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MINIREVIEW

Heterogeneity of the Myocardium. Function of the Left and Right Ventricle under Normal and Pathological Conditions

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Summary

A number of important differences can be found between the left ventricle (LV) and right ventricle (RV) of the heart under physiological conditions. In anatomy, the most important is probably the architecture of the atrioventricular valve and its annulus. The LV has a mitral valve (with two cusps) and a firm annulus, while the RV has a tricuspid valve with a greater total area, but relatively small cuspid areas, and an elastic annulus. The difference in the blood supply is important. Owing to high intramural pressure, the coronary flow in the wall of the LV occurs only during the diastole; in the RV it is limited only in the presence of a significant increase in intracavitary pressure. The LV myocardium is functionally "accustomed" to short-term marked changes in the systolic load (in extreme static exercise the arterial pressure rises for a short time to three times the normal value), while the RV is adapted to changes in the diastolic load (marked filling changes associated with deep breathing, for instance).

The difference in the response to a long-term volume load is difficult to evaluate: between a defect of the interatrial septum and aortic insufficiency there are too many differences. A long-term pressure load seems to be tolerated better by the right ventricle: patients with severe pulmonary stenosis and a pressure six times higher than the physiological value have lived 25 years and patients with isolated corrected L-transposition of the great arteries can reach 35 years without any signs of impaired RV function. Adaptation to RV pressure overloading which develops in adulthood is much poorer: in primary pulmonary hypertension the pressure in the RV at the time of diagnosis is only double the normal value, but mean survival is only three years after it has been diagnosed. In almost half the cases tricuspid insufficiency can be diagnosed clinically.

Adaptation to overloading is evidently influenced by three factors: 1) the coronary supply of the ventricle (in patients with RV overloading coronary reserves are less limited), 2) atrioventricular valvular insufficiency (tricuspidal insufficiency develops more readily, both in acute pressure overloading and in hypertrophic ventricular failure – in both cases evidently in association with a relatively rapid increase in ventricular volume), 3) the age at which overloading occurs. The pressure overload in congenital defects is tolerated better than an acquired overload because young RV has a larger number of myocytes.

Teleologically, the heart is a single functional unit (Ferlinz 1982) and it is therefore somewhat surprising to see how many marked differences exist in the anatomy and function of the left and right ventricle under physiological conditions. Under pathological conditions the differences are even more striking and comparison is almost impossible.

In this report we first of all present a brief summing-up of clinically relevant differences between the normal left and right ventricle of the heart. This will be used as a reference for examining the function of the two ventricles in acute injury and in long-term volume and pressure overloading. The most interesting question seems to be whether adaptation to stress under pathological conditions is influenced only by genetically determined factors (e.g. the anatomy of the ventricle and the valve), or whether further factors also play a role.

The size of the ventricles is morphologically comparable (Edwards 1987), but the wall of the left ventricle is 3–4 times thicker than the free wall of the right ventricle. The left ventricle is more ovoid and the right ventricle irregularly conical. The trabeculation of the middle and septal wall of the left ventricle is fine and inconspicuous, while in the right ventricle it is coarse. Whereas the annulus of the mitral valve touches the annulus of the aortic valve, a diagnostically important feature of the right ventricle is the angiographically and echographically determinable discontinuity between the tricuspid and pulmonary valves (Gussenhoven and Becker 1983), known to the anatomist as the crista supraventricularis. Among the anatomical differences, diagrammatic illustrations do not usually show the disproportion between the venous orifices – the left one oval, with a relatively firm annulus and the right one with a substantially (30–50%) greater cross-sectional area, but a less firm (and more expansible), roughly semicircular annulus. The most important, however, is the difference in the architecture of the valves, the right venous orifice is closed during the systole by a complicated apparatus composed of three short cusps, one of which (also identifiable echographically) is inserted directly into the interventricular septum. Their total area is relatively small and it is certainly no coincidence that in postmortem pressure filling of the ventricles with water, the two large cusps of the mitral valve completely prevent reflux from the ventricle into the atrium, while the tricuspid valve does not prevent water to escape from the ventricle into the atrium at a high filling pressure.

The difference in the functional organization of the coronary circulation is enormous (Olsson and Bugni 1986). Under physiological conditions, systolic intramyocardial pressure is close to intraventricular pressure and so the coronary flow in the musculature stops during the systole. Conversely, the intramyocardial pressure in the wall of the right ventricle, in all phases of the cardiac cycle, is significantly lower than in the coronary arteries and the myocardial flow is therefore ensured during the systole as well as the diastole. When determining the ratio of the number of capillaries to cell volume or surface area in different types of overloading of the heart, one should never forget that the effective flow in the same number of capillaries, in otherwise the same situation, may be lower on the left than on the right. For the systolic pressure of the right ventricular myocardium to be limited by a mechanism similar to that in the left ventricle, there would have to be a marked increase of the pressure in the right ventricle (greater than ever occurs under physiological conditions).

The most interesting differences for the physiologist are probably those in the systolic and diastolic function of the myocardium and in the mechanism of contraction regulation. The average systolic pressure (and therefore also the thickness of the wall) is roughly four times greater in the left ventricle than in the right ventricle. During heavy static work of short duration (e.g. in top wrestlers), invasively measured intraarterial pressure may rise to as much as 480/350 mm Hg (MacDougall *et. al.* 1985). Though the ventricular transmural pressure (the intracavitary pressure minus the pressure in the pericardial cavity) is certainly lower, there is no doubt that the left ventricle can cope for a short time with an incredible pressure load. The right ventricle, on the other hand, shows striking capacity for dealing with marked changes in the diastolic load. In one catheterized patient with a minor valvular defect, we measured the output of the right and left ventricle by the dilution method in association with deep breathing (injection of the dye into the right atrium and collection from the pulmonary artery; dye injection into the left atrium and collection from the aorta). Fluctuation of the pressure in both atria was the same (its amplitude was 12 mm Hg). At the peak of deep inspiration, the output of the left ventricle fell by about 10 % (only slightly above the level of error of our method), while the values obtained in maximum expiration rose by 48%. Simple arithmetic shows that, whereas the systolic load of the myocardium of both ventricles is comparable (fourfold intracavitary pressure in the left ventricle is overcome by fourfold greater thickness of the ventricular wall), the changes in transmural expansion per myocardial fibre are several times greater in the right ventricle (the fluctuation of distension pressure in relation to breathing is roughly equal, but the right ventricle has a four times thinner wall than the left ventricle). Under physiological conditions, however, there are marked differences not only in the work regimen, but also in the mechanism regulating contraction. In mild physical exercise, both ventricles are regulated primarily homoeometrically (Braunwald *et al.* 1963, Shepherd 1987); the filling pressures do not change very noticeably and all that really alters is sympathetic-regulated contraction of the myocardium. In the right ventricle, Starling's heterometric regulation principle also plays a role (Robotham *et al.* 1978), i.e. the output of the right ventricle is "brought into tune" so as to correspond exactly to the output of the left ventricle. The left ventricular myocardium is thus evidently "accustomed" to short-term changes in the pressure load (changes in the systemic arterial pressure), whereas the right ventricle is "accustomed" to short-term changes in the volume load (filling changes). This raises the urgent question whether there are any differences in the response of the myocardium of the left and the right ventricle to acute injury or in their adaptability to different types of long-term overloading.

Clinical differences in the function of the two ventricles in acute heart injury are an interesting, but rare problem. In sudden disturbances of the myocardial oxygen supply (e.g. in acute hypoxaemia or carboxyhaemoglobinaemia), the brain always suffers more than the heart and the clinical picture is therefore determined by the brain damage. Nevertheless, there is one disease beriberi (hypovitaminosis B_1) that is characterized by very rapid impairment of the contraction function of the entire myocardium. Those who have come across this syndrome know that it can develop within a few days and sometimes even hours. Clinically, it is characterized by low systemic arterial resistance, a high cardiac output, signs of both left and right ventricular failure and lactacidaemia. If the patient's state is critical, both atrial

pressures are usually high (in our patient they were identical – Gajdošová *et al.* 1988). Dyspnoea is not a dominant sign and at first glance it might therefore seem that right ventricular failure is more serious than left heart failure (systemic congestion is pronounced, but there are no serious signs of pulmonary congestion). A detailed analysis shows, however, that the interpretation of the pathological changes is ambiguous and complicated. Since systemic arterial resistance falls very low, the failing left ventricle counteracts the reduced resistance of the systemic bed. On the other hand, the right ventricle ejects the blood against a raised resistance of the pulmonary bed (raised pressure in the left atrium is accompanied by raised pressure in the pulmonary artery and raised total resistance of the pulmonary bed). In acute beriberi, therefore, left ventricular failure is "treated" very effectively by the disease itself, through reduction of the afterload. The situation is further complicated by acute dilatation of all compartments of the heart, which is limited by the normal – and hence little distensible – pericardium. In the presence of high pulmonary pressures the heart is therefore "constricted", as it were, by the normal pericardium, which thus helps to equilibrate the pressure in the left and right atrium (Janicki and Weber 1986).

It is common knowledge that classic volume overloading of the right ventricle (an atrial septal defect) is tolerated very well. In 1934, when this disease was not yet treated surgically, Roessler put the time of survival at 35 years (Wood 1956) – an age that will no doubt surprise most clinicians now by being too low. The most common form of the left ventricle overloading in clinical practice is isolated aortic valve insufficiency. This defect is also characterized by good long-term tolerance (Rapaport 1975) and up to 50 % of patients with the fully developed syndrome live for over 10 years after it has been diagnosed (Wood 1956). A female patient who recently died in our clinic at the age of 74 had been treated for 12 years as an outpatient for syphilitic aortic insufficiency and at many control examinations over the last eight years she repeatedly had a diastolic pressure of 40 mm Hg or under. The pathophysiology and clinical picture of aortic insufficiency and atrial septal defect are, of course, incomparable. Aortic valve insufficiency usually develops during childhood, but sometimes in adulthood; sometimes (e.g. in patients with Marfan's syndrome) the defect becomes greater with advancing age, while the decrease in diastolic pressure in the ascending aorta reduces the coronary reserve. An atrial septal defect, on the other hand, is a congenital condition, the size of the defect does not increase with advancing age and the coronary reserve is unaffected.

It is therefore far more interesting to compare a chronic pressure overload of the ventricles, if only because, in the case of the right ventricle, it is often said to be tolerated badly. The classic form of left ventricular pressure overloading is isolated aortic stenosis, i.e. narrowing of the aortic valve. In most patients it is a congenital defect, but in early adulthood it is usually haemodynamically less serious. Severe aortic stenosis sometimes develops from an originally bicuspidal, but non-stenotic valve or even from a completely normal valve (Rapaport 1975, Roberts *et al.* 1971). In symptomatic defects the gradient is usually about 70 mm Hg and it is very rare for the systolic load of the ventricle to attain double the physiological value. About 70 % of symptomatic patients suffer from angina pectoris, but in about half of them the coronary artery findings are normal. Mitral insufficiency is not part of the clinical picture of a compensated defect. In patients with a morphologically normal mitral valve it may be – rather exceptionally – a manifestation of an advanced

disturbance of contraction function and of marked dilatation of the ventricle (Schulman *et al.* 1989). In pulmonary stenosis, on the other hand, we frequently encounter overloading which (compared with physiological conditions) attains a significantly higher degree. Wood (1956), for instance, catheterized 30 patients with pulmonary stenosis and a systolic ventricular pressure of over 105 mm Hg, whose mean intraventricular pressure was 165 mm Hg. Although the systolic pressure was thus roughly six times higher than normal, only one third of them suffered from anginose symptoms. In 1949, Green put the survival time at 26 years and it is almost certain that his patients were similar to those catheterized by Wood. Every clinical cardiologist knows the good tolerance of chronic overloading of the right ventricle in patients with Eisenmenger's syndrome (in which the pressure in both ventricles is the same). The mean survival time of these patients is 25 years and Wood himself catheterized four patients aged over 50 years. At repeated out-patient controls, a number of these patients show no clinical echographic or X-ray signs of right ventricular and right atrial hypertrophy and no signs of tricuspidal insufficiency. Some of them actually die as a result of thrombotic complications of the polycythemia accompanying the increasing right-to-left shunt and only shortly before death show signs of right ventricular failure. It is thus certain that pressure overloading can be tolerated very well over a long period by the right ventricle, which is able to overcome a load 4–6 times greater than under normal conditions for several decades. It is evidently important that only an extreme load (in which the systolic pressure in the ventricle is higher than in the aorta) is accompanied by a disturbance of the blood supply of the hypertrophied myocardium. Two factors seem to be of prognostic importance: congenital overloading is tolerated well – as long as the size of the ventricle remains within normal limits.

It is interesting to compare pressure overloading accompanying congenital defects with pressure overload which develops in adulthood (e.g. in primary pulmonary hypertension). Wood (1956) – and in 1981 the national register of primary pulmonary hypertension in the USA (Rich 1988, Rich *et al.* 1987) – show that although the mean pressure values found in the pulmonary artery at catheterization are not actually high (systolic pressure is usually between 60 and 90 mm Hg and the mean pressure between 50 and 60 mm Hg), survival is short, averaging three years from diagnosis. It is remarkable that tricuspidal insufficiency can be demonstrated, by rough clinical methods, in almost half the patients. If overpressure develops suddenly in a previously normal right ventricle (e.g. in the presence of massive pulmonary embolism), it is tolerated exceptionally badly, although the maximum pressure in the pulmonary artery is generally low (usually 50 mm Hg or under) (McDonald *et al.* 1972). Tricuspidal insufficiency likely plays a role, but it has not been analyzed in any detail in this situation. It would thus seem that tricuspidal insufficiency plays a key role in the long-term course of pressure overloading of the right ventricle. The development of insufficiency is no doubt associated with the complicated architecture of the valve. The trigger mechanism is probably acute dilatation of the ventricle in the presence of simultaneous systolic overloading (under physiological conditions diastolic filling of the ventricle changes markedly, but systolic pressure remains within normal limits). The possibility that tricuspidal insufficiency is a kind of physiological safety-valve (King 1837) preventing overfilling of the pulmonary bed in the presence of an acute overload has even been considered. In patients with chronic pressure overload, however, there is

no doubt that it leads to rapid deterioration of haemodynamics, with serious prognostic consequences.

Lastly, it must be asked whether a genetically predisposed right ventricle is able to tolerate the working regimen of the systemic bed, i.e. whether it can act as a ventricle ejecting arterialized blood into the ascending aorta. The answer is provided by an experiment performed by nature, i.e. a patient with corrected L-transposition (Hudson 1965). The very name of this defect ("corrected transposition") indicates the simplified conception of the morphologist that the two ventricles have merely changed places and that everything is functionally in order. The number of documented cases of this serious defect is small, but it seems certain that the contraction function of the highly hypertrophied right ventricle remains normal up to adulthood (Graham *et al.* 1983, Masden and French 1980). On the other hand, the mean survival time is short and a number of patients die between the ages of 30 and 50 from failure of the hypertrophied ventricle, even when no other complicating defects of the abnormal heart can be demonstrated. The genetically predisposed right ventricle can evidently tolerate, for several decades, a load which is actually four times greater than the one it was originally intended to withstand. At first, the thickness of its wall is only slightly different from that of the normally functioning left ventricle, but later the ventricle hypertrophies and fails, for apparently no reason. From the clinical point of view it is therefore clear that systolic overloading appearing in adulthood is tolerated by the right ventricle significantly less well than systolic overloading due to a congenital defect. For an explanation we shall probably have to turn to the number of myocytes in the free wall of the right ventricle, which, in a patient in whom overloading does not occur until adulthood, is significantly smaller than the number in the left ventricle. In congenital defects the number of myocytes in the hypertrophied ventricle is greater (the definitive number is decided in the perinatal period) (Ferrans and Rodriguez 1987). The total number of myocytes in the genetically predisposed right ventricle evidently does not attain its optimum even in congenital defects of the corrected L-transposition type. At the time when the thickness of the ventricular wall is still normal, the myocytes are therefore hypertrophic, while prolonged hypertrophy eventually culminates in a functional disturbance of the fibres and in ventricular failure.

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