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ANALYTICAL INTERPRETATION OF HEMODYNAMIC DATA IN PATIENTS WITH INTRACARDIAC SHUNTS: ROLE OF MATHEMATICAL MODELING

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ABSTRACT

Introduction

Shunt lesions are categorized into pre- and post-tricuspid. Although it is well recognized that these two entities have a different pathophysiology, hemodynamic variables involved are still poorly understood. This paper aims to analytically appraise shunt physiology exploiting a lumped parameters mathematical model.

Methods

Circulatory system was split into arterial and venous compartments, each of them being described by resistive, capacitive and inductive components. The model was modified including a communication between atria and ventricles. Predicted changes in the ratio between pulmonary blood flow and systemic blood flow (Qp/Qs), obtained by manipulating pulmonary resistances (PVR) and ventricular stiffness were computed.

Results

A twofold rise of pulmonary vascular resistance resulted in a significant reduction of Qp/Qs in the setting of isolated ventricular septal defect (VSD) and VSD associated with atrial septal defect (ASD) but did not produced a sizable effect in case of isolated ASD. In the model describing an isolated ASD, a similar magnitude of Qp/Qs reduction was predicted by simulating an increase of right ventricular passive elastance and relaxation time. In this type of shunt, the dependance of Qp/Qs from PVR and ventricular elastance appeared analytically linked.

Conclusions

According to this model, shunt through an ASD is minimally affected by PVRs. The marginal change of pulmonary flow produced by large variations of PVR appeared mediated by changes in right ventricular elastance. According to the model the effect of pulmonary vasodilators in patients with ASD can be concealed or enhanced by increased stiffness of the right or left ventricle, respectively.

Keywords: Shunt, pulmonary vascular resistances, model, pre-tricuspid

1. INTRODUCTION

Intracardiac and extracardiac shunts occur as a result of congenital heart defects that allow communication between cardiac chambers or major vessels. The direction of the shunt is most often systemic-to-pulmonary (left-to-right), resulting in higher pulmonary blood flow (Qp) compared to systemic blood flow (Qs). The cornerstone of the hemodynamic assessment of patients with intracardiac shunts is the calculation of shunt fraction (Qp/Qs), and the measurement of the transpulmonary gradient and Qp that allow estimation of the pulmonary resistances (PVR). From an anatomical point of view, shunt lesions are classified into pre-tricuspid, typically atrial septal defects (ASD), versus post tricuspid (ventricular septal defects (VSD), patent ducts arteriosus (PDA) or aortopulmonary window).[1,2] The direction and severity of a post-tricuspid shunt depends heavily on the size of the defect and ratio between systemic and pulmonary vascular resistance (SVR and PVR, respectively) whereas, in pre-tricuspid shunts, the diastolic properties of the ventricles play a significant role, by determining the pressure gradient between the atria.

To calculate PVR, pulmonary artery pressure (PAP), Qp and PVR are assumed to be linearly related. Similarly to Ohm's law the transpulmonary gradient is deemed proportionate to Qp and PVR.

$$TPG = Qp \times PVR \quad \text{hence} \quad PVR = \frac{TPG}{Qp} = \frac{mPAP - mLAP}{Qp} \quad \textit{(equation 1)}$$

Where TPG is transpulmonary gradient, mPAP is mean PA pressure, and mLAP is mean left atrial pressure. Equation 1 is routinely applied in the assessment of all patients with suspected pulmonary hypertension and patients considered for repair of a congenital heart defect regardless of anatomical location of the shunt. This is, however, an oversimplification of the physiology of the pulmonary circulation, ignoring flow pulsatility, ventricular elastance, pulmonary artery capacitance and blood inertia. These obvious limitations can be overcome by exploiting an electric

circuit analogues, analytically described by a zero-dimensional lumped parameter mathematical model, that can be used to better understand shunt physiology in different anatomical scenarios. Such models are particularly valuable, as they can be adapted to almost all anatomic variants of congenital heart disease and allows us to analytically compute the effect of simulated changes in physiological variables.

In this paper we appraise the hemodynamic variables governing shunt fraction using a modified zero dimensional mathematical model representing an ASD, a VSD, and an ASD associated with VSD.

METHODS

The mathematical formulation of the model has been previously described [3-5]. Briefly, the cardiac chambers are modeled as pressure generators by means of time-varying elastances that mimic the periodic contraction of the cardiac chambers. The circulatory system is split into several compartments, each represented by a Windkessel circuit. Systemic and pulmonary circulations are subdivided into arterial, venous and capillary compartments. The Windkessel circuits describe each compartment by means of resistors, representing the resistance to blood flow, capacitors representing vessels compliance, and inductors representing blood inertia. This model has been tailored to describe a shunt through an ASD and/or VSD defect and has been calibrated by introducing pressure measurement from real patients (Figure1A and B). Quantitative variations of Qp/Qs in different hemodynamic conditions were investigated by introducing PVR and ventricular compliance changes. The effect of right ventricular (RV) and left ventricular (LV) compliance was assessed by simulating an increase in either RV passive elastance (EB-RV) or relaxation time

relative to the cycle length, that have been shown to be reliable metrics of ventricular diastolic properties.[6]

The quantitative changes of shunt flow through the ASD (Q_{ASD}) and VSD (Q_{VSD}) during the entire cycle length predicted by the model were also plotted.

RESULTS

VSD modeling

In the case of a VSD, an increase in PVR (keeping all other variables constant) results in an exponential decrease in Qp/Qs. By simulating a 2-fold increase in PVR (from 2 to 4 Wood units) a Qp/Qs decrease of approximately one unit is predicted by the model. On the other hand, changes in both RV passive elastance and relaxation time had a negligible effect (Figure 2B and C). Q_{VSD} predicted by the model displayed a major systolic component during the isovolumetric contraction and ejection phase and a two other minor peaks coincident with ventricular relaxation and atrial contraction (Figure 3B).

ASD modeling

Symmetrically, in the case of an isolated ASD, a PVR increase resulted in a negligible decrease in Qp/Qs. (Figure 2A) while RV passive elastance showed the greatest effect on shunt fraction: indeed by simulating a passive elastance increase an exponential fall of Qp/Qs is predicted. Similarly, an increase of relaxation time again produced significant linear decrease of Qp/Qs (Figure 2B and C).

Differently from the case of VSD, shunt flow through the ASD takes place during the entire cycle length with two major peaks occurring during ventricular relaxation and atrial contraction (Figure 3A)

ASD and VSD modeling

According to the model, in the case of a VSD in combined with ASD, an increase on PVR elicited a Qp/Qs decrease of a similar magnitude and with a similar course to the one observed in isolated VSD (Figure 2A). Passive elastance increase, again caused a sizable reduction of shunt fraction. (Figure 2B) whereas simulated increase of ventricular relaxation time did not produced a significant effect on Qp/Qs (Figure 2C).

DISCUSSION

It has previously been shown that congenital conditions can be reliably simulated by a lumped parameter mathematical model[5]. Quantitative estimation of the effect of different hemodynamic determinants of pulmonary flow in the presence of simple or complex shunts can enhance the interpretation of invasive and non-invasive parameters, and may assist clinical decision making.

In this zero dimensional model of a VSD, isolated or associated with an ASD, a steep but non-linear relation between Qp/Qs and PVR can be demonstrated, suggesting a more complex relation between these two parameters, beyond what is predicted from simple formulas based on a simple application of "Ohm's law". The observed non-linear relation means that, for a given absolute increase or decrease in PVR, a greater change in Qp/Qs is expected in patients with a normal or near-normal PVR than in those with established pulmonary arterial hypertension. This observation might have some clinical relevance whenever a vasodilator test is performed. Conversely, the model predicts that, in a patient with an ASD, changes in PVR have a little impact on Qp/Qs suggesting that other mechanisms are responsible for the effect of pulmonary arterial hypertension (PAH) on shunt fraction observed in clinical practice.

Indeed, changes in ventricular passive elastance (Figure 3B) are more likely to influence shunt fraction in ASDs, with a negligible effect in VSDs. This is also confirmed by the model that shows a mainly systolic pattern of shunted flow through the VSD and a mainly diastolic flow through the ASD. While a rise in PVR is the cornerstone of PAH physiology, these results analytically show that PAH affects shunt fraction differently in pre- vs post-tricuspid defects. (Figure 2A and B). Shunting through a post-tricuspid defect is directly affected by PVR while in pre-tricuspid defects, only at a later stage, RV adaptation to PVR increase induces RV hypertrophy and other changes that are likely to affect RV filling pressure and passive elastance, eventually affecting shunt fraction, less so in a VSD where the shunt is predominantly systolic.

According to this mathematical model, utilization of a pulmonary vasodilator is expected to elicit a fairly reproducible and predictable change in Qp/Qs is patients with a VSD, but less so in isolated ASDs, unless reverse RV remodeling occurs[7]. Similarly, a decrease in left ventricular compliance, e.g. as a result of ageing, uncontrolled hypertension, diabetes, obesity etc., is likely to drive an increase in shunt fraction at atrial level, a phenomenon that explains the surge of late diagnoses of ASDs (but not VSDs) after the 5th decade of life.[8]

Interestingly, in the clinical scenario characterized by VSD associated with ASD the model predicts that passive elastance but not relaxation time is able to significantly affect Qp/Qs. This finding ca be explained by considering that the increase in relaxation time represents a milder degree of ventricular stiffness which is not able to affect the global shunt generated by the VSD component by modulating the shunt through the ASD component.

CONCLUSIONS

In this paper we analytically appraise quantitative effect of hemodynamic variables on shunt physiology produced by cardiac communications at different anatomic levels. Validated zero dimensional lumped parameters mathematical model of the human circulation can be tailored and manipulated, aiding in the interpretation of challenging cases and advancing our understanding of shunt lesions and their management.

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Author Contributions Statement

Paolo Ferrero: Conceptualization and manuscript writing

Andrea Tonini: Data analysis, manuscript writing and figure production

Giulio Valenti: Data analysis

Stiljan Hoxha: Conceptualization and manuscript review

Pier Paolo Bassareo: Conceptual conceiving and manuscript review

Luca Dedè: Manuscript and figure editing

Alfio Quarteroni: Data analysis and manuscript review

Konstantinos Dimopoulos : Manuscript writing and review.

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Figure Legend

Figure 1

Diagram illustrating the electric analogue model representing the shunt through ASD **(panelA)** and VSD **(panel B)**. RPUL.AR: pulmonary arteries resistance; LPUL.AR: pulmonary arteries inductance; RPUL.VEN: pulmonary veins resistances; LPUL.VEN: pulmonary veins inductance; RSYS.AR: systemic arteries resistances; RSYS.VEN: systemic veins resistances; LSYS.AR: systemic arteries inductance; LSYS.VEN: systemic veins inductance; CPUL.AR: pulmonary artery capacitance; CPUL.VEN: pulmonary veins capacitance; R.ASD: atrial septal defect resistance; RVSD: Ventricular septal defect resistance; R.TV: Tricuspid valve resistance; R.MV: Mitral valve resistance; R.PV: pulmonary valve resistance; R.AV: aortic valve resistance; Q.ASD: blood flow across atrial septal defect; Q.VSD: blood flow across ventricular septal defect; E.RV: right ventricle elastance; E.LV: left ventricle elastance

Figure 2

Panel A Relationship between pulmonary vascular resistances and Qp/Qs
Panel B Relationship between right ventricular elastance and Qp/Qs
Panel C Relationship between relaxation time and Qp/Qs
ASD: atrial septal defect, VSD: ventricular septal defect, RPUL.AR: arteriolar resistances, EB.RV: right ventricular elastance.

Figure 3

Blood flow across atrial **(panel A)** and ventricular **(panel B)** septal defect. Q.ASD: blood flow across atrial septal defect; Q.VSD: blood flow across ventricular septal defect

Figure 1

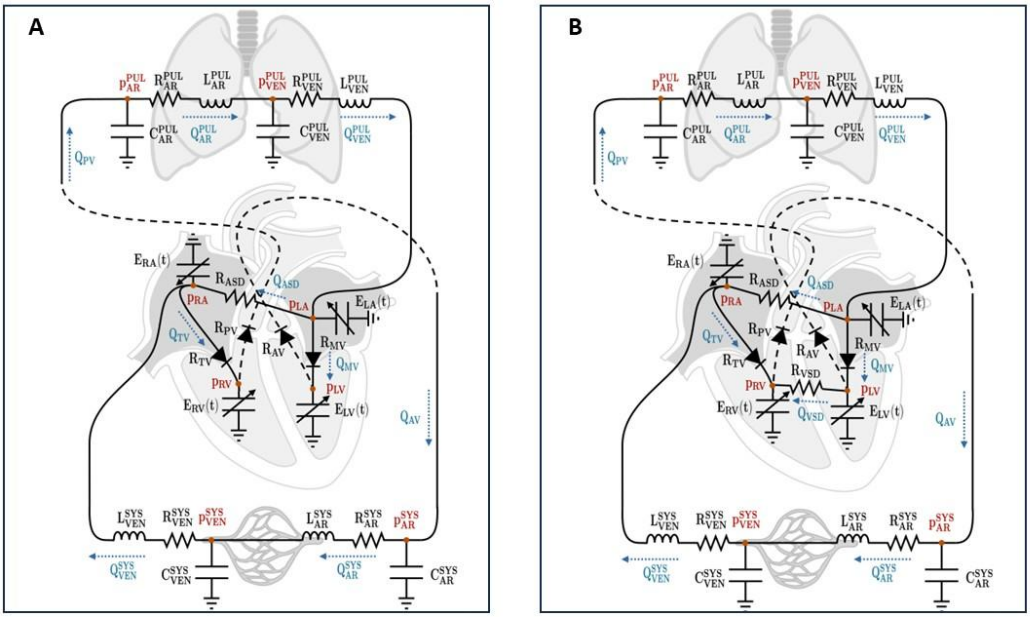


Figure 2

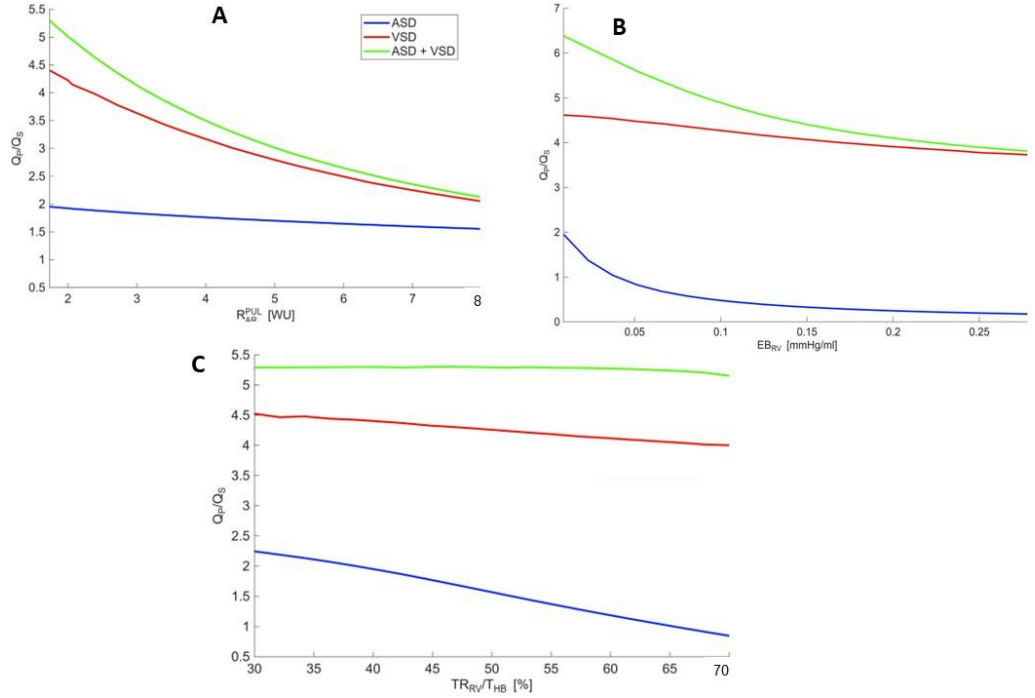
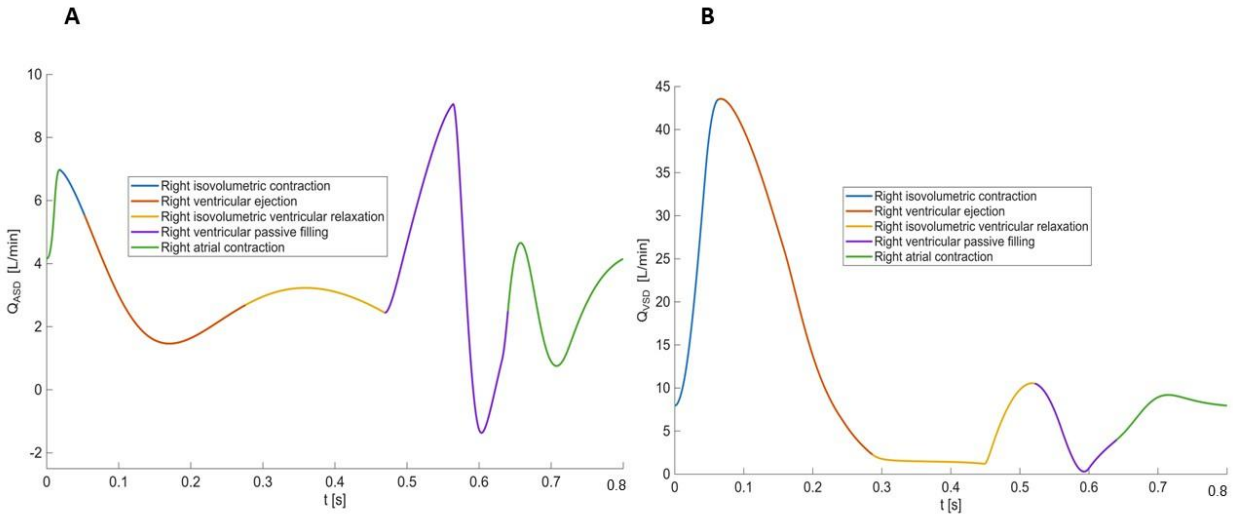


Figure 3


A
B
Right isovolumetric contraction
Right ventricular ejection
Right isovolumetric ventricular relaxation
Right ventricular passive filling
Right atrial contraction
Q_{ASD} [L/min]
Q_{VSD} [L/min]
t [s]

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