algorithms.[2]

There is great complexity underlying the programming to manage data produced from scRNA-seq experiments. An in-depth understanding of the computing behind informatics is not necessary, but an ability to utilise and navigate algorithms to interpret data is likely to become an essential part of research in the future.

Single cell RNA-sequencing in immunology

The seminal study demonstrating the utility of scRNA-seq to define immune cell types without prior selection was performed on mouse spleen.[3] More recent research in human immunology exploits scRNA-seq. I will focus on two studies of human dendritic cells to demonstrate the underlying scRNA-seq experimental approach and bioinformatics concepts in interpreting scRNA-seq data. Villani et al. performed full length mRNA transcript measurement whereas See et al. measured short sequences at the 3' end of mRNA transcripts which were coupled to a unique molecular identifier for each gene.[4-5]

Figure 1. Human blood Dendritic Cell (DC) heterogeneity delineated by single-cell RNA sequencing. t-SNE visualisation of scRNA-seq datasets of 742 cells. Up to five top discriminators are listed next to each cluster. Each dot represents an individual cell. (From Figure 1C Villani et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science. 2017; 356(6335). Copyright© (2017) [The American Association for the Advancement of Science]. Reprinted with permission from The American Association for the Advancement of Science.



Next generation sequencing of the cDNA from single cells produces millions of short reads which need to be aligned to the reference human genome. There are several packages such as Seurat which provide an all-in-one application suite to undertake quality control, analysis, exploration and visualisation of scRNA-seq data. One of the main analyses undertaken is to cluster cells by their respective transcriptome profiles. Cell clusters can be visually displayed using t-distributed stochastic neighbour embedding (t-SNE), which enables high-dimensional datasets to be represented in two dimensions (***Figure 1***).[4]

Genes that best characterise each cell cluster identified can also be represented as a heat map, used by Villani et al. (***Figure 2***).[4]

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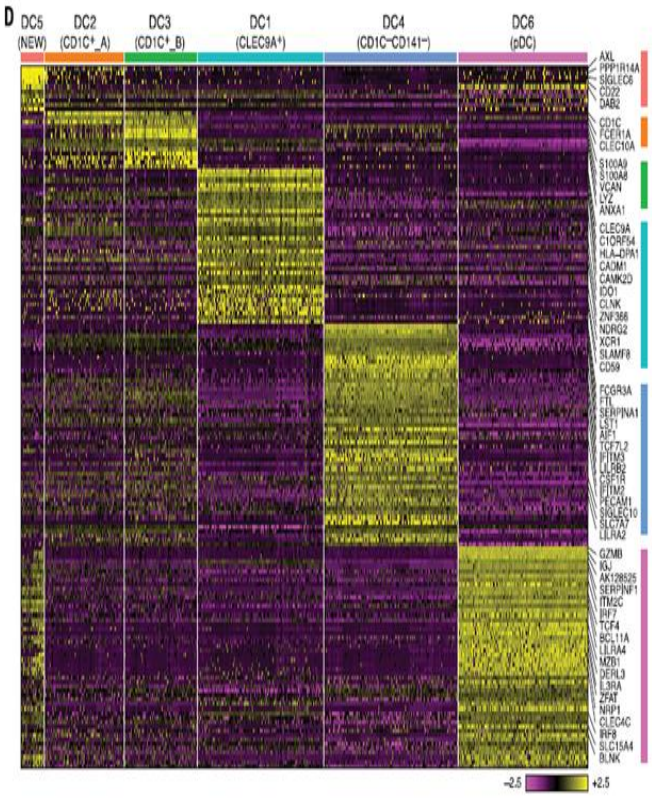
Figure 2. Heat map display of quantified gene expression. (Figure 1D from Villani et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science. 2017; 356(6335). Copyright© (2017) [The American Association for the Advancement of Science]. Reprinted with permission from The American Association for the Advancement of Science).



This displays the expression profile for the relevant discriminatory gene for each cell (represented by each column). High intensity expression (indicated in yellow) for the respective genes distinguish the various cell types identified from the scRNA-seq analysis.

Further understanding of cellular heterogeneity coupled with experiments exploring responses to various stimuli (e.g. viruses) and different cancer microenvironments are radically changing biomedical science. Combining this powerful methodology with proteomics and metabolomics technologies will provide unprecedented resolution to redefine disease classification, pathogenesis and identification of novel therapeutic targets. One existing example is immunotherapy for certain cancers, an area of research that is already showing remarkable promise.[6-8]

Conclusion

This placement was a wonderful opportunity to engage first-hand with world-leading immunological research. I was able to learn about the changing landscape of biomedical research and the increasingly important role of bioinformatics. I would highly recommend that fellow medical students seek out similar opportunities throughout their training as biomedical research is a rapidly evolving field that will impact on how medicine will be practised in the future.

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Experience

Put Your Mask On First Before Assisting Others! A Wellness Retreat for Students of Peer Support Groups

Joanie Mélançon,[1] Laurence Petitclerc,[1] Alexandre Lafleur,[1] Andrée Vézina.[1]

The Experience

Students in health sciences are at higher risk of burnout and depression when compared with population controls.[1] Dedicated to change this situation, the student community and faculty members of our institution are united to improve the global health of all trainees. Working under the Office of Student Affairs, our peer support groups at Laval University Faculty of Medicine provide personal and group support to more than three thousand students in health sciences.

We know from the literature that relying on peer support and engaging in wellness activities are useful coping mechanisms.[2-5] But before helping other students, you must have the habits and tools necessary to be healthy and resilient in your own life. With that in mind, the Office of Student Affairs organised a three-day wellness retreat for students of peer support groups. The twenty participants were undergraduate students in medicine and physical rehabilitation, and graduate students in health sciences research. We slept in a contemporary centre of holistic health within the historic *Monastère des Augustines* (Québec, Canada). The program's goals were to experience a wide range of wellness activities, reflect on global health habits, engage in interdisciplinary networking and cultivate peer support skills.

Figure 1. Yoga Exercises during a Wellness Retreat for Students of Peer-Support Groups within the Historic *Monastère Des Augustines* (Québec City, Canada).

Our suggestions for wellness retreat activities

The retreat was an opportunity to experience various ways to be more relaxed, more centered and to attain better physical and mental health. Divided into one-hour sessions, the group participated in mindfulness meditation, breathing exercises, singing bowls and hand pan concerts, yoga, and self-massage with therapeutic balls and tai chi (***Figure 1*** and ***Figure 2***). We asked professional trainers for advice, in particular on how to introduce these activities to our peers. Group discussions and reflexive activities focused on caregivers' roles and how to implement lasting changes in students' life habits (***Figure 3***).

Figure 2. Students Discovered New Relaxation Exercises that They Would Not Have Thought of, Like this Activity with Therapeutic Balls.

Location, location, location

The location of the retreat greatly contributed to its success. The Monastère is the restored former cloister of the Augustinian Sisters. While the activities encouraged spirituality, no form of worship was offered. Interestingly, the building is adjacent to *l'Hôtel-Dieu de Québec* where the sisters provided care, and it has become a major teaching hospital in which we have clinical rotations.

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Having the opportunity to sleep onsite helped us to focus on our objectives. We had limited access to electronic devices. The environment was calm and serene. The meals were prepared with local and organic food, and we were invited to participate in mindful eating (***Figure 4***). Everything about this place was healthy, which led us to reflect on how our own daily habits can contribute to our wellbeing.

Figure 3. Group Discussions on Caregivers' Roles and Challenges Took Place in a Respectful and Supportive Climate.

Findings

We collected qualitative data through a group interview and written comments at the end of the retreat. The group was made up mainly of women, since 75 % of the students enrolled in health sciences programs at our institution are females. Our colleagues commented on the importance of having this dedicated time for wellness activities and reflection. They appreciated that faculty leaders cared about their wellbeing and organised this retreat with enlightening new activities that they would not have thought of. While students are highly dedicated to helping others, they often forget to take care of their own wellbeing. They discovered simple relaxation techniques that they hope to share with students experiencing difficulty. The schedule facilitated rest and health habits that they wish to pursue. Through reflexive activities, sharing common goals and values as caregivers, the participants strengthened their group spirit. They were able to better articulate why they want to pursue their training in health sciences and guide their peers to do the same. Interdisciplinarity was highlighted as a key aspect of the retreat. It reminded the participants that most students of health sciences face similar challenges that could be tackled effectively with a collaborative approach.

Figure 4. Students Were Invited to Participate in Mindful Eating, Revisiting Healthy Habits Like Sitting with Friends to Eat Meals Made with Organic Fruits and Vegetables.

What was unique about this retreat?

We believe that some aspects of this retreat can be inspiring to other students around the world. We believe that students of peer-support groups represent a major asset for student affairs offices.[3, 6-9] Given the large cohorts of students in health sciences, selecting the students of peer support groups for a retreat is a resource-effective way to disseminate those interventions within the student community. Finding a location that offered a calm and healthy environment and a large choice of activities certainly enriched the experience. Inviting support groups from many programs lead to rich, interdisciplinary discussions.

Why should you be involved in a peer-support group?

To be involved in a peer-support group requires active listening, empathy, generosity, altruism, optimism, resourcefulness and recognition of our limits. Knowing our own difficulties allows us to connect more easily with our colleagues. We are breaking the misconception that caregivers are immune to physical and mental health problems. We think we can change the way students view their difficulties, help them to manage their stress, and eventually overcome their problems. Helping our colleagues has become part of our training, motivating us even more to help our future patients.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Interview

The AIDS Frontline, PhD Reformation and Our Definition of Scientific Rigor - An Interview with Professor Arturo Casadevall

Paul MacDaragh Ryan.[1]

The Interview

Professor Arturo Casadevall is the current Chair of Molecular Microbiology & Immunology at the Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine. Following completion of his MD/PhD at New York University and an internal medicine residency at Bellevue Hospital, he became a prolific physician-scientist who has made major contributions to the realm of infectious disease and host immunology. In addition, Professor Casadevall is the founder and Editor-in-Chief of the highly regarded open-access general microbiology journal *mBio*, a long-standing advocate for underrepresented minorities in science and a central figure in the promotion of scientific rigor, reproducibility and responsibility.

Professor Casadevall and his like-minded collaborator Professor Ferric Fang have published about the idea of scientific rigor, as well as on the central scientific process of grant peer review. The two have described the inequity of the grant review process and presented evidence indicating that there is no relationship between grant score and productivity. As a result, Professor Casadevall and his colleague shocked many by suggesting that the National Institute of Health should undergo a fundamental reformation in its grant system and implement a process in which funds would be allocated by a lottery, in which only meritorious applications would hold a ticket. This type of perpendicular thinking, along with an impeccably ethical mind and an outstanding medical research portfolio make Professor Casadevall an ideal role model for all trainees within the medical and scientific profession.

After finishing your bachelors in chemistry, what drew you to a career in medicine?

I had always been interested in medicine. Perhaps it was because my grandfather was a surgeon and he was a major formative influence in my early life. A career in medicine offered the opportunity to combine my interests in science and investigation in a field devoted to promoting human well-being.

In light of current discussion around the death of the modern clinician-scientist, what would you say to promising medics with research aspirations who are considering following the MD/PhD route that you followed?

I think the death of the modern clinician-scientist has been overplayed. Medicine needs clinician-scientists to make progress since clinical practice is a great observatory for new insights into the pathogenesis of human disease. Given this need, there will always be a route for physicians interested in investigation to develop successful careers. I admit that it is harder today to combine a career that includes clinical medicine practice with investigation given the enormous demands placed on clinicians. The MD/PhD approach is a natural route for physicians who are interested in investigation. However, other routes such as research residencies and post-graduate training programs can train aspiring clinician-scientists on the methods of investigation.

You came into your internal medicine residency at Bellevue Hospital at a pivotal moment in 20th century history. What was it like to be a junior doctor in the United States during the AIDS epidemic and did this inspire your choice in specialty?

The HIV epidemic was a formative experience for many of us who became physicians in the 1980s. Today, when an HIV infection is treatable, it is difficult to convey the magnitude of the calamity that became the AIDS epidemic and how it influenced medicine. Basically, you had a new organism emerge that destroyed the immune system. In retrospect, it is remarkable how much progress was accomplished so quickly. The syndrome was described in 1981, the virus was described in 1984, the first antiviral therapy was available in 1987 and the highly effective therapy became available in 1996. Although clearly a decade and a half is too long for those afflicted at the time, it is nonetheless remarkable how rapidly progress was made considering that we were dealing with a new agent. The progress with HIV has given me a lot of hope that science and human ingenuity can one day solve many of today's intractable medical problems.

While listening to a recent JAMA Network podcast entitled "Working on the Precipice: On the Frontlines of the AIDS Epidemic at the CDC", I heard Dr. David Auerbach reflect on the camaraderie and sense of greater purpose that he discovered while working on the AIDS epidemic (referred to at the time as Kaposi Sarcoma with Opportunistic Infections) for the CDC.[1] Although there may not be any directly comparable crises in today's terms, we are facing our own plethora of global and local health challenges. In what area do you believe the doctors of tomorrow may be able to contribute in a similar manner to health and society (i.e. vaccines/antimicrobial resistance/metabolic syndrome etc.)?

The AIDS epidemic in the 1980s was a terrible time and difficult times have a way of solidifying bonds between caretakers. I suspect similar experiences occurred during the recent Ebola outbreak in West Africa. I think every crisis is different and every generation of physicians faces their own trials. Although I do not have a crystal ball for the problems that doctors of tomorrow will face, I suspect that they will have to confront similar problems as those of the past. In every crisis, the answer to new challenges is to deliver the best care possible while also carrying out investigative work to push back the boundaries of science and improve medicine.

You have mentioned previously -perhaps in a tongue-in-cheek manner- that you are not sure that you would be able to get educated in New York today, as your alma mater (City University of New York) is now a fee-paying institute. As an open advocate for the underrepresented, do you think that the outlook is good for minority groups within science and medicine? If not, what can be done to rectify this?

It is true that we were so poor that the only place that I could have attended college when I finished high school was the City University of New York, which at the time guaranteed a place to every applicant and

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was free. Eventually, they were forced to charge tuition but even today, it remains modest relative to what other Institutions charge. I think the demise of free higher education in the United States was a terrible loss to society and I am a big proponent and supporter of public education. I think the road for the underrepresented and minority groups is rockier but I am encouraged by all the progress made in recent years. I am optimistic that things will continue to get better although improvements may be slow and incremental.

Do you believe that free-to-publish, open-access journals like IJMS are removing barriers for curious medical students and young scientists?
I think having a free and peer reviewed journal for medical students and young scientists is terrific because it encourages scholarship and investigation.

In 2016, you and Prof. Fang authored an editorial in which you produced a novel definition of scientific rigor.[1] Could you give us some insight into this definition and why you felt it needed to be explicitly outlined?
We were very surprised that despite all the talk and emphasis on greater rigor there was not a good definition for how to accomplish it. I think our major contribution was to argue that to achieve rigor one needs the five components that we identified. In other words, it is important to bring different approaches to test conclusions and results to reduce the likelihood that these are spurious or faulty.

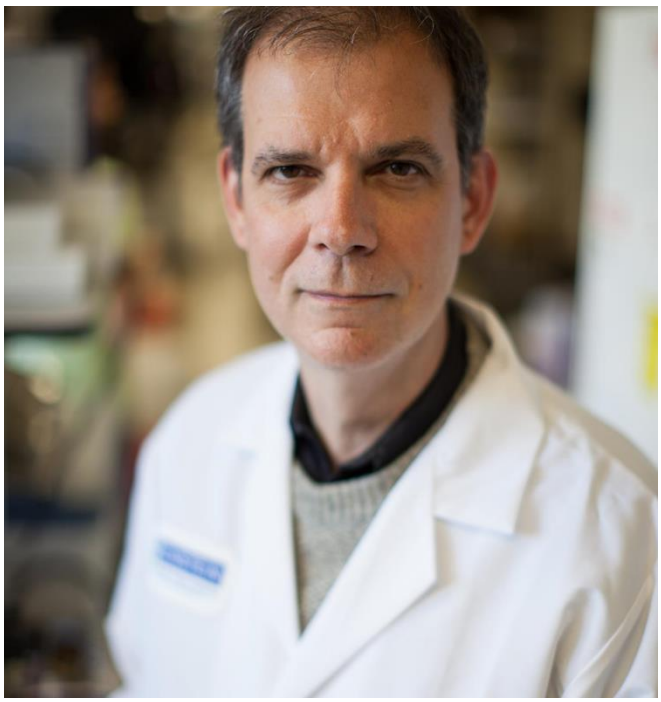
You have been doing some revolutionary work within the realms of PhD education and scientific training. Could you tell us a bit about the R3 programme which you developed and what you intend to achieve with it?
We (Ferric Fang and I) argued in 2012 in an article titled 'Reforming Science' that there was a need to improve the training of scientists.[2] Current PhD programs are excellent at teaching students how to do deep work and that needs to be protected and encouraged. However, current programs do not do a good job of teaching critical thinking or developing broadly trained scientists. The goal of the R3 program is to maintain the rigorous training in laboratory research while also teaching didactically the fundamentals of good science, rigor, communication, etc. The program was created at the Johns Hopkins School of Public Health and we have been very gratified by the interest and success of the initial efforts.

The R3 programme currently appears to be targeting PhD trainees; however, you have previously indicated that you believe it should be compulsory curriculum for researchers of all experience levels (including principal investigators), in a manner similar to continuous medical education. Do you foresee that a standardised continuous scientific education curriculum may become a global reality?
The R3 program is currently focused on PhD training but we hope that some of the principles that we are trying to develop, such as teaching critical thinking, could be applicable to other disciplines such as medicine. One of the problems in setting up the R3 program was there are few faculty who can teach it. However, if scientists make the effort to learn critical thinking, logical traps and the basis of good experimental design then many can become teachers and it may improve their own science. I believe there is a need for programs similar to continuing medical education for scientists that would provide continuing scientific education. These programs would allow them to keep up and remain current. We hope to take that on in future years.

As you outline, up to this point junior researchers have generally learned their trade from their mentor in a form of scientific apprenticeship. For those who do not yet have access to the R3 programme, what characteristics would you advise an early-stage researcher to look for in potential mentors?
I think all graduate students should ask their prospective mentors some basic questions like: 1) How do you plan to train me? 2) What is a PhD degree to you? 3) How do you know when a student is ready to finish to finish their PhD? Even these simple questions will encourage discussion between students and prospective mentors that would help the student understand what training is like in that particular laboratory and that could lead to better decisions in selecting laboratories.

Several years ago, you called for a reformation of the National Institute of Health grant review process and called for a system of funding by lottery.[3] Presumably, this concept consistently alarms and confuses your audiences, yet your rationale is in fact extremely compelling. Could you briefly explain this concept for our readership?
Current review panels tend to stratify applications based on their perceived excellence. However, we showed that scientists cannot stratify applications in the upper 20% range where most funding paylines fall. Hence, asking scientists to stratify grants is futile for identifying the best work and has the debit that it brings in conscious and unconscious biases. Although scientists are not very good at stratifying proposals they can certainly make two piles - meritorious and non-meritorious since most reviewers can discriminate between good and not so good proposals. We have suggested that funding in the meritorious pile is then allocated by lottery. Current review systems are already a lottery but without the benefit of It being truly random. The modified lottery system that we have proposed would preserve peer review and could result in more innovative work funded. This system is already used in New Zealand and by some European funding agencies. I believe it could one day be broadly used to distribute scarce research funds

Figure 1. Professor Arturo Casadevall, Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health



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Letter to the Editor

Is it all in our Heads? The Role of CaMKII in Neurogenic Hypertension

Nathaniel Edward Hayward,[1] Paul MacDaragh Ryan,[1] Ryan Taylor Sless.[1]

The letter

We wish to draw the attention of your readership to an intriguing development in neurogenic hypertension that was reported in the *Journal of Neuroscience* late last year.[1] While 1 in every 3 American adults now experience elevated blood pressures, the majority present with primary hypertension, the pathology of which is incompletely understood. It has been postulated that many cases of treatment refractory primary hypertension may be of a neurological origin [2] – *i.e.* sympathetically-driven increases in the vasoconstrictor tone of resistance vessels, leading to elevated arterial blood pressure.[3]

The presympathetic neurons of the hypothalamic paraventricular nucleus (PVN) regulate sympathetic outflow through projections to the rostral ventrolateral medulla. It is therefore biologically plausible that hyperactivity of this pathway may contribute towards hypertension.[4] Increases in glutamatergic output on *N*-methyl-D-aspartate receptors (NMDARs) in the PVN have previously been shown to increase vasomotor tone in a hypertensive rat model, with increases in both presynaptic and postsynaptic NMDAR activity in PVN neurons.[4] These NMDARs are activated through phosphorylation by numerous kinases including the calcium/calmodulin-dependent protein kinase II (CaMKII), which itself is activated by increases in cytoplasmic calcium.[5] Although there is a strong association between CaMKII and NMDA activity, its role in the hypertension-promoting PVN NMDAR activity currently remains unclear. Therefore, Li *et al.* set out to determine the role of CaMKII in regulating synaptic NMDAR activity of PVN presympathetic neurons and sympathetic motor tone in spontaneously hypertensive rats (SHRs).[1]

Elevated sympathetic outflow has previously been implicated in the development of essential hypertension in SHRs. Sympathetic outflow is regulated via PVN projections to the rostral ventrolateral medulla and the intermediolateral cell column of the spinal cord, which were the targets of these experiments. The major strength of this study lies in the meticulous confirmation of PVN location, which was predicated on several previous proof-of-principle experiments.[4-6] In the current study, Li and colleagues test the role of both pre- and postsynaptic CaMKII modulation of NMDARs by selective blockade of the suspected constituents involved in elevated sympathetic outflow in SHRs, as summarised in ***Figure 1***.

Coronal brain slices were incubated in autocamtide 2-related inhibitory peptide (AIP), a selective CaMKII inhibitor, and electrophysiological recordings of the hypothalamus were made. CaMKII blockade normalized both the inherent raised baseline amplitude of NMDAR-excitatory postsynaptic current (EPSC) and the NMDAR-EPSC/AMPAR-EPSC ratio in SHRs compared to the control group. Subsequent puff-application of NMDA on post-synaptic NMDARs was shown to increase SHR receptor current, while receptor currents were not increased in Wiskar-Kyoto control rats suggesting the role of PVN NMDAR activity in the pathogenesis of spontaneous hypertension. AIP blockade in conjunction with puff NMDA diminished SHR receptor current, indicating the direct role of CaMKII on increased postsynaptic activity in SHRs.

In attempt to assess the specific presynaptic role of CaMKII, miniature-EPSC (mEPSC) activity was measured with NMDAR channels blocked by Dizocilpine (MK-801), a non-competitive NMDAR antagonist. The blockade significantly increased mEPSC frequency in SHRs, which was subsequently normalized by application of 2-amino-5-phosphonopentanoic acid (AP-5), a competitive NMDAR antagonist. Increased mEPSC can thus be directly attributed to NMDAR activity. To illustrate the role of CaMKII in this pathway, slices were incubated once again with AIP and a decreased mEPSC frequency was observed. Subsequent application of AP-5 had no effect suggesting that CaMKII is directly responsible for the tonic basal increase in SHR PVN activity.

We currently know that expression of NMDARs is modulated by casein kinase (CK)2-mediated phosphorylation of receptor subunits, which is regulated by CaMKII. Li *et. al.* previously demonstrated the role of 5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole (DRB), a selective CK2 inhibitor, in reducing mEPSC activity in the PVN of SHRs.[5] However, AIP treatment coupled with DRB was not shown to further decrease either NMDAR current amplitude or mEPSC frequency versus AIP treatment alone. This indicates a common role of CaMKII and CK2 in both pre- and postsynaptic presympathetic neurons of SHRs.

Intriguingly, Li *et al.* revealed raised CaMKII phosphorylation of the GluN2M subunit exclusive to the PVN of SHRs versus controls through Western blot analysis,[1] while celiac ganglionectomy surgery did not reduce CaMKII phosphorylation levels compared to sham surgery. This indicates that high blood pressure does not directly increase CaMKII phosphorylation. Importantly, the authors further probed this result by injecting AIP directly into the PVN. In turn, results observed demonstrated a reduction in lumbar sympathetic nerve activity as well as arterial blood pressure in SHR.[1] A similar effect was found with exclusive AP-5 injection, which suggests that CaMKII is responsible for the increased sympathetic activity in SHRs.

The authors acknowledge that it is currently unclear as to the role of NMDAR activity of hypothalamic PVN presympathetic neurons in secondary hypertensive states, such as salt and obesity-induced hypertension. In this regard, a porcine model of mineralocorticoid-induced, metabolic syndrome-associated hypertension may represent a useful tool in exploring the potential role of this pathway.[7] Overall the study was well designed as the involved pathways were isolated with utmost precision with a focus on probing potential redundancies in the CaMKII-mediated increase in vasomotor tone in SHRs. The stringent attention to detail removed the effect of peripheral mediators in order to define the role of CaMKII alone on the vasomotor pathway. Sequential blockade of constituents in both the presynaptic and

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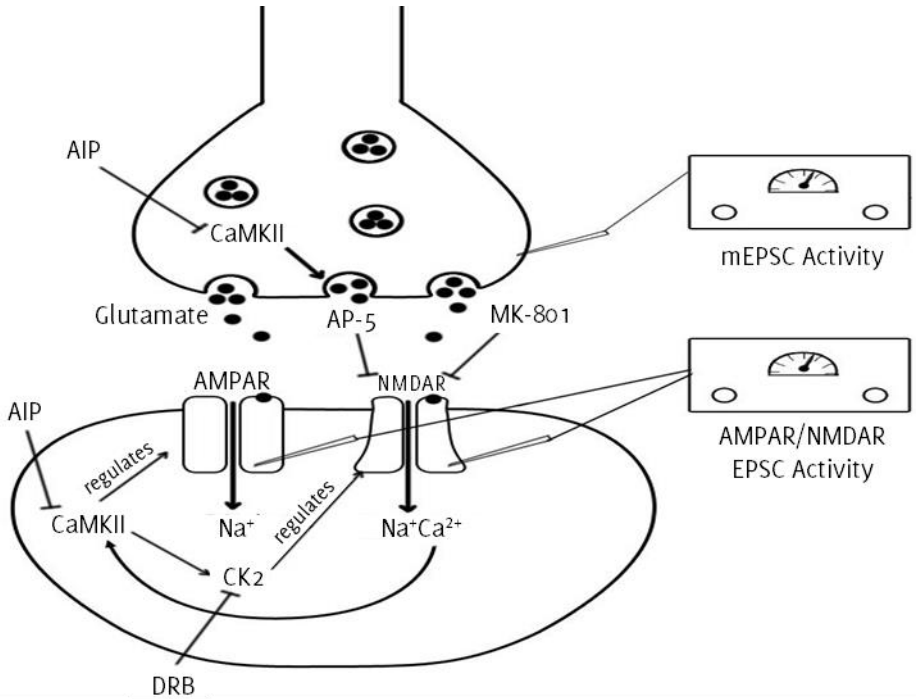
postsynaptic environment, aided in illustrating the direct role of CaMKII in raised sympathetic outflow.

This data represents a significant step in our understandings of neurogenic hypertension molecular underpinnings and provides novel information regarding the central role of CaMKII in synaptic plasticity, thereby revealing potential targets for the future development of pharmacologic treatments. However, further *in vivo* models are warranted to quantify the degree of antihypertensive effects prior to conclusively targeting this pathway for the treatment of hypertension. Previously, there had been indications that treatment-resistant, neurological pathology was mediated by neuro-inflammation – more specifically, the chronic inflammation of the hypothalamic PVN mediated by obesity and the renin angiotensin system.[8] Indeed, it is difficult to determine whether this represents an entirely alternate hypothesis of neurogenic hypertension or, rather, a contributory/resultant factor of the neuropathology.

While this research is primarily an academic advancement for the field, it is difficult not to extrapolate the translational potential. Despite the armoury of pharmaceuticals currently available, essential hypertension is managed satisfactorily in less than half of patients.[9] Indeed, it has been proposed that much of this discrepancy may be neurologic in origin,[10] indicating that the CaMKII pathway may represent a novel molecular target in the fight against hypertension. We must now assess whether there are any suitably selective drugs currently available, such as the NMDA receptor antagonist Memantine or whether a novel therapy could be designed for this purpose. In terms of the alternate PVN inflammation hypothesis, currently available pharmaceuticals such as angiotensin receptor blockers, immunosuppressants and reactive oxygen species scavengers may offer potency as adjunct therapeutics.

With such insightful data, it may now be time to ask ourselves: is hypertension all in our heads?

Figure 1. Summary of pathways in the PVN of the hypothalamus illustrating the pre- and postsynaptic role of CaMKII and associated locations of EPSC measurement. The drugs used in the study and their associated targets are also shown: AIP, autocamtide 2-related inhibitory peptide; AP-5, 2-amino-5-phosphonopentanoic acid; DRB, 5,6-Dichloro-1-β-D-ribofuranosylbenzimidazol;, MK-801, Dizocilpine; CaMKII, Calcium/Calmodulin dependent protein kinase II; CK2, Casein kinase 2; AMPAR, AMPA receptor; NMDAR, NMDA receptor; EPSC, Excitatory post-synaptic current; mEPSC, miniature excitatory post-synaptic current.



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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Letter to the Editor

Students' Surgical Training - A Continuous Challenge

Bogdan Socea.[1]

The Letter

I read with great interest the papers published in the International Journal of Medical Students regarding teaching practices of medical students worldwide.[1-4] Nekkanti et al and Althubaiti et al stressed out important trends in the manner medical students perceive the curriculum proposed by their universities: there is an increasing desire among undergraduates enrolled in medical schools for changes in the current manner medicine is taught; students wish their training to be focused more on research and hands-on activities rather than theoretical courses.[1-2] Important progress seems to have been made already, with some universities offering opportunities for medical students to partake in extracurricular activities centered on educational policies, such as the report of Allard et al on how undergraduates contributed to the development of an OSCE (objective structured clinical examinations) guide for their peers.[3] Hussain et al also commented on the important role peer-learning can play in medical education and how learning sessions among peers can provide a stimulating environment for students.[4]

As a surgeon, I believe that recent trends in medical education should stimulate us to rethink the way in which we teach Surgery to our students and fellows. In recent years, the increasingly important role of hands-on training sessions for surgeons has become evident. Gradually, these types of activities have been expanded for medical students as well, with the essential contribution of student scientific societies. Many medical students choose to acquire general or specialty-specific clinical experience, to further explore career opportunities and to increase their chances to enter their preferred specialty.

As lecturers, we have a rich experience in training programs and thus we are able to enjoy the participants' satisfaction and to get a confirmation of the utility of such programs. During 2014 and 2015, as a member of the development team of the two scientific grants, financed via the "Human Resources Development" Sectorial Operational Programme of the European Union, POSDRU/161/2.1/G/134858 (**Program of counseling for pupils and medical students and Surgical training**) and POSDRU/189/2.1/G/155735 (**Practical training in general surgery and gynecology and Counseling for medical students**), I could coordinate groups of students and teach them surgical maneuvers and abdominal ultrasound. The students enrolled in the project participated in a medical exchange program with the Urology Department of Hospital de Mollet, Barcelona, Spain. Thus, their experience was enriched by a one-week surgical internship at a European hospital.

Moreover, during the first edition of the **International Medical Students' Congress of Bucharest (IMSCB)**, we coordinated several hands-on lectures and tutorials of surgical sutures, surgical basic skills, surgical skills in digestive surgery, abdominal ultrasound (general ultrasound or emergency ultrasound) and thoracic ultrasound (ultrasonography of the intercostal space). Every time, the participation was numerous and the feedback we received from the participants was positive. The students were extremely pleased with the training that they received during these workshops. As a confirmation of our work, we were pleased to organize a FAST (Focused Assessment with Sonography for Trauma) workshop during the second edition of the **International Medical Students' Congress of Bucharest** in December 2018. The success of these educational activities has prompted us not only to continue but also to improve, diversify and increase their number. Moreover, the partnership between the International Journal of Medical Students and IMSCB has increased the number of foreign students attending the event, allowing us to compare and contrast the way in which surgery in taught across Europe by receiving direct and post-congress feedback from the participants.

Another part of the surgical education of students is represented by live surgical demonstrations, which are very useful for surgical training to achieve or improve surgical skills. Either transmitted in a conference hall or online, the training value of these events is very high. Interactive questions increase their value nevertheless.[5] We organized such live video sessions for students in our hospital and some surgical procedures (especially laparoscopic interventions) have been transmitted live in a lecture hall for all students to follow.

Besides their scientific value, educational programs also contribute significantly to the personal development of medical students. Empathy is a core element of the doctor-patient relationship and empathy in medical students can be improved by specific training.[6] Students also have the opportunity to get in contact with surgeons and lecturers and to establishing new professional contacts. These networking opportunities may serve as the basis for further scientific collaboration for the benefit of all parties involved. The social role of congresses and medical meetings cannot be ignored, since these events may encourage the creation of a professional network, the exchange of new ideas and the birth of future collaboration projects.[7] Students' surgical training programs are a continuous challenge - for lecturers to improve their teaching skills and practical applications and for students to be actively involved and receptive to new concepts. It is high time for a transition from the theoretical-based educational system to a more practical-based approach to teaching medicine (and surgery) and my opinion is that the **International Journal of Medical Students** could play a keyrole in the dissemination and implementation of new concepts in medical education, as well as research conducted by undergraduates.

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