REVIEW

Arrhythmogenic mechanisms in left ventricular hypertrophy

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An important mechanism contributing to the high mortality and sudden death in patients with left ventricular hypertrophy (LVH) is ventricular arrhythmia. Part of the risk is associated with the pro-arrhythmic electrophysiological phenotype of the hypertrophied myocardium. The most consistently observed abnormality is prolongation of the action potential duration and refractoriness, which sets the stage for arrhythmias based on early or delayed afterdepolarizations and triggered activity. In addition, non-uniform prolongation of the action potential in LVH may be pro-arrhythmic by leading to increased dispersion of repolarization or refractoriness and favouring re-entry. The occurrence of delayed afterdepolarization-induced triggered activity and other ventricular arrhythmias are also related to the impaired ability to handle intracellular calcium due to changes in the density of ryanodine receptors and the Ca²⁺-ATPase of the sarcoplasmic reticulum. Slowing and fractionation of ventricular conduction, creating the conditions for micro-reentry and arrhythmogenesis, are characteristic of severe LVH, as is the expression of the Iₗ current (which may be a source of increased automaticity).

The pro-arrhythmic potential of LVH is also related to the presence of coexisting ‘extrinsic’ factors. The most important and pro-arrhythmic association of LVH is that with myocardial ischaemia. Other conditions include neuroendocrine factors, ventricular wall stress or electrolyte disturbances. The electrophysiological mechanisms of the interactions between these ‘extrinsic’ factors and LVH have not been fully elucidated. Further research into these mechanisms is required and may have important implications for our understanding of the mechanisms of cardiac arrhythmias in LVH and the appropriate use of antiarrhythmic drug therapy.

Key Words: Sudden death, hypertrophy, arrhythmias, ischaemia.

Introduction

Left ventricular hypertrophy (LVH) has been identified as a powerful independent risk factor not only for total and cardiovascular mortality, but also for sudden cardiac death[1]. An important mechanism contributing to the high mortality and sudden death in patients with LVH is ventricular arrhythmia[2]. The relationship between LVH and the incidence and severity of ventricular arrhythmias is continuous and graded[3–5] and, in fact, may possibly be absent in early (more physiological) or milder LVH[6–8]. The association between LVH and spontaneous or induced ventricular arrhythmias has also been documented in well-controlled experimental studies[9–12]. In addition, there is both clinical and experimental evidence that regression of LVH leads to restoration of normal electrical and structural properties of the myocardium and to a decrease in the frequency and complexity of ventricular arrhythmias[11,13–18]. Part of the risk is associated with the pro-arrhythmic electrophysiological phenotype of the hypertrophied myocardium, but it is also related to the presence of myocardial ischaemia as well as some other factors.

From the clinical point of view, it is important to realize that the correlation between LVH and arrhythmic sudden death is well established not only in hypertensive LVH, but also in LVH associated with...
hypertrophic cardiomyopathy, aortic stenosis or coarctation of the aorta. Also, it appears that a more sensitive predictor of cardiovascular mortality and sudden death may be left ventricular geometry rather than simply left ventricular mass. For example, in hypertensive LVH, mortality and cardiovascular events have been reported to occur most commonly in patients with concentric LVH (defined as increased left ventricular mass index together with increased relative wall thickness), followed by eccentric LVH (increased mass index without an increase in relative wall thickness) and concentric remodelling (increased relative wall thickness)\textsuperscript{19,20}. However, whereas concentric LVH shows a strong association with increased overall cardiovascular mortality, eccentric LVH has been associated more strongly with ventricular arrhythmias\textsuperscript{21}. In another study, isolated septal hypertrophy (an early and frequent structural adaptation in hypertension) increased the frequency and complexity of ventricular ectopics to a degree similar to that of concentric LVH\textsuperscript{22}. Finally, it has to be recognized that the transition of LVH into the phase of haemodynamic decompensation increases the risk of cardiac arrhythmias and sudden death (the latter occurs at a rate six times greater than the general population rate). Firstly, arrhythmogenic electrophysiological changes produced by LVH and fibrosis progress. Secondly, associated risk factors (such as myocardial ischaemia or neuro-endocrine activation) become more advanced. Thirdly, changes in ventricular size lead to changes in intraventricular pressures and wall stresses, which may be arrhythmogenic by exacerbating myocardial ischaemia and producing electrophysiological effects (mechano-electrical feedback). Indeed, the frequency and complexity of ventricular arrhythmias in decompensated LVH are related to ventricular dysfunction, increasing the lower the ejection fraction\textsuperscript{23}. In fact, even in hypertensive patients with non-dilated LVH, a relationship has been found between the frequency and severity of ventricular ectopics and chamber volume, and indices of contractility or pump function\textsuperscript{24}. All the above considerations show that LVH is a complex entity, and the relationship between LVH and arrhythmogenesis is no less complex. The present review will focus on the arrhythmogenic mechanisms of the hypertrophy process itself and its possible interactions with a variety of clinically relevant extrinsic factors. However, the reader has to keep in mind that the interpretation of the available experimental data is limited due to a variety of experimental models and species used, the variation in the duration and degree of hypertrophy, methodological differences, insufficient statistical power to detect physiologically meaningful changes, etc. Therefore, only the most consistent findings regarding the electrophysiological effects of myocardial hypertrophy will be reported. Also, although epidemiological studies strongly suggest important interactions between various extrinsic factors (especially ischaemia) and LVH in arrhythmogenesis, the evidence is often circumstantial and experimental data are sparse.

Therefore, the pathophysiological mechanisms of such interactions proposed by the author, although based on sound data and logical associations, should be seen as an incentive for further research.

**Intrinsic mechanisms of arrhythmias in LVH**

Various intrinsic electrophysiological abnormalities of hypertrophied myocytes have been implicated in the pathogenesis of arrhythmias. These abnormalities have been extensively reviewed\textsuperscript{[24–26]} and will not be discussed in detail in this review. Importantly, it should be recognized that different mechanisms may play a role at different stages of LVH.

**Mechanisms of arrhythmias in mild to moderate LVH**

The most consistently observed abnormality in hypertrophied myocardium is prolongation of the action potential duration and refractoriness, although this effect is not uniform between models. Also, the underlying ionic mechanisms vary between models and species\textsuperscript{[24–26]}. However, as recently discussed by Hart, ‘as a broad generalization it would appear that changes in calcium and Na-Ca exchange currents are important in prolongation of action potential duration in mild hypertrophy, and in severe hypertrophy reductions in potassium currents (I\textsubscript{k1} and I\textsubscript{Na}) are more important’\textsuperscript{[25]}. The prolonged duration of repolarization may provide an arrhythmogenic substrate upon which early or delayed afterdepolarizations may develop\textsuperscript{27}. Indeed, ventricular hypertrophy has been shown to predispose to early afterdepolarizations and early afterdepolarization-induced triggered activity\textsuperscript{28–30}. In addition, prolongation of the action potential duration would be expected to increase intracellular calcium and predispose to delayed afterdepolarizations.

Importantly, prolongation of action potential in LVH is not uniform. For example, several studies have demonstrated that in hypertrophied hearts, epicardial action potentials are more prolonged than those in the endocardium, altering the endo-epicardial gradient seen in normal hearts\textsuperscript{[31–34]}. The basis for this heterogeneous prolongation of the action potential duration may be a differential effect on I\textsubscript{Ca} in rabbit and rat hearts\textsuperscript{32,33}. In guinea-pig hearts, I\textsubscript{Ca} density was reduced by hypertrophy in endocardial myocytes, but increased in epicardial myocytes\textsuperscript{31}. Differential regional effects of myocardial hypertrophy on the action potential duration have also been found between the tip and the base of the papillary muscle\textsuperscript{35}. Non-uniform prolongation of the action potential duration may be pro-arrhythmic by increasing dispersion of repolarization or refractoriness and changing electrical gradients. Indeed, increased dispersion of repolarization and refractoriness within the
left ventricle of hypertrophied hearts has been reported in vivo and associated with increased inducibility of polymorphic ventricular tachycardia or ventricular fibrillation[9–11].

Another important early adaptation to increased haemodynamic burden is the expression of a new myocardial phenotype that is characterized by a non-induction of the genes encoding for the proteins of the sarcoplasmic reticulum[36]. Consequent impairment of the ability to handle intracellular calcium may favour the occurrence of delayed afterdepolarization-induced triggered activity and other ventricular arrhythmias[26,36–39]. Interestingly, the diminished density of the Ca^{2+}-ATPase of the sarcoplasmic reticulum is proportional to the degree of cardiac hypertrophy[40]. Also, ryanodine receptors may be affected by LVH — the effect that is related to the extent of LVH and is heterogeneous across the ventricular wall[41].

Conduction disturbances are an unlikely cause of arrhythmias in the early stages of LVH[42,43]. In fact, the content of connexin43 (the major gap junctional protein of the heart) has been shown to be increased in guinea-pig hearts in the early stages of renovascular hypertension and the pattern of gap junction distribution at this stage is normal[44].

**Mechanisms of arrhythmias in severe LVH**

In contrast to mild LVH, severe LVH is characterized by delayed conduction, resulting from an increase in junctional (but not intracellular) resistance[42,43]. This is consistent with the finding in human hearts that levels of connexin43 are markedly decreased in chronic myocardial hypertrophy[45,46]. In addition, in hypertrophied hearts, the gap junction surface area per unit cell volume has been shown to be reduced and the distribution of gap junctions is altered[45–47]. The consequent slowing of conduction may, therefore, be an important pro-arrhythmic mechanism by facilitating the creation of re-entry circuits[49].

A hallmark of chronic LVH is interstitial fibrosis and collagen deposition[49–51]. The occurrence of abundant collagenous septa would lead to obliteration of side-to-side electrical coupling between small groups of fibres, with consequent disturbances of conduction and electrotic interactions. Resultant non-uniform anisotropy seems to be a prominent feature of hypertrophied myocardium and may be a mechanism for increased dispersion of repolarization and inhomogeneity of intraventricular conduction, creating the conditions for micro-reentry and arrhythmogenesis[52].

Interestingly, it has recently been reported that the I_{K1} current is expressed in LVH and is responsible for diastolic depolarization in hypertrophied hearts[53,54]. A correlation has been found between I_{K1} density and the degree of myocardial hypertrophy: I_{K1} is absent in mild LVH (in which prolongation of the action potential duration is already significant), but is present in severe LVH. Its functional role (for example as a source of increased automaticity) is suggested by the observation that in hypertrophied myocytes, I_{K1} activates at voltages near the physiological diastolic potential and isoproterenol can shift its activation curve towards more positive potentials, facilitating its activation within the physiological range of membrane potentials[53,54].

**Factors modifying a pro-arrhythmic potential of LVH**

**Myocardial ischaemia**

The most important and pro-arrhythmic association of LVH is that with myocardial ischaemia[2] and it will be discussed in more detail. Myocardial ischaemia can result from the presence of atherosclerotic disease of the epicardial coronary arteries, for which hypertension is an independent risk factor[55], or it may occur in the absence of coronary artery disease, as the result of perivascular fibrosis[56] and a reduction in coronary flow reserve[57,58]. Exacerbation of ischaemia-induced arrhythmias by LVH[59–62] suggests that a combination of electrophysiological changes induced by LVH and myocardial ischaemia may be particularly important in creating a pro-arrhythmic milieu. The mechanisms of this interaction have not been fully elucidated. The following possibilities should be considered.

**Electrical dispersion between the ischaemic and the non-ischaemic areas**

Dispersion of repolarization and refractoriness between ischaemic and non-ischaemic areas is an important pro-arrhythmic mechanism during acute ischaemia[63]. One possible electrophysiological mechanism of the interaction between myocardial hypertrophy and ischaemia is accentuation by myocardial hypertrophy of action potential shortening, postrepolarization refractoriness or conduction delay in the ischaemic area[16,42,61,62,64,65]. In these reports, dispersion of repolarization during ischaemia was not directly measured and its existence was inferred indirectly from a greater degree of regional ischaemia-induced action potential shortening observed in hypertrophied hearts. We have recently demonstrated directly that LVH can increase ischaemia-induced dispersion of repolarization in the whole heart[34]. These phenomena can be explained by altered properties of the K_{ATP} channels in hypertrophied myocytes, i.e. an increased open-state probability of the K_{ATP} channels at lowered pH levels and depleted ATP conditions, by a decreased effectiveness of glycolysis to inhibit K_{ATP} channel activity or by a greater reduction in the calcium current during metabolic inhibition[66–69]. These effects could be pro-arrhythmic by increasing the magnitude of electrical dispersion required for re-entry to be initiated and sustained. It is possible that increased dispersion of repolarization could
facilitate the occurrence of spontaneous arrhythmias during ischaemia by increasing injury currents and triggering re-entry.

**Electrical dispersion within the ischaemic area**

Electrical dispersion within the ischaemic area is determined by a number of different factors. These include non-uniform extracellular $K^+$ accumulation, extracellular and intracellular acidification, adrenoceptor stimulation, different intrinsic electrophysiological properties of myocytes within the epicardium and across the ventricular wall, as well as electrical uncoupling and increased anisotropy.[63] It appears that all these mechanisms can be exacerbated by the presence of cardiac hypertrophy.

Firstly, it has been reported that the $Na^+/K^+$ pump activity is decreased in hypertrophied myocardium in normoxic conditions.[70] The $Na^+/K^+$ pump is partially inhibited during acute ischaemia and it is possible that its function would be further impaired by myocardial hypertrophy. This would result in a greater impairment of the restoration of the potassium gradient in hypertrophied than in non-hypertrophied myocardium subjected to acute ischaemia. Indeed, it has been demonstrated that in failing rabbit myocardium (with $67\%$ LVH), extracellular $K^+$ accumulation is non-uniform and increased compared with normal hearts.[71] With regards to ischaemia-induced acidification, it has been reported that intracellular $H^+$ buffering and electrical sensitivity to lowered pH are altered by hypertrophy.[69,72,73]

Secondly, it is not unreasonable to speculate that the processes associated with ischaemia-induced catecholamine release, activation of adrenergic and effector systems[74–78] could be influenced by LVH. For example, the sensitivity of hypertrophied myocardium to the electrophysiological effects of $\alpha$- and $\beta$-adrenoceptor stimulation has been reported to be enhanced.[29,30] Also, activation of protein kinase C has been found to be increased in hypertrophy.[79,80] Finally, hypertrophy enhances the activity of the Na$^+$/H$^+$ exchanger and blockade of Na$^+$/H$^+$ exchange reduces ischaemia–reperfusion injury in hypertrophied rat hearts.[81,82]

Thirdly, as discussed earlier, hypertrophy alone exerts non-uniform effects on the action potential duration in different regions of the heart, thereby increasing dispersion of repolarization. This dispersion may be additive to that produced by myocardial ischaemia, leading to an accentuation of electrical heterogeneity. Hypertrophy-induced changes in the properties of individual ion currents may also alter the sensitivity of adjacent myocytes to the electrophysiological consequences of ischaemia.

Finally, hypertrophy, especially when associated with interstitial fibrosis, leads to gap junction abnormalities and intercellular uncoupling, conducive to disturbances of conduction and electrotic interactions.[83] Since ischaemia results in intercellular electrical uncoupling in its own right, it is possible that this effect will be more pronounced when ischaemia is superimposed on myocardial hypertrophy. Consequently, marked non-uniform anisotropy may lead to an increase in dispersion of repolarization and inhomogeneity of intraventricular conduction, and will favour micro-reentry and arrhythmogenesis.

**Triggering arrhythmias**

Apart from creating the environment for sustaining arrhythmias based on re-entry, the combination of myocardial ischaemia and hypertrophy may be particularly effective in triggering these arrhythmias through non-reentrant mechanisms. In particular, as a result of action potential prolongation, disturbances in intracellular calcium handling (which are further exacerbated by ischaemia) and expression of the $I_a$ current, hypertrophy is likely to facilitate triggered activity and abnormal automaticity. In addition, as discussed earlier, exacerbation by hypertrophy of ischaemia-induced dispersion of repolarization could trigger arrhythmias by increasing injury currents.

**Neuroendocrine factors**

Sympathetic activation and plasma catecholamines may exert direct pro-arrhythmic effects by facilitating reentry, triggered activity, automaticity or increasing excitability.[84] In fact, sympathetic hyperactivity has been implicated in the pathogenesis of sudden cardiac death.[85] Sympathetic tone is increased in hypertensive patients as well as in hypertrophic cardiomyopathy.[86–88] Also, the sensitivity of hypertrophied myocardium to the electrophysiological effects of sympathomimetics is increased.[29,30] Not surprisingly, ventricular arrhythmias in patients with LVH have been found to depend (at least partially) on sympathetic stimulation or a failure to downregulate sympathetic tone during sleep.[89–91]

On the other hand, it has to be recognized that LVH-induced changes in $\alpha$- and $\beta$-adrenoceptors are still controversial (in the level of receptor density, ligand affinity, as well as transmembrane and intracellular signal transduction). An increase, a decrease or no change in adrenoceptors have been reported, depending on the model, species, degree and duration of LVH, coexistence of heart failure, etc.[92–98] Therefore, further research is needed into the pathophysiological mechanisms underlying the altered electrophysiological effects of catecholamines in hypertrophied hearts.

**Ventricular wall stress**

Mechanical stretch may have profound electrophysiological effects and produce arrhythmias.[99] In hypertensive patients ventricular wall stretch is likely to be a physiologically relevant stimulus because of labile blood pressure which may cause fluctuations in ventricular wall stress. In fact, there is evidence in humans that ventricular ectopics can be produced by acute increases
in blood pressure\textsuperscript{100,101}. Such a pro-arrhythmic effect is particularly likely in hearts with LVH, which have been shown to be more susceptible to wall stress-induced arrhythmias than normal hearts\textsuperscript{102–105}. The clinical significance of wall stress-induced arrhythmias in LVH remains to be established.

Disturbances of ion homeostasis

Changes in extracellular ion concentrations exert multiple electrophysiological effects which may be pro-arrhythmic. In particular, hypokalaemia has been shown to increase action potential duration and dispersion of the recovery of excitability, to enhance automaticity, to decrease conduction velocity or to facilitate the occurrence of early and delayed afterdepolarizations\textsuperscript{106,107}. Importantly, hypertensive patients with LVH are likely to have hypokalaemia (and hypomagnesaemia) due to the prolonged administration of thiazide and loop diuretics, which may lead to an increase in the incidence of ventricular arrhythmias\textsuperscript{108–111}. Also in newly presenting hypertensive patients (not on therapy) serum potassium level (apart from age) has been shown to be the most important independent factor contributing to the prevalence of arrhythmias\textsuperscript{112}. In the same study, patients with LVH were more prone to arrhythmias if LVH was accompanied by hypokalaemia. In some larger clinical trials, it has been proposed that increased mortality and sudden cardiac death in hypertensive patients may be associated with hypokalaemia and thiazide treatment\textsuperscript{113–115}. There is evidence that hypokalaemia is synergistic in increasing ventricular ectopy with increased sympathetic activity during exercise\textsuperscript{109}. In addition, it has been suggested to interact synergistically with wall stress in producing arrhythmias in LVH\textsuperscript{102,104,105}.

Conclusions

It is clear from this review that the arrhythmogenic mechanisms in LVH are very complex. On the one hand, they include modification of intrinsic electrical properties of individual myocytes in various regions of the heart and of the extracellular matrix. On the other, they are related to a number of extrinsic pro-arrhythmic factors that interact with the hypertrophied myocardium. Further research into the mechanisms of these interactions is required and may have important implications for our understanding of the mechanisms of cardiac arrhythmias in LVH and the appropriate use of antiarrhythmic drug therapy. For the time being, the only effective therapeutic approach to the management of ventricular arrhythmias in LVH is regression of myocardial hypertrophy and preventing myocardial ischaemia, as well as implantation of cardioverter defibrillators in selected high-risk groups of patients\textsuperscript{82}.

References

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