Integrating sex and gender in model simulations of cardiovascular flows: a narrative review

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Pre-print version of the paper published in the JOURNAL OF SEX- AND GENDER-SPECIFIC MEDICINE, Issn: 2974-8194.

Summary

Gender medicine is providing increasingly abundant evidence of the pivotal role played by sex and gender in the pathophysiology of the human circulatory system[1]. Therefore, any medical or nonmedical scientific activity focused on cardiovascular issues must integrate sex and/or gender among the variables that drive blood circulation in order to guarantee the accuracy of the methodological approach, improve the understanding of cardiovascular biomechanical processes, promote a truly personalised medicine, and, last but not least, foster gender equality in healthcare[2].

A preliminary review of the most recent literature in the field of cardiovascular flows (CVF) simulation models is given here, aimed at highlighting if engineering replicas of blood circulation are usually developed according to a gender perspective i.e., if they pay appropriate attention to sex differences and/or gender factors along the entire process of modelling. The proposed examples show that there seems to be a lack of awareness of the basic concepts and alerts spread by gender medicine in the community of cardiovascular flows modellers. Possible reasons and mitigation strategies for such a situation are discussed in the conclusions.

Keywords

Cardiovascular Flows Models, Gender Medicine, Gendered Innovation, Engineering Tools, Sex and Gender Analysis, Gender Equality

1. Cardiovascular flows models

The present section provides some basic information on cardiovascular flows models in order to introduce the reader to the contents of the subsequent sections and allow her or him to better appreciate why engineering studies in the cardiovascular field must be developed according to a gender perspective.

Cardiovascular flows models are engineering tools nowadays widely adopted to simulate blood circulation in the human body under healthy and diseased conditions[3, 4]. They replicate the real-world phenomenon (e.g., the flow across the aortic valve) by means of mathematical equations that govern the physics of the problem or in-vitro objects that mimic the anatomy and function of the reproduced system. Whatever their kind i.e., *computational* or *experimental*, CVF models are aimed at quantifying relevant hemodynamic quantities such as blood velocity, flow rate and volumes, pressure waves, pressure gradients, and wall shear stress in the anatomical region under investigation (e.g., from the left ventricular outflow tract to the ascending aorta) during the entire cardiac cycle. Furthermore, any related hemodynamic index can be calculated from the models' output, e. g. the effective orifice area and the acceleration time in aortic stenosis. Quite recently, moving (e.g. aortic valve leaflets) or deforming (e.g. ascending aorta) boundaries have also been included among elements mimicked in models, to better simulate the real environment. In that case, the behaviour of the solid portion of the system is also part of the models' results (e.g. the geometric aortic valve area in time).

In general, CVF models are helpful in the achievement of various goals in the medical and bioengineering areas. They allow a better understanding of the cause-effect relationships in cardiovascular pathophysiology by simulating various scenarios as the diseased condition worsens. For example, Comunale et al.[5] explored the effect on both pulmonary and systemic circulation of isolated active, passive, and combined right ventricular dysfunction from absent to complete, and their results corroborated the emerging clinical evidence that the filling and pumping efficiency of the right ventricle is far from being less important than that of the left one. The assessment of the hemodynamic performance of medical devices is routinely performed using either computational or experimental models[6], as also suggested or even required by international standards[7]. As for the clinical practice, both diagnosis and treatment of cardiovascular diseases can greatly benefit from CVF models. For example, in-silico twins might substitute invasive procedures such as cardiac catheterization for the grading of aortic stenosis severity. To this aim, models that calculate the transvalvular pressure gradient at the level of the ascending aorta i.e., after pressure recovery has occurred, have been proposed so far[8, 9]. Note that the latter requires routine echo-Doppler data and

thus could be easily adopted in clinical practice. Last but not least, the use of CVF models for surgical planning is rapidly expanding, mainly thanks to the possibility of obtaining an accurate reconstruction of the patient-specific cardiovascular anatomy from medical imaging data[10].

It is worth recalling that CVF models can be population- or patient-specific. In the first case, the model replicates a reference subject i.e., an ideal subject that on average represents the investigated population. In the second case, the model is tailored to a specific patient, at least in the limit of clinical data available from that patient. Whatever the case, CVF models usually contain a large number of parameters that describe the anatomy and mechanical response of the cardiovascular functional elements of the modelled subject. To give an example, a model of blood flow in the thoracic aorta will include the size and length of the vessel, the viscosity of blood, the deformability of the aorta, and the cardiac frequency, among other parameters.

Finally, accuracy and reliability of models' results are key issues in the field of modelling. They both depend on many factors, which range from purely technical aspects (e. g., the accuracy of measurement instruments or numerical algorithms), to more 'operational' aspects such as the the modeller's experience[11], her or his level of knowledge of the pathophysiology of the cardiovascular condition to be replicated, the availability and reliability of the anatomical and functional data required to build the model. However, any CVF model has to be validated before being adopted as a predictive tool. Validation is usually performed by comparing model results mimicking a given real-world scenario (e.g. flow and pressure waves across the healthy aortic valve) and equivalent clinical data. A certain level of mismatch is always present in the comparison, if only because approximation typically affects not only models but also clinical data[12], [13]. Therefore, the question whether the mismatch is or is not acceptable in essence depends on the expertise and experience of the modeller only.

2. Sex and gender in cardiovascular flows modelling

Engineering studies and applications have been considered neutral with respect to sex and gender until recently, when the research on gendered innovations, and a large number of practical case studies spanning from transportation to environmental and, as expectable, biomedical engineering, have shown that they are not[14]. In the field of CVF modelling, the reasons and scopes for integrating sex and/or gender among driving variables should be rather intuitive, given the key role played by biological and socio-cultural peculiarities in cardiovascular pathophysiology[15]. Nevertheless, the existing CVF modelling literature does not seem to pay adequate attention to sex or gender-related aspects, probably due to the unawareness of the modellers of the issue.

In the following subsections, examples from recently published studies are proposed, aimed at pointing out weaknesses of CVF modelling when biological and/or sociocultural diversities among individuals are not taken into account.

2.1 Population-specific CVF models

CVF models have been applied to a large number of cardiovascular conditions common to both sexes so far: healthy, diseased, acquired, congenital, surgically treated, and supported by artificial devices. A quick search on Google Scholar with appropriate keywords can be useful for an example overview.

The vast majority of published works develop population-specific models i.e., they should consider, and refer to, a population group unambiguously defined and expected to have a similar circulatory response among the individuals belonging to the group itself. Rather, the description of the mimicked population is often provided in quite a generic or vague way if not left to the reader's interpretation, particularly with respect to the sex. Frequently, modellers refer to "human circulation", "human beings" or even "human-specific models" i.e., without making mention of sexual peculiarities[16] and implicitly assuming that the male and the female circulations, are interchangeable. Further emblematic observations come from the examination of the calibration process i.e., the assignment of realistic values to the parameters that describe the anatomy and the function of the cardiovascular system. In some models, the sex chosen for calibration is not declared at all, although schematic representations of the model domain and/or parameters' values reported in the text allow the reader to presume that a male subject is mimicked[17]. However, this might not be true, since it is not uncommon that literature clinical data used to estimate models' parameters were collected from individuals of both sexes, with no differentiation between men and women. In that case, the resulting model twin is neither male- nor female-specific. Some other models are calibrated adopting contemporarily data collected in part from male and in part from female patients [18] i.e., in that case a sort of sex-unspecific circulation is simulated. Finally, when the sex of the reference patient is clearly stated, it is the average adult (Caucasian) man the subject usually considered[19]. It is worth noting that in population-specific CVF models not only the calibration but also the validation process typically does not account for sex differences. Again, real data adopted for comparison to model results may refer to samples of male subjects only, both male and female subjects but not differentiated when averaging data, or subjects of unknown/undeclared sex. Finally, population-specific models should be tested with respect to their sensitivity i.e., the variation of models output as an effect of a prescribed variation in parameters values should be calculated. The rationale of the sensitivity analysis is to estimate to what extent the intrinsic uncertainty of calibration affects models predictions, and to highlight the anatomical or functional parameters that mostly affect blood flow properties. As such,

the sensitivity analysis can be an excellent tool to give evidence of the role played by sex-related differences in a given cardiovascular condition, provided that parameters values are varied in a range that covers both sexes. However, in models proposed so far the parameters are simply varied of a given percentage around their input value (usually ± 10%) i.e., no information can be inferred for sex effects.

Finally, one may wonder if the sex-specific calibration of population-specific CVF models matters, that is, if sex-specific models are actually capable of reproducing the differences between male and female blood circulation found in clinical research. Indeed, the question is almost unexplored, and to the best of my knowledge, only two contributions have been proposed so far, both focused on the case of healthy young reference subjects[20, 21]. Models predictions of blood pressures, flow rates and cardiac volumes have been found to differ between the two sexes as expected. Moreover, it has been shown that differences do not vanish when results are indexed with respect to body mass or body surface area i.e., blood circulation in women is confirmed to differ from that in men not only because of the different size. These results corroborate the idea that sex-specific CVF models can greatly contribute to improve the knowledge of the role that sex differences play in cardiovascular pathophysiology. A similar conclusion has recently been reached for what the modelling of cardiac form and function is concerned with[22].

2.2 Patient-specific CVF models

Patient-specific models of blood circulation are among the engineering tools that can be of help in the development of the so called personalized medicine i.e., the possibility of tailoring prevention, diagnosis and treatment of diseases on the single individual characteristics. Indeed, recent advances in clinical imaging allow accurate estimation of the anatomical parameters of the examined patient, thus promoting the rapid growth of patient-specific modelling. However, a large number of other functional parameters (e.g., heart chambers elastance) still remain hardly valuable for the patient unless invasive procedures are adopted, and they are rather calibrated starting from cardiovascular data measured in groups of individuals. As a result, calibration of patient-specific models may be affected by the same criticalities highlighted in subsection 2.1. However, the literature shows that both female and male patient-specific models have been proposed so far[23], and in both cases models are inherently sex-specific in a sense, at least in the limit of a sex-specific calibration of relevant parameters[24]. For what validation is concerned, it is typically performed by comparing model predictions to data measured on the modelled patient himself/herself, and hence the effects of sex peculiarities are inherently, although implicitly, accounted for. However, most of the time the sex of the patient under examination is not recognized as one of the variables that can influence the mimicked circulation, so that model results are analysed and commented without seeking for possible

sex-related issues[23]. Interestingly, quite a recent work has successfully adopted the patient-specific modelling approach to investigate sex differences in mice hemodynamics[25].

2.3 Sex-exclusive cardiovascular conditions in CVF models

Cardiovascular conditions exclusive to one or the other of the two sexes e.g., pregnancy[26] and erectile function[27, 28], have also been replicated by CVF models. In this case, the first noticeable observation is that sex-exclusive conditions are highly under-represented in the world of cardiovascular flows modelling, with even less attention paid to male than to female circulation. To the best of my knowledge, the works cited above are the only two proposed to investigate cardiovascular issues in erectile dysfunction so far, despite the recognised negative effects on the quality of life of patients due to such a condition. Simulation of blood circulation in pregnant women has received some more attention. Models have been proposed to reproduce hemodynamic changes in healthy pregnancy[26], with cardiac chambers[29] or vascular[30] remodelling eventually taken into account. Cardiovascular conditions that may arise during gestation, e.g. pre-eclampsia[31], or post-partum, e.g. haemorrhage caused by pernicious placenta previa, have also been investigated[32]. Importantly, the potential of CVF models as tools capable of assisting cardiologists in predicting pros and cons of pregnancy in women with congenital heart disease starts to be recognized[33].

2.4 Gender and non-binary issues

Clinical research is giving increasing credit to socio-cultural factors as possible determinants of the cause and outcome of cardiovascular diseases[2]. Tako-tsubo syndrome is a good example to refer to, as it seems to be typically associated with the experience of emotional or physical stress as is the case for familiar caregivers, and it affects women much more than men[34]. However, the biochemical and mechanistic processes that may trigger Tako-tsubo, and their dependence on factors associated with sex, gender, or both, are far from trivial and "easily" detectable, and this circumstance may be one of the reasons why no CVF model of the syndrome has yet been developed.

Finally, it is relevant that cardiovascular pathophysiology of neither intersex nor transgender individuals has been the focus of CVF modelling so far. Indeed, at first sight the topic seems to receive little attention also in the clinical research area, which would explain the absence of engineering models.

3 Conclusions

An overview of whether and how sex and/or gender are included in engineering models that mimic blood circulation has been proposed. Overall, the main observation that can be inferred from the literature is that modellers are substantially unaware of the role played by both biological and socio-cultural factors in determining the circulatory response in humans.

For what sex effects are concerned, models are frequently calibrated adopting sex-unspecific anatomical and functional cardiovascular parameters (that is, obtained from a 'mixed' population), and there are cases where the model reference subject presents in part female- and in part male-specific parameters. The same applies to the choice of real cardiovascular data adopted for models validation. It is very possible that such a confused situation is the signal of an insufficient contamination between the clinical sex-specific cardiovascular research and the community of CVF modellers. Therefore, strategic actions aimed at spreading the basic concepts of gender medicine among (bio)engineers have to be reinforced and promoted as much as possible, to foster the birth of the *gender (CVF) engineering*. At the same time, it seems appropriate, if not necessary, that clinical researchers working on sex- and gender-related cardiovascular issues become aware of the existence of CVF models and their enormous potential when built following a sex/gender-specific approach. Dedicated conferences and scientific journals capable of effectively mixing the two communities may be of help. Moreover, journals where CVF models are usually published should adopt editorial policies that ask the reviewers to verify if submitted CVF models pay adequate attention to sex and/or gender. Guidelines detailing the steps required to integrate sex and gender in CVF models have not yet been proposed and seem necessary to that aim.

Models that clearly state the sex of the simulated subject(s) consider male patients in most of the cases but attribute the results of simulations to the whole population. This is possibly a consequence of the preferential attention that clinical research itself has historically devoted to male cardiovascular patients. As a result, diagnostic tools, guidelines, and therapeutic strategies and devices, which may benefit from models' predictions, are at risk of being less accurate for women than for men. However, it should be stressed that, to date, female-specific cardiovascular parameters are only poorly and/or inconsistently present in the clinical literature. Hence, planning and execution of extended cardiovascular parameter data collection campaigns in female samples is paramount, as well as the production of technical guidelines for the consistency of measured data. Technical guidelines should be drawn up by working groups of both engineers and clinicians.

Interestingly, it has emerged that some models dedicated to sex-exclusive cardiovascular conditions have been produced. However, they are far less numerous than those that mimic conditions common to both sexes. Furthermore, cardiovascular issues possibly related to gender factors have not attracted CVF modellers so far, as is also the case for blood circulation in intersex and transgender individuals. On the one hand, such a gap may be due to the intrinsic high complexity of the above problems, which are still debated and/or poorly known also in the clinical field. On the other hand, it may be one further signal that minorities are under-represented in the area of health-related research.

The present brief review is the first attempt to organically describe the state of the art of CVF modelling from a gender perspective, with the aim of highlighting the current technical, methodological, and ethical criticalities, and providing a first proposal of possible mitigation strategies, actions, and practises.

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