REVIEW

Ventricular Interdependence and Biventricular Failure: Key Concept for Heart Failure Management

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Keywords: Heart failure, biventricular dysfunction, ventricular interdependence, interventricular septum, myocardial fibers

INTRODUCTION

Ventricular interdependence corresponds to the impact of a ventricle on another in physiological but also pathological conditions[1].

The concept of biventricular interactions is not recent. In 1910, Bernheim postulated, in LV hypertrophy or dilation, that interventricular septum (IVS) bulging towards the right ventricle (RV) would generate an elevation of central venous pressures at the origin of right congestive signs whose presence is then poorly understood[2]. The first demonstration of ventricular interdependence was described in 1914 by Henderson and Prince[3], showing how a ventricle output decreases as feeling pressure of contralateral ventricle increases.

In this review, we will first detail the anatomical and physiological determinants of ventricular interdependence and then the different resulting interactions. We want to highlight the practical implications in the management of heart failure patients.

ANATOMICAL AND PHYSIOLOGICAL APPROACH

Interactions between LV and RV are primarily based on an unique anatomy comprising an „in-series" circulation, a common interventricular septum, shared myocardial fibers and a common pericardium[4]. Consequently, event on one ventricle affects necessarily the other one. Always!

„*In series*" circulation

The left heart and the right heart constitute a system operating „in series". The systemic circulation, whose flow is generated by LV, ensures capillary perfusion of the various organs and is associated with a venous return converging with the right atrium (RA). The pulmonary circulation, whose flow is generated by RV, ensures constant gas exchanges in pulmonary capillaries and is followed by a venous return of oxygenated blood to the left atrium.

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Cardiac output variation of one ventricle therefore impacts the preload of the second. In ventricular septal defect, the left to right post tricuspid shunt can generate a prolonged RV increased blood flow leading to a progressive LV dilation in order to cope with the resulting excessive preload[5]. Conversely, LV Filling pressure variation can impact RV afterload trough pulmonary arterial hypertension, an acknowledged complication of left heart diseases constituting a cause of RV failure[6].

Shared septal and parietal myofibers.

Myocardial architecture is the consequence of phenomena occurring during cardiac embryogenesis6. It begins at the third week of gestation, starting from the primary (at the origin of LV) and secondary (at the origin of RV) heart fields, leading to the formation of the primitive heart tube which, after a series of twists and folding, will generate a single primitive ventricle with a common outflow tube called Truncus Arteriosus. The interventricular septum emerges, by the end of the fourth week, from the floor of the primitive ventricle forming the beginnings of a distinct LV and RV. Between the fifth and the eighth week, the aorticopulmonary septum develops which, fusing with the endocardial cushions and the interventricular septum, forms the membranous septum.

Torsion and fusion phenomena are at the origin of a complex network of myocardial helicoidal fibers[7]. The main consequence is a transmural inhomogeneity of myocardium whose characterization and relevant modeling remains a challenge. Indeed, LV free wall contains mainly transverse fibers predominant on the mid-layer, associated with longitudinal and helical fibers ranging from +60° at the sub-endocardium to -60° at the sub-epicardium[7]. The interventricular septum consists of oblique helical fibers crossing at 60°. The RV free wall is mainly composed of transverse fibers associated with scanty subendocardial longitudinal fibers[8]. Torrent-Guasp et al.[9] proposed a model making the anatomical description of helical muscle bands interconnected, with transverse fibers generating a basal loop and encircling LV and RV, while oblique fibers forming two clockwise (in the sub endocardium) and counterclockwise (in the sub epicardium) helices will crisscross the interventricular septum and connect to the apex. This model was debated by other investigators[7], acknowledging the helicoidal nature of myocardial architecture but, jugging it too simplistic considering histologic evidences describing a transmural continuum between 2 helical fiber geometries, where right-handed helical geometry in the LV subendocardial region gradually changes into left-handed geometry in the LV subepicardial region. Beyond these controversies, evidences support the existence of a „biventricular" and „helicoidal" septum supported by advances in velocity vector imaging and diffusion tensor MRI[10,11] confirming common myocardial fibers between LV and RV within septal and apical region. Epicardial fibers are also directly shared trough each free wall.

The anatomical orientation of myocardial fibers has a major functional impact. Longitudinal deformation is mainly responsible for the RV ejection. However, the too scanty RV subendocardial longitudinal fibers alone cannot provide a majority stake to this process[8]. Twisting deformation was shown to be a major mechanism of LV ventricular ejection and is related to oblique fibers[12]. It has been[8,13], based on the Torrent-Guasp model, proposed to attribute this longitudinal deformation to the oblique character of septal fibers during coiling and shortening of both helical arms. Septum stretching is associated to a more transversal orientation of fibers and therefore decreases twisting and longitudinal deformation[12]. This highlights biventricular systolic interactions where the septum holds a central position (Figure 1).

Moreover, RV is the site of numerous myocardial trabeculations and includes the Crista Supraventricularis. This muscle bridge separates the RV inlet (tricuspid annulus) from the outlet (pulmonary annulus), unlike the shared annulus of the aortic and mitral valves. It shares muscle fibers with the interventricular septum and the RV free wall. It contraction and shortening pull the RV free wall towards the interventricular septum during systole contributing to RV ejection[6,14].

A complementary geometry in a common pericardium

The pericardial cavity is inextensible and therefore implies that volumetric or barometric variation within a ventricle must occur at the expense of the other.

Geometric disparities between RV and LV can be explained by their embryological origins and their different hemodynamic environments. At birth, decrease of pulmonary resistances, increase in systemic resistances and closure of the Foramen Ovale and the Ductus Arteriosus in physiological situation leads during the first year of life to the following anatomical differences between RV and LV[15]. The resulting left to right trans septal gradient causes rightward shift of the interventricular septum giving RV a crescent shape

in the longitudinal plane and a triangle shape in the transverse plane. LV acquires a conical shape in the longitudinal plane and a circular shape in the transverse plane. The thickness of the RV free wall is less important given a lower pressure regime associated with higher compliance.

This complementary geometry within an inextensible pericardium constitutes the physiological basis of the LV and RV interactions, partly mediated by septal pressure gradient and compliance. Single ventricle symbolizes the functional importance of geometric complementarity through interventricular septum. Indeed, real-time 3-dimensional echocardiography allowed to identify that its absence, in these patients, could modify tricuspid annulus conformation and worsening tricuspid regurgitation (TR) whose prognosis impact is major[16].

DIFFERENT TYPES OF INTERACTIONS WITHIN CARDIAC CYCLE

Diastolic interactions

They can be defined as the impact of the change in ventricular volume on the diastolic compliance of the contralateral ventricle[17].

It has been shown in healthy volunteers that a decrease in intra-thoracic pressures during an inspiration effort against a closed airway (increasing venous return) generates an increase in RV volume, at the expense of LV volume, concomitant with a septal flattening in diastole[18]. Santamore et al.[19] described in isolated rabbit heart that the more RV volume increases, the more resulting LV diastolic pressure increases. This effect is greater for larger LV volumes and correlated to the septal radius of curvature. Indeed, in patients with RV volume overload via atrial septal

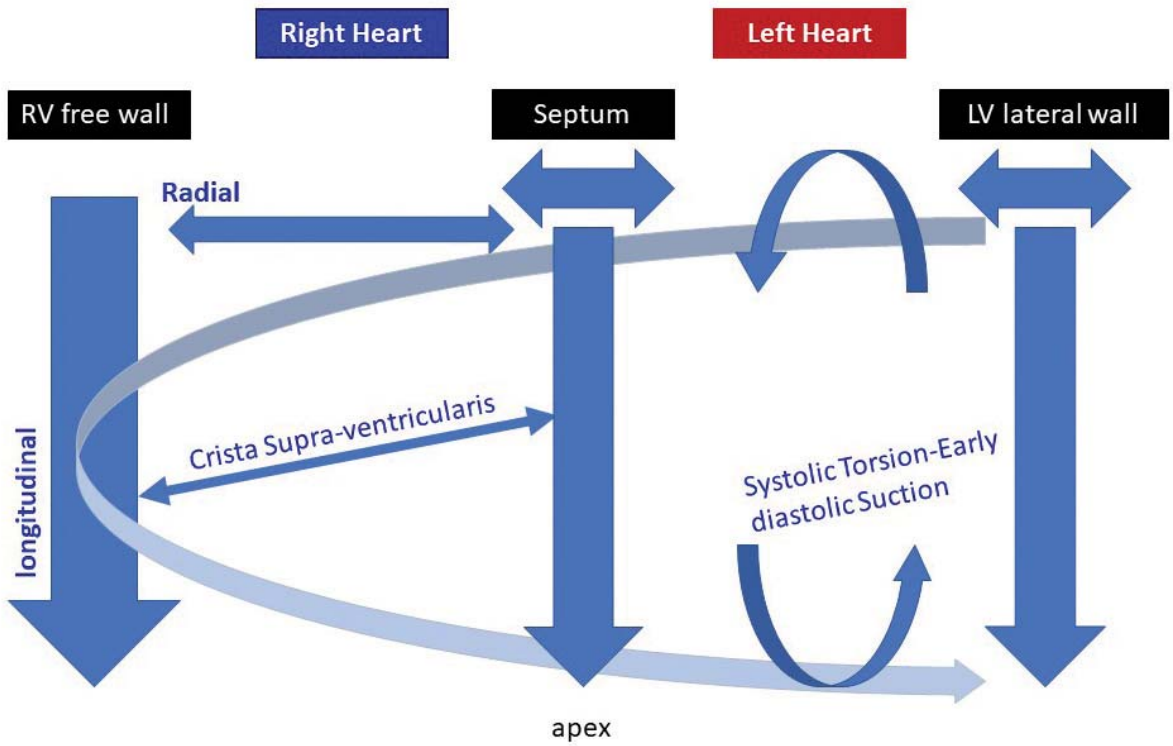

Figure 1. Fundamental functions and impact of the septum between both ventricle.

defect, tricuspid or pulmonary regurgitation, there is an altered septal curvature ranging from flattening to complete reversal in diastole[20]. The complete correction of this anomaly in systole leads to the description of a so-called "paradoxical" septum (Figure 2). The main consequence is an impairment of LV compliance decreasing its filling. LV volume decrease in response to RV volume overload through the example of children with atrial septal defect[21].

LV volume loading can, conversely, be the modulator of RV compliance and volume. Again on rabbits[19], the more LV volume increases, the largest is the decrease in RV diastolic pressure. This effect is enhanced for larger RV volumes. In aortic regurgitation (AR), LV volume overload was shown to be associated to abnormal RV relaxation and feeling[23]. Authors rise the hypothesis that dilated LV and diastolic rightward septal shift could explain these results. This is in accordance with jugular diastolic venous pulse described in acute AR[24]. However, RV response to LV volume overload through the example of children with isolated ductus arteriosus was non-significant in term of change in volume[21].

Curiously, volume impact seems to be lower in „left to right" than „right to left" diastolic interactions. Septal configuration preserving ventricular geometry might have a role.

The pericardium is fundamental when looking at diastolic interactions. Great demonstrations have been made in model of RV infarction[25]. With an intact pericardium, there is a concomitant reduction in LV volume with a drop in LV contractility indexes. When opening the pericardium, no change is observed on LV volume but there is still a decrease, to a less extent, in LV load-independent contractility indexes. This argues in favor of a pivotal role. Chronic constrictive pericarditis, characterized by increased pericardial constraint on a presumed healthy myocardium, provides a unique opportunity to assess the influence of the pericardium and septal configuration to diastolic ventricular interdependence[26]. Indeed, the dissociation between intrathoracic and intracardiac pressures leads to an excessive variation in mitral inflow and aortic outflow, inversely correlated to tricuspid inflow and septal leftward shift during the respiratory cycle (Figure 3). The paradoxical greater value of e' septal (>e' lateral) is also a clear consequence of this interaction and this simple measurement of e' makes the diagnostic of constriction much easier!

Diastolic interactions impacting systole.

Beyond diastolic interactions, a real impact on the contralateral systole exists. When the atrial filling pressure is increased on one side, it has been found that the output from the opposite side decreases[27]. This effect is more pronounced with intact pericardium but can also be demonstrated when this structure is removed.

Small RV volume enhances LV generated pressures, but large RV volume leads to decreased LV generated pressure[19]. Decrease in LV compliance and end diastolic volume is necessarily associated with a drop of stroke volume. As part of experimental provocation of RV ischemia generating RV dilation, LV contractility and relaxation indexes are reduced[28]. The establishment of a cavo-pulmonary bypass allows normalization of RV volume and LV relaxation. LV systolic dysfunction

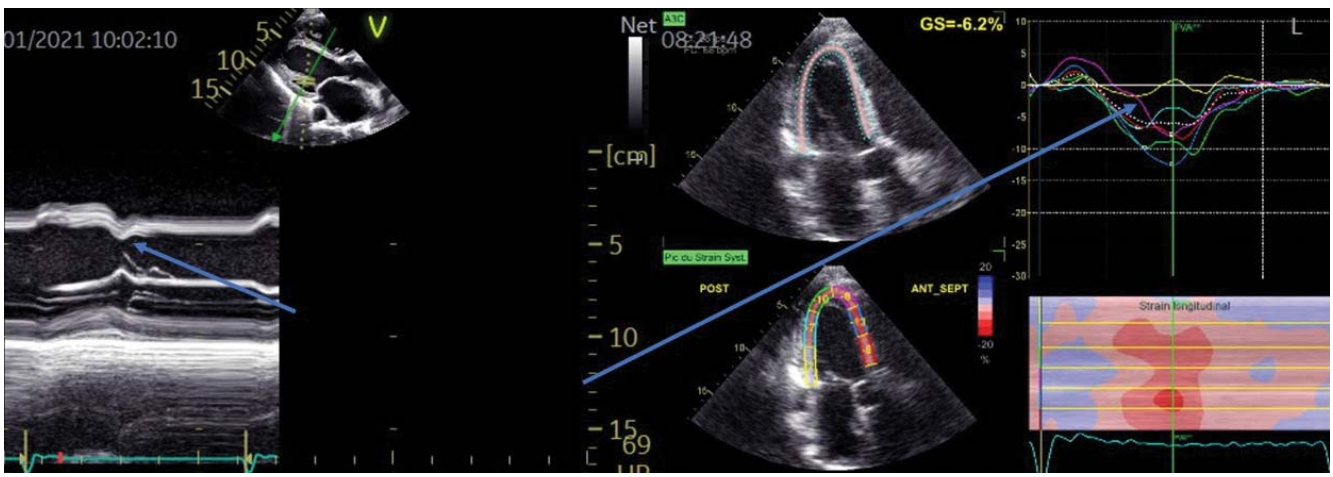

Figure 2. Look at the septal motion (or deformation): the interdependent leads to a paradoxical motion seen in M-mode and with the strain modality (yellow and light blue curves.

is also partially improved. These results demonstrate that RV dilation and LV filling impairment necessarily affects its contractility. The absence of complete recovery suggests a contribution of RV contraction to LV ejection. In clinical model, RV volume overload is conventionally associated with a decrease in LVEF[17]. Lin et al.[29] observed that resection of the post-endocarditis tricuspid valve leading to RV volume overload is associated with a decrease in LVEF. The sequence of the „paradoxical" septum composed of a return to normal (therefore to the right) in systole would be potentially harmful to LV contraction but could explain the maintenance of a longtime conserved RVEF in these patients[20].

Conversely, gradual LV volume loading increases RV developed pressures and detrimental effect appears only for combination of very large LV and RV volume[19]. It was also observed on experimental rabbit model that gradual LV volume reduction was not followed by RV pressure decrease unless, reducing the LV volume to zero leading to only a 5.7% decrease[30]. LV volume overload can occur in left heart valvular insufficiency or post tricuspid shunt, but pulmonary hypertension often associated (increasing RV afterload) does not easily allow to establish a direct accountability for LV volume overload on RV function.

Therefore, LV volume overload on contralateral systolic (or diastolic as described above) function seems to be less important than RV volume overload, possibly explained by the persistence of an anatomical septal position despite a variation of its curvature radius. A better RV baseline compliance could also explain a quite preserved RV feeling despite diastolic pressure rising (Figure 4-5).

Systolic interactions

They can be defined as the influence of ventricular contractility on the contractility of the other one[17].

The first cavo-pulmonary anastomosis, commonly known as the "*Fontan circulation*", was performed in 1971 in a patient with tricuspid atresia with a single ventricle[31]. Patients who benefited from this procedure subsequently demonstrated a correct but sedentary quality of life in the absence of pulmonary hypertension. Although this observation may question the usefulness of the right ventricle, Fontan's circulation

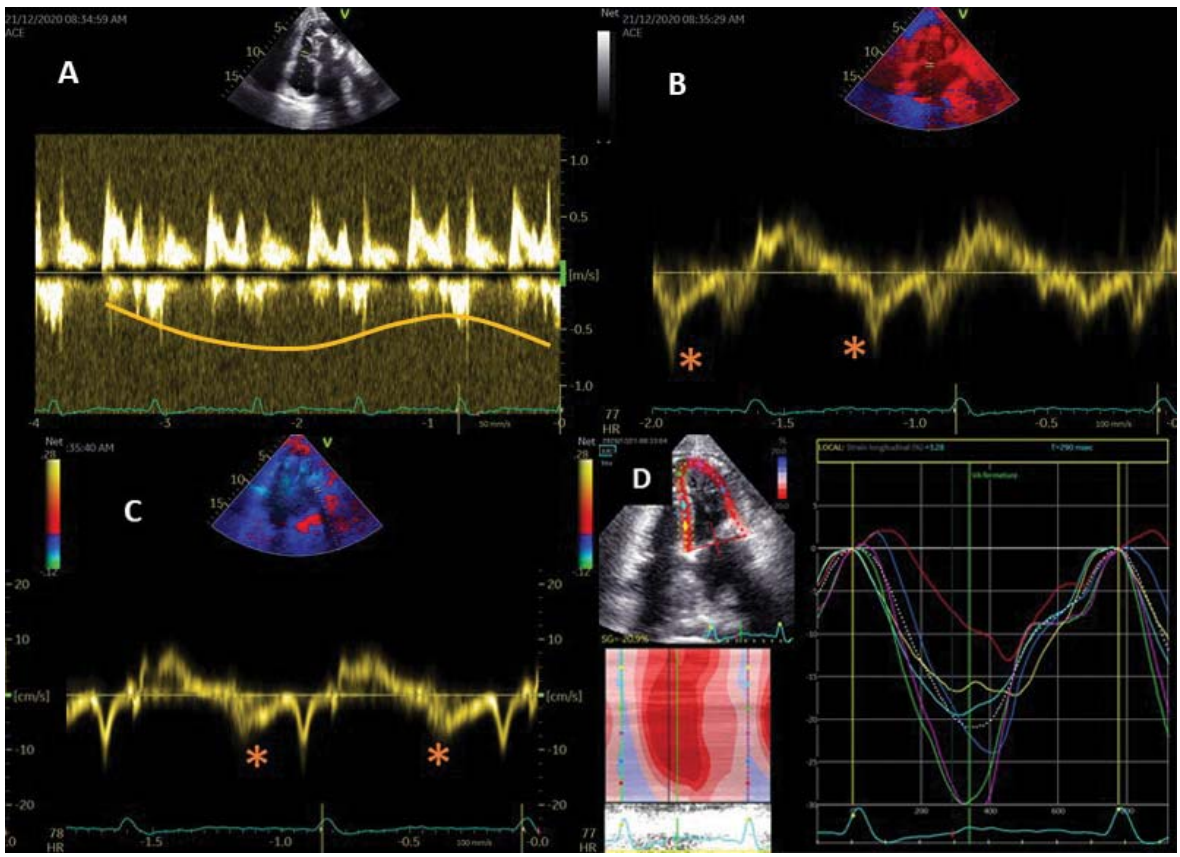

Figure 3. A) amplitude change of the mitral inflow according to the inspiration / expiration >25%. **B-C)** e' septal >e' lateral. **D)** delayed and weaker longitudinal deformation at the base than at the apex.

is only viable in the presence of a pressure gradient ensuring flow to the pulmonary circulation and the left heart. Given the low values of venous pressure, increase in pulmonary arterial pressures, whatever the origin, is associated with functional degradation in these patients[31].

The right ventricle is therefore essential to deal with hemodynamic variations, whether physiological or pathological, but the free wall does not seem to be mainly responsible for RV ejection. In 1943, Starr et al.[32] demonstrate that ablation of the free wall RV does not cause a significant increase in central venous pressure. Replacement of this free wall by a non-contractile prosthesis does not alter the maintenance of a normal RV pressure curve[33]. However, surgical destruction of this free wall does not prevent preservation of exercise capacity which can be attributed to the remaining interventricular septum.

LV contribution to RV systolic function, supported by these latest results, is well established. On intact explanted hearts in which LV and RV was electrically isolated, LV stimulation was followed by the detection of mechanical activity in the RV. RV pressure curve and pulmonary flow are then almost normal in favor of a major contribution of LV to RV ejection[30]. Obo-ler et al.[34] observed a double peaked RV dP/dt with one corresponding in time to LV dP/dt. Experimental model estimated this contribution to 37%[35] whereas Hoffman et al.[33] reported a contribution of 24% of the RV systolic pressure rising to 37% in the face of increased pulmonary afterload. In addition, the interruption of the coronary vascularization of the LV free wall leads to a 9.3% reduction in the pressure generated by the RV[30]. Cutting this LV free wall creates a further 45% decrease. An associated variation of septal movement and curvature was also described. This underlines the role of LV contraction in the generation of RV mechanical work possibly through myocardial fibers shared with interventricular septum and LV free wall. A favorable septal configuration seems to be involved.

RV contribution to LV systolic pressure exists, to a lesser extent, estimated at 4 to 10%[35,36].

Therapeutic impact of systolic interactions was identified in dilated cardiomyopathy, pulmonary hypertension as cardiac surgery and will be described below.

The pericardium does not seem to be as important in systolic interactions as in diastolic interactions, demonstrated by the absence of significant variations before and after pericardiotomy in animal models[37].

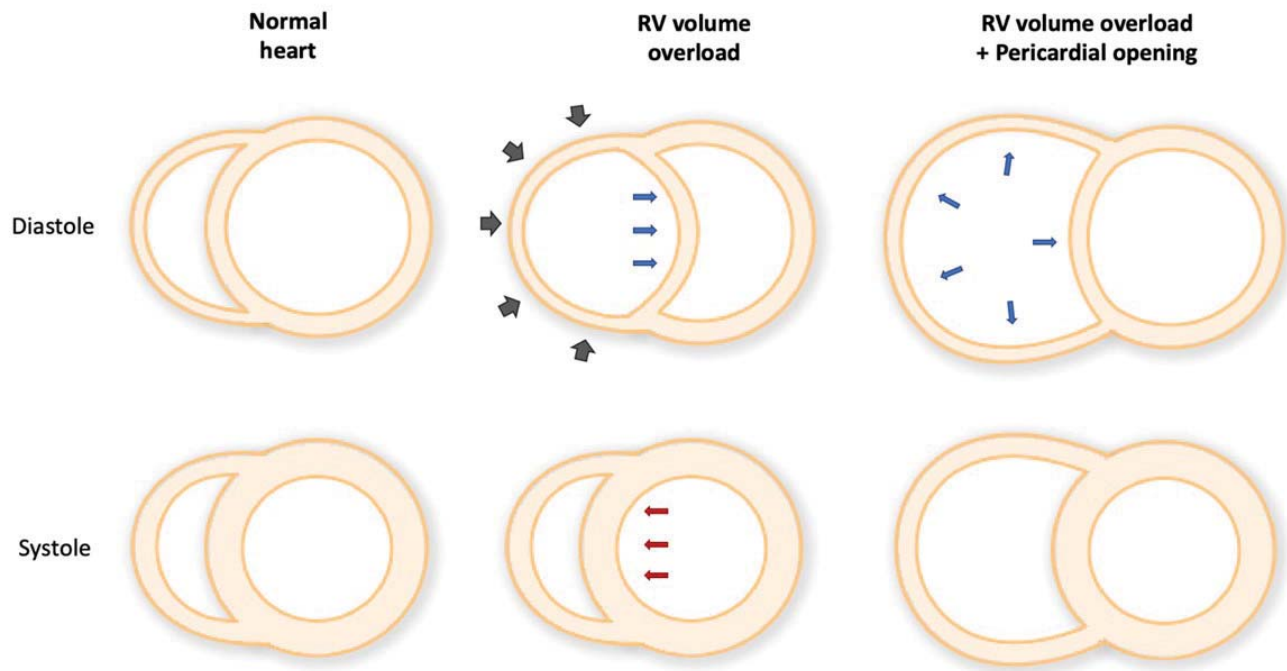

Figure 4. Functional role of complementary geometry in a common pericardium: Example of RV volume overload.

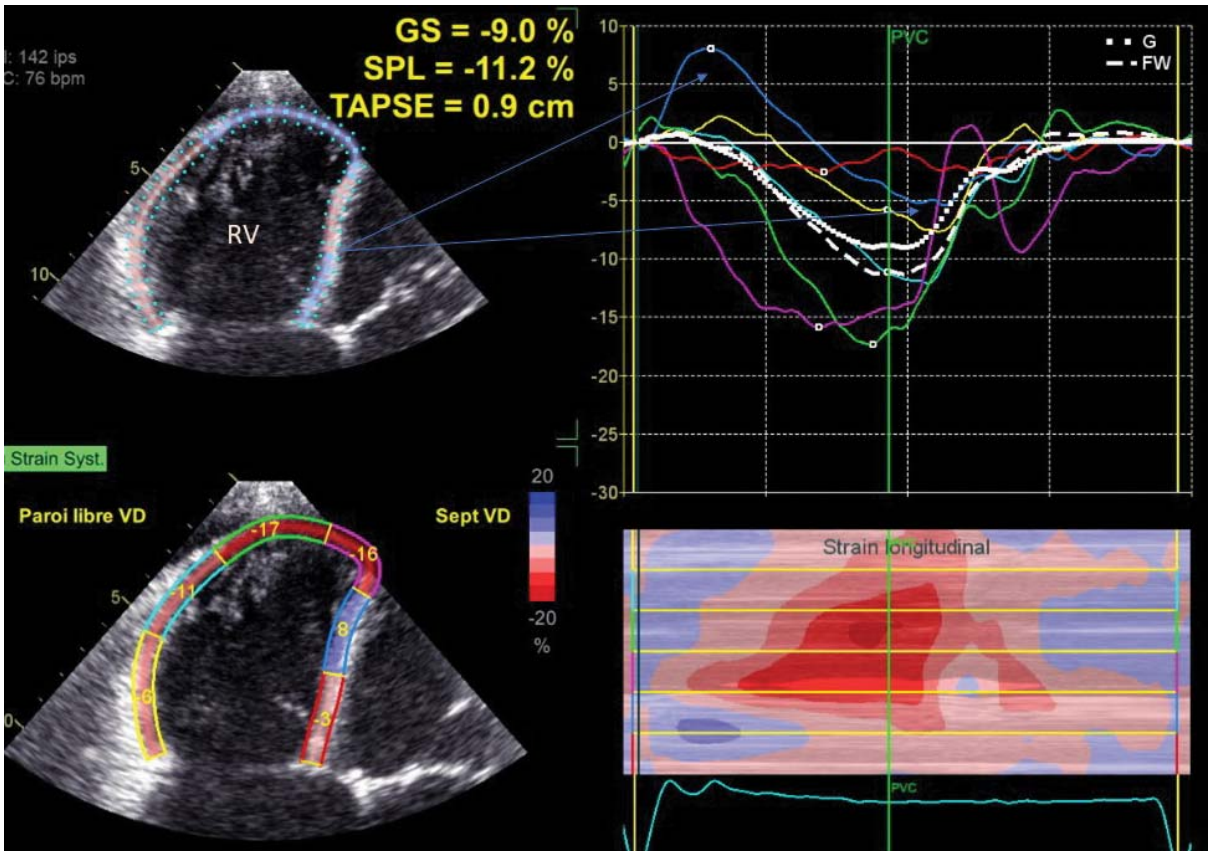

Figure 5. A) As a consequence of the right ventricle dilatation and dysfunction, the interaction with the left ventricle lead to a left ventricular dysfunction. **B)** Delayed deformation of the septum, even elongation in early systole: consequence of the volume overload of the right ventricle in a patient with a severe tricuspid regurgitation.

Intra and inter-ventricular asynchrony

The temporality, beyond the importance, of geometric modifications plays a major role in these interactions.

RV pressure overload is associated with a desynchronization of the RV mechanic responsible for a mechanical interventricular desynchronization. The latter is not linked to an electrical anomaly as can be observed in an authentic left bundle branch block but rather to an inhomogeneous wall constraint[38]. Mauritz et al.[39] confirmed the mechanical nature of this desynchronization, demonstrating complete resynchronization of the LV and RV after pulmonary endarterectomy alone.

RV mechanical dispersion, which shows inhomogeneity of wall contractility, is greater in case of pulmonary hypertension[40]. It can be noticed on the Strain curves a post systolic shortening (after pulmonary valve closure) of the RV free wall, absent for the interventricular septum and the LV, in favor of an intra and interventricular desynchrony. Indeed, the elevation of RV afterload leads to a prolongation of the contraction by lengthening isovolumic contractions and relaxation times even if ejection time is shortened. This results in a prolongation of the leftward septal shift up to LV diastole responsible for a decrease in LV filling and a drop in cardiac output which has been well demonstrated in patients with pulmonary hypertension (PH)[41]. This phenomenon is more pronounced in case of tachycardia, shortening the diastole, and could explain the marked clinical deterioration following the onset of supraventricular arrhythmias in this patients[42].

LEFT CARDIOMYOPATHIES AND VENTRICULAR INTERDEPENDENCE

Heart failure with reduced ejection fraction

Dilated cardiomyopathy (DCM) is characterized by LV dilatation and dysfunction related to a lack of contractility. RV failure occurs frequently, and his prognosis value is major in terms of mortality and hospitalization[43].

The first hypothesis explaining RV dysfunction can be a direct involvement by the causative disease. For this reason, interventricular interactions can be di-

fficult to characterized especially in ischemic DCM because coronary vessels often supply septal wall or biventricular territory. However, causative disease might not always be in the foreground. Bodez et al.[44] demonstrated in cardiac amyloidosis patients that TAPSE impairment is an independent predictor of major cardiovascular events correlated with LVEF, E/e', NTproBNP and PAP, but not with RV late gadolinium enhancement in MRI. This would suggest that PH or ventricular interactions may have greater impact than amyloid deposits in RV failure.

The second hypothesis explaining RV dysfunction in DCM is the LV spherization leading to an alteration of septal fibers helical orientation, turning to a more transversal pattern, and therefore of longitudinal deformation mediated by the interventricular septum. It results in lower mechanical efficiency responsible for RV dysfunction followed by dilation. The appearance of secondary tricuspid regurgitation increasing RV dilation contributes to the vicious circle of heart failure[8,43]. Bosch et al.[45] demonstrated, in the case of HFrEF, that the impairment of right ventricular function is correlated with LVEF decrease but not pulmonary artery pressures (PAP) rising, suggesting ventricular interactions involving the interventricular septum or common myocardial fibers. Other authors also reported a strong correlation between LVEF and RV dysfunction[46].

The third hypothesis is the elevation of RV afterload cause of an increase of LV filling pressures, pulmonary wedge pressure and ultimately pulmonary resistance. The interventricular septum, already weakened by LV geometry alterations, plays a predominant role in adaptation to the afterload. Indeed, the decrease in RV contractile reserve on exertion, in the event of myocardial ischemia of septal location has been demonstrated[47]. RV afterload adaptation, when exhausted, is followed by RV dilation contributing to the vicious circle of heart failure (HF). Atherton et al.[48] demonstrated that drop in venous return with reduction in the RV end diastolic volume in healthy volunteers is accompanied, as expected, by a reduction in the LV end diastolic volume. Same experience, in subjects suffering from heart failure with excessive PAP leads to a paradoxical increase in LV end diastolic volume concomitant with an increase in rightward shift of the septum. Although these results suggest a prior RV dilation and therefore an already exhausted adaptation mechanism, they suggest that the use of nitrates could improve cardiac output in some of these patients[49].

In the absence of RV dysfunction, pulmonary banding of 12 DCM children was associated with reduced LV volumes, increased LVEF and decreased mitral regurgitation[50]. Therefore, mobilization of RV contractile reserve would therefore delay the development of DCM, possibly mediated by shared myocardial fibers or reduction in trans septal pressure gradient. These results, although preliminary, are surprising because they imply that the increase of RV afterload might be beneficial, going against the theory of RV failure trough pulmonary hypertension in DCM. They deserve special consideration and further investigations.

In dyssynchronous LV cardiomyopathies with left bundle branch bloc, whether RV failure is the direct consequence of desynchrony or secondary to LV dysfunction or both remains poorly understood. The place of RV, as a predictor of CRT response, remains controversial associated to conflicting result about the effects of CRT on RV function[51-55]. A meta-analysis gathering 1541 patient, described a significant improvement of several RV parameters following CRT, but statistically dependent of age, QRS duration and especially LVEF[56]. In MADIT-CRT trial, RV function improved significantly and was correlated with change in LVEF and LV end diastolic volume but not in PAP[54]. These results are in accordance with published data by Donal et al.[55] demonstrating early LV reverse remodeling and RV function improvement after CRT without any change in RV dimensions and pulmonary artery pressure. It suggests that the increase in systolic RV function could be not related to changes in RV workload but maybe ventricular interactions. Correlation with RV desynchrony and better results with septal lead than apical lead highlights the importance of septal function. Martens el al.[57] demonstrated the positive chronic effect of CRT on RV-arterial coupling during exercise explained by mitral regurgitation and PAP decrease, but also LV reverse remodeling enhancing ventricular interaction.

Heart failure with preserved ejection fraction

A real impairment of contractile function is acknowledged in HFpEF[58], longtime considered an isolated diastolic function disorder. RV dysfunction is not uncommon in HFpEF, but its prevalence remains heterogeneous depending on the indices used. Bosch et al.[45] described a prevalence, in this population, reaching 42% (TAPSE) and 32% (RV free wall Strain). PAP increase in this population is also common reaching 68% in some meta-analysis[59].

RV dysfunction might be secondary to pulmonary hypertension (PH). Ghio et al.[60] demonstrated in HF patients with preserved or mid-range LVEF that elevation of PAP is independently associated with TAPSE decrease. This association is absent in HFrEF where the importance of ventricular interactions through the septum appears to be more substantial. However, they specified that parameter best correlated with TAPSE, on all HF patients, remains LVEF, which can question the involvement of biventricular interactions or causative disease in the onset of RV failure. A meta-analysis gathering 4835 patients reports both a correlation with PAP rising but also LVEF decrease[59].

RV dysfunction could therefore also be independent of PH. Damy et al.[61] reported TAPSE impairment in 20% of this population but did not find significant correlation between the alteration of TAPSE and PAP. This confirms the results of Morris et al.[62] describing RV global longitudinal Strain (including the septum) significantly altered in HFpEF, as RV longitudinal diastolic strain. These anomalies are independently correlated to the LV global longitudinal strain but not PAP, suggesting a direct link between LV pathological process and RV.

HFpEF is a heterogeneous syndrome gathering several comorbidity associations such as hypertension, diabetes, COPD, obesity, atrial fibrillation, ischemic heart disease, which can each affect RV function[59]. Therefore, it is difficult to assess the direct place of ventricular interdependence. Nevertheless, a significant correlation between the RV fractional area change (FAC) and systolic velocities of septal myocardium has been demosntrated[63]. This underlines the importance of the septal contribution to RV function and implies in clinical practice to track myocardial ischemia, in patients often combining cardiovascular risk factors, likely to impair septal performance and RV adaptation to afterload. In addition, blood pressure optimal control is essential considering a predominant and earlier impairment in septal longitudinal deformation in hypertensive cardiomyopathy[64].

All these studies correlating RV dysfunction to LV function highlight a continuum in LVEF impairment despite the so-called „preserved EF" consistent with SGL decrease. The prognosis impact[59] encourages to consider a careful RV evaluation to better identify patients at risk. Further studies are needed to assess the value of RV failure to predict the onset of „reduced LVEF" which would justify targeting this population in clinical trials conception.

RIGHT CARDIOMYOPATHIES AND VENTRICULAR INTERDEPENDENCE

Pulmonary arterial hypertension.

PH is an interesting example of excessive LV/RV interactions but there analysis remains difficult, however, because they are different depending on the progress of the disease which can be separated into 2 phases[15]. The first one exhibits an adapted afterload compensation with an increase in RV contractility (Anrep law) allowed by myocardial hypertrophy and followed by the onset of fibrosis. Functional status, exercise capacity, and cardiac output remains relatively well preserved. The second one corresponds to a loose of this compensation mechanism characterized by a degradation of the ventricular-arterial coupling, drop in cardiac output followed by RV dilation (Starling law). Remodeling becomes maladaptive, adding a volume constraint to ventricular interaction.

The question of preserved or reduced LVEF in PH remains controversial[17]. RV afterload will exceed LV afterload leading first to an inversion of systolic trans septal gradient. The „paradoxical" septum composed of an inversion of the septal curvature in systole would participate in the LV fractional shortening helping in its contraction[74]. Eccentricity index and RV/LV ratio are, in clinical practice, simple echocardiographic indices quantifying the importance of LV compression by dilated RV and predict mortality[26]. RV increased contractility could also support LV contraction. This explains why, during the first phase, this pathology is classically associated with preserved LVEF[17]. However, LV global longitudinal strain can sometimes be altered in the presence of a normal LVEF[75] and could be more sensitive in clinical practice to detect early LV impairment possible attributable to the development of fibrosis through common myocardial fibers hypertrophy. LVEF seems to be lowered in advanced PH with RV failure[17] and some authors would even suggest the idea of atrophic remodeling regressing after pulmonary endarterectomy[76]. Indeed, the supplementary volume constraint in the second phase of the disease causes additional diastolic septal leftward shift impairing LV feeling. This atrophic remodeling is consistent with an insufficient LV preload given the correlation between myocytic mass and load[77].

The involvement of systolic interactions mediated by common septum and myocardial fibers is demonstrated in rabbit model undergoing increased acute or chronic RV afterload by adjustable pulmonary artery banding[78]. This experiment leads to an expected RV

dysfunction but also a LV dysfunction associated both with histological remodeling characterized by myocyte hypertrophy and increased fibrosis. RV hypertrophy is expected, but LV hypertrophy is surprising. Kitahori et al.[79] have been able to describe that these histological anomalies were particularly localized in the interventricular septum with an extension in the LV free wall. Furthermore, similar electrophysiological changes have been observed between LV and RV in thromboembolic PH in favor of shared myocardial fibers[80]. Increased LV afterload by norepinephrine or mild aortic banding allows an increase in LV and RV load-independent contractility indexes associated with a reduction in myocyte hypertrophy and fibrosis[78,81]. Beyond the positive impact of trans septal gradient reduction on fibrosis signaling, Friedberg et al.[4] mentioned that septal leftward configuration, itself, exposes to an increases septal shear stress especially on RV septal insertion points. This is consistent with MRI studies in PH patients demonstrating predominant septal fibrosis correlated with afterload[82]. This highlights the negative impact of septal configuration changes in PH.

The negative hemodynamic impact of mechanical interventricular desynchrony in PH was described above. It has been shown that RV pacing, shortening atrioventricular (A-V) delay (advancing RV contraction) could significantly reduce diastolic interventricular delay (by 59 ± 19 to 3 ± 22 ms)[83]. Improvement in LV filling and ejection volume is concomitant with an increase in RV contractility reminding the synergic LV contribution to RV ejection.

Acute right ventricular dysfunction

Excessive ventricular interdependence detrimental to LV function has been demonstrated in advanced COPD exacerbation[84], pulmonary embolism[85] or RV infarction[25].

Although management often involves volume expansion in these patients in order to improve LV preload and maintain cardiac output, this could primarily worsen the reversal of the septal curvature and thereby LV function. The major role played by the pericardium in these interactions has led some authors to propose a limited pericardiotomy in massive pulmonary embolism[86]. Systemic vasoconstrictors would seem to have a place by reducing the right-left trans septal gradient when LV function is preserved[4,81] (Figure 6).

VENTRICULAR INTERDEPENDENCE AND CARDIAC SURGERY

Left ventricular assist device

Common myocardial fibers, septal function and complementary geometry in an inextensible pericardial cavity play a key role in the presence of a left ventricular assist device (LVAD) with RV failure. The adjustment of pump flow will immediately be followed by RV function variations. Several hypotheses can explain RV failure. First, excessive pump speed leading to an excessive pump outflow exposes to a risk of suctioning septal wall, cause of LV volume decrease and septal leftward shift[89]. Septal function is therefore jeopardized leading to RV failure which cannot cope with the concomitant increased venous return8. Transesophageal echocardiography, before cardiopulmonary bypass discontinuing, provides the identification of leftward septal shift and, then allows to adjust pump outflow. Secondly, Saleh et al.[12] rise the hypothesis, conversely, that preexistent septal injury and delayed pulmonary resistance increase can lead to RV failure followed by RV dilation, septal leftward shift and LV volume collapsing increasing the risk of LV suction. This highlights the need of an optimal intra operative myocardial protection to avoid septal dysfunction. Third, prior RV dysfunction worsens this phenomenon underlining the controversies about RV function assessment before LVAD implantation. Therefore, pulmonary vasodilators can be used firstly, to delay the need of RV assist devices[12]. Fourth, some authors also hypothesized that RV failure could be induced partly by LVAD apical position, thus altering "LV twisting" required for septal function[6] (Figure 7).

Right ventricular dysfunction after cardiac surgery.

Right ventricular dysfunction after cardiac surgery is still a subject of debate[91]. Despite controversies about compensatory circumferential deformation increase which could maintain RVEF and stroke volume, it seems acknowledged that longitudinal deformation is impaired[92,93,94]. Underlining mechanism are still misunderstood.

The role of pericardiotomy remains longtime emphasized but can be debated because it is not consistent with experimental studies underlining only a diastolic contribution. Singh el al.[95] recently reported RV impairment during cardiac surgery regarding of TAPSE, RV strain and FAC independently of procedural characteristics, reoperative status or pericardiotomy.

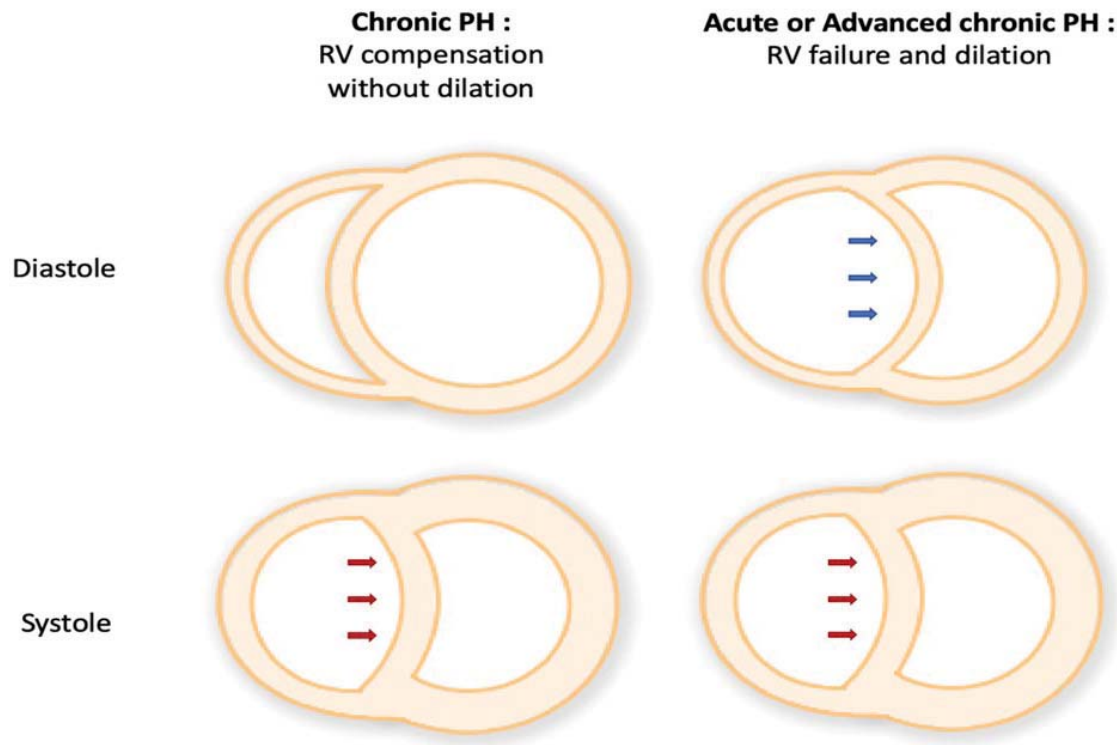

Figure 6. Ventricular interdependence in acute or chronic pulmonary hypertension.

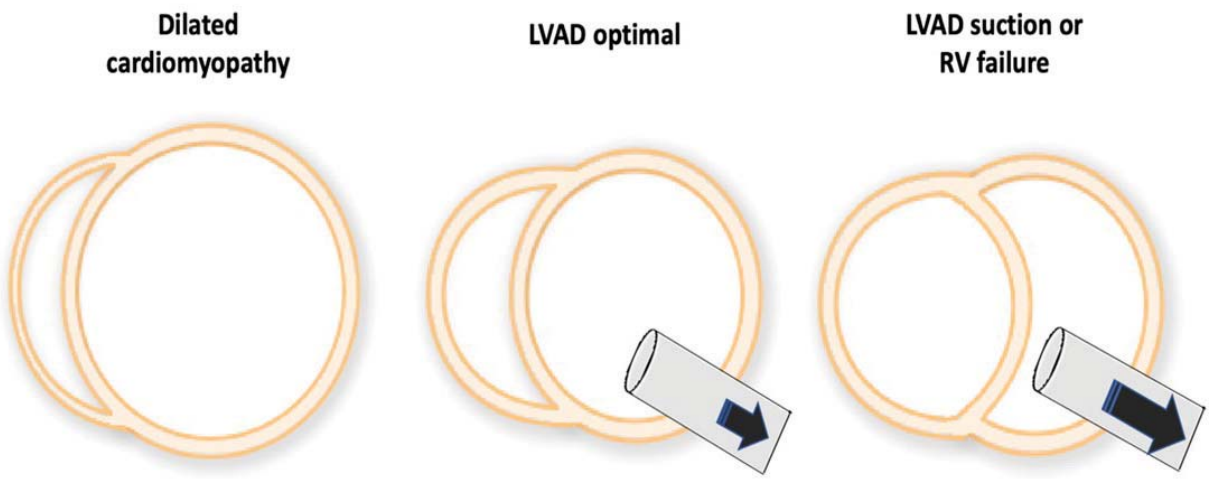

Figure 7. Ventricular interdependence in the presence of LVAD (Adapted from Meineri et al.[90]).

The impairment of postoperative septal function has long been considered commonplace and the prevalence "*paradoxical septum*" can reach 50% in some cohorts[96]. Increased central venous pressure observed after cardiopulmonary bypass discontinuing, despite normal visual free wall contraction, could suggest that RV dysfunction be mediated by the septum according to some authors[8,12]. Buckberg et al.[8] raised the hypothesis of a septal involvement, linked to insufficient intraoperatively myocardial protection,

and assess that integrative cardioplegia could be associated with a better myocardial protection. Bhaya et al.[97] demonstrated that the latter, in comparison to an antegrade cardioplegia, is associated with an elevation of the postoperative septal function considering global circumferential, radial and longitudinal 3D Strain. The correlation with RV dysfunction needs further investigations.

Surgical perspectives

Importance of septal function is taken into account in re-operative surgery of patients with repaired tetralogy of Fallot complicated by pulmonary regurgitation. The association of a ventriculoplasty with pulmonary valve replacement (PVR), comprising reduction of an aneurysmal or akinetic portion of RV free wall followed by a linear suture rebuilding an anatomical septal position, is associated with an improvement in RV performance compared to isolated PVR[98]. Sano et al.[99] reported a small cohort of 5 children with terminal RV failure related to ARVD or Ebstein anomaly. They underwent RV free wall exclusion best preserving myocardial architecture with return of a central septal position. All patients had RV function improvement and were in functional class 1. Some patients even exhibited LVEF improvement. Saleh et al.[12] insists on the importance of septal viability assed by MRI before reduction in RV free wall.

Reduction of the trans septal gradient is used in congenitally corrected transposition of the great arteries with systemic RV failure. Pulmonary artery banding limits the left septal curvature, modifying contralateral tricuspid annulus configuration. Tricuspid regurgitation, usually involved in RV function impairment, is reduced[100].

CONCLUSION

Similarities and differences, between LV and RV, in terms of geometry, anatomy and hemodynamics generate major interactions. Common myocardial fibers, septal configuration and pericardial space play a pivotal role. This must be taken into account in clinical practice, considering major pathophysiological implications, to approach more appropriately biventricular dysfunction whose prognosis value is major. This is another argument in favor of a continuum in HF, beyond LVEF cut off points and resulting diagnosis and therapeutic impact could be major.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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