Multilevel modelling for decision support in hypertrophic cardiomyopathy in the SMASH-HCM project

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inherited genetic heart disease, and its most feared outcome is a sudden death even in a young otherwise healthy adult. The EU-funded project SMASH-HCM aims at dramatically improving HCM stratification and disease management, both for clinicians and patients. The project combines data from the patients at multiple levels, from genetic and molecular data to in-silico physiological and family history data and creates in-vitro and computational models of the disease at these various levels. A digital twin of the patient will be formed based on these data modelling tasks. Modelling approaches, data-driven artificial intelligence and knowledge existing in literature will complement each other to provide decision support for the clinicians to optimize interventions, and actionable information about the disease status and development will be offered to the patient.

Keywords: hypertrophic cardiomyopathy, modelling, artificial intelligence, decision support

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease. Its estimated clinical prevalence approaches 1:200 in the general population [1]. It is estimated that 15-20 million people suffer from it worldwide [2]. Unlike more common heart diseases, HCM is not only a disease of the old, but people of all ages can be affected by it [3]. HCM can cause progressive dyspnea, angina, heart failure (HF) with or without left ventricular (LV) systolic dysfunction, atrial fibrillation (AF), and – the most feared consequence - sudden cardiac death (SCD) [1]. More than one-third of the sudden deaths in competitive athletes are accounted for by HCM, which is more than for any other single disease [2].

Fortunately, HCM has become a manageable disease with good outcomes thanks to the improved and more accurate diagnosis methods and various treatment options [3]. As HCM has a diverse phenotypic and genetic expression, clinical presentation, and natural history [4], it is difficult to diagnose accurately without an extensive test palette. For example, the thickening of cardiac walls is typical for

the disease, but it does not happen to all patients [2]. Also, for this reason, Maron et al. suggest an initial clinical evaluation and testing algorithm with diagnosed or suspected HCM cases, which ranges from family history evaluation, and ECG measurements to even genetic testing in some patients [2].

To tackle this plurality of diagnosis methods and treatment options, a large-scale research and development project financed by the European Union Horizon Europe programme was started in January 2024. The main aim of the SMASH-HCM project [5] (GA 101137115) is to dramatically improve HCM stratification and disease management, both for clinicians and patients. This major improvement is only possible, if the project succeeds in integrating the methods ranging from the molecular and genetic levels up to the analysis of the patient's symptoms into a multi-level analysis framework by combining modelling approaches with data-driven artificial intelligence (AI). The central research question is what are the computational methods that make this possible and implement them in a usable solution in a decision support platform.

As it is not possible for a single research group to master all these levels, the project needs the top expertise of all the relevant levels and the skills to combine the information to a complete solution. The project consortium consists of 12 partners from the European Union and two partners from the United Kingdom with a total funding of ten million euro for four years. The consortium consists mainly of universities and university clinics, and it includes a major medical device manufacturer and three small or middle-sized companies. The project is coordinated by Tampere University.

Material and methods

As the research problem is a multi-level one, material and data need to be available from different levels as well. Functional cardiovascular data will be collected from HCM patients using non-invasive methods. Among others, these include electrocardiograms and routine laboratory analyses of elevated blood pressure, special hormonal laboratory analyses related to cardiovascular regulation, 24-hour recordings of ambulatory blood pressure, and body composition analyses using bioimpedance spectroscopy. Information about patients' symptoms will be obtained from doctor — patient interviews. Genetic information will be collected from samples of the patients. Population-based data will be obtained from data banks. In-silico simulations produce data for model development. All these data require well-planned management and quality control to enable the application of machine learning methods. The project is committed to follow open science practices in making the data available to other researchers and the principle of being as open as possible, as closed as necessary [6]. For this purpose, the available data need to be anonymized while maintaining as much as possible of the details required for reliable scientific use.

In addition to the above, information from the literature also plays an important role. Unstructured knowledge from guidelines [7] and literature [8] are also needed to provide decision support for disease management and lifestyle guidance to the patients.

At cell and tissue level, existing stem cell lines derived cardiomyocytes and engineered heart tissues in-vitro will be leveraged to test the functional effects caused by HCMs mutations [9]. Further the functional characteristics and effects of the drugs on real patient myocardial tissues will be tested in the laboratory. These provide the insight on the disease and drug mechanisms and provides patient specific data completing the clinical data.

Modelling is a cross-cutting theme throughout the project. Modelling ranges from in-vitro tools, in-

silico simulations from molecular to entire heart and finally systemic level computational models, and finally to structured and unstructured data analysis [10,11]. For example, the personalized HCM heart models will be used to dissect the contributions of cardiac structural and functional anomalies to the ECG. These sub-models will be integrated into a multiscale vascular and multi-organ model. The aim is to build a so-called digital twin of a patient with HCM.

EDITH [12], a Coordination and Support Action, funded by the European Commission which coordinates the developments of digital technologies for healthcare in Europe defines a virtual human twin (VHT) the following way: "Virtual Human Twin is an integrated multiscale, multi-time, and multi-discipline representation of quantitative human physiology and pathology."

In this project, an accurate digital twin would enable the simulation of the model with various treatment options and the prediction of their outcomes. Biophysical mechanistic models are employed to gain functional understanding of the disease mechanisms and to simulate patient and population biomarkers such as ECGs or vascular function. Machine learning is applied to the model development whenever appropriate, the limiting factor being the amount of relevant training and validation data. The aim is to develop and apply trustworthy and explainable artificial intelligence methods as much as possible because these not only alleviate the regulatory approval processes but also increase the trust of the clinicians towards the developed decision support system. For this we use the trustworthiness research infrastructure [13] and co-operation network at Tampere University. Additional requirements from the regulation include bias minimisation, ensuring the robustness of the AI models and support for human oversight. The fluent use of the decision support tool also requires continuous involvement of end-users (healthcare professionals and patients) in the requirements specification and development cycles and the implementation of standards-based interfaces to selected electronic health record systems to avoid the manual re-entry of existing patient data to the system.

The flawless management of patient consent documents, data transfer agreements and ethical approvals is a necessity in projects like this. To enable smooth transfer of research results to commercialization, the clinical trials must be carried out according to the best practices providing the necessary evidence of the safety and performance of the developed decision support methods.

Results

At the time of writing (May 2024), the project is still in its early stages. Each project partner has accumulated knowledge of the HCM problems at their own level and developed their research methods for further studies. The kick-off meeting has been held and the project partners have presented their expertise, including some yet unpublished most recent research results to the other partners.

Patients were also represented in the kick-off meeting by the Cardiomyopathy UK charity [14]. The patients have been asked what they would like especially as outputs from research. They have responded that they want better diagnoses and referrals, improved specialised care including genetics, personalised care and treatment, participation, and overall holistic care. The project partners are committed to make this possible.

The project plan contains 57 deliverables to be submitted to the European Commission financing the project. Most of the deliverables, i.e. project results

will be publicly available after they have been approved by the Commission.

Discussion

The SMASH-HCM project is a challenging project because it aims to integrate all relevant information relating to HCM into a decision support system with a clearly better precision than the present methods allow. To reach success, the partners need to learn new information from other levels (molecular, genetic, tissue, physiology, signal interpretation) than where they have been experts before. If success is reached, the benefits to the HCM care will be significant.

Large projects like this also have several possible risks that can jeopardize the optimal outcomes. Our experience from past projects suggests that the data to train the AI models often arrive later than hoped for in sufficient quantities. This naturally delays the following steps, the AI model development and its validation. The project consortium has prepared for these delays by thinking of alternative ways to obtain data and by planning the use of less data-intensive algorithms or by applying expert knowledge from literature. Even if data became available early enough in sufficient quantities and in sufficient quality, there is always the possibility that the prediction results will not be accurate enough for clinical use. The algorithms also need to cope with the situation that all the wanted input data is not available due to various reasons. Fortunately, there are algorithms for these cases, too [15]. As these prediction systems would be medical devices in the regulatory sense, they need to be sufficiently validated before bringing them to market to minimise the risks to the patients. The privacy risks to the patients participating in this study are minimal because data anonymisation is used as much as possible.

One of the risks in these kinds of co-operation projects is that a key partner does not deliver the expected result what the other partners need as their input. In this case, this risk is not very high because many of the partners are leading experts in their field and have worked together successfully in past projects, too, and are expected to do the same in this project as well.

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Conflict of interest statement

The authors are researchers in the project that is described here but they have no conflicts of interests with the producers of the equipment or producers of the data used in this study.

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