

Transient ventricular fibrillation and myosin heavy chain isoform profile

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Abstract

The present paper deals with spontaneous ventricular defibrillation in mammals and the possibility to facilitate its occurrence. Clinical and experimental evidence suggest that in the majority of cases, ventricular fibrillation (VF) is permanent, requiring defibrillation by electric shock. However, a growing number of reports show that VF can terminate spontaneously in various mammals, including human beings. The mechanisms involved in spontaneous ventricular defibrillation are controversial. Available reports imply that intracellular Ca^{2+} overload is the key event triggering VF and preventing its reversal. Since the sarcoplasmic reticulum is the main intracellular Ca^{2+} regulating organelle and the activity of the cardiac SR Ca^{2+} ATPase (SERCA 2a) is its prime element of Ca^{2+} sequestration, spontaneous ventricular defibrillation likely requires high level of SERCA 2a activity. We suggest that mammalian hearts with high SERCA 2a activity defibrillate spontaneously and those with low activity only after its enhancement. Since high SERCA 2a activity is co-expressed with the myosin heavy chain (MHC) isoform V1, we assumed that those hearts preferentially expressing V1 MHC are able to defibrillate spontaneously. Hearts with small amounts of V1 MHC and correspondingly lower level of SERCA 2a activity can only defibrillate following administration of compounds that augment SERCA 2a activity and prevent intracellular Ca^{2+} overload.

Keywords: transient ventricular fibrillation • myosin heavy chain • SERCA 2a

Background

Ventricular fibrillation (VF) is one of the most life-threatening cardiac events. It accounts for a large number of human mortalities and, if survived, is a common cause of debility due to accompanying brain damage. Until now, it is widely believed that VF does not cease spontaneously and that electric shock is mandatory to revert it. However, there is

growing evidence to prove that VF can also regress spontaneously to sinus rhythm [1]. The available reports indicate that there are two types of VF, first, sustained VF requiring electrical defibrillation and secondly, transient VF that spontaneously reverts to sinus rhythm without electrical defibrillation.

Many hypotheses have been put forward to explain the mechanisms involved in transient VF considering species [1], age [2, 3], heart muscle mass variations [4]; sympatho/vagal predominance [2]; multiple wavelets hypothesis [5]; cellular refractoriness [6]; wavelength hypothesis [7], etc. In the past it was widely accepted that transient VF is a special

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phenomenon of rodents and small mammals [1]. The findings that it appears also in puppies [3] and human beings opposed this postulation.

Drug induced transformation of sustained into transient VF

There is a common agreement that Ca^{2+} overload is involved in the triggering of sustained VF [8, 9]. Studies carried out on various experimental animals showed that self ventricular defibrillation requires high level of intercellular coupling and synchronization [2,10] that depends on $[Ca^{2+}]_i$ [8]. Elevation of $[Ca^{2+}]_i$ may cause cell to cell uncoupling and inhibition of intercellular communication [11,12]. Deterioration of myocardial intercellular synchronization may increase the number of the fibrillating micro-areas [13]. It allows VF to sustain [9] and decreases the ability of the heart to defibrillate spontaneously [10].

Treatment of adult mammals, normally exhibiting sustained VF, with compounds that decrease $[Ca^{2+}]_i$ caused transformation of sustained VF into transient VF [14–17]. These defibrillating agents are likely to enhance the activity of the Ca^{2+} -ATPase SERCA2, which sequesters Ca^{2+} into the sarcoplasmic reticulum. Following these finding we pointed out [18] that transient VF requires good intercellular coupling and synchronization, low $[Ca^{2+}]_i$ and high level of sarcoplasmic Ca^{2+} ATPase activity (SERCA 2a).

SERCA 2a activity and cardiac myosin heavy chain isoforms

The mammalian myocardium expresses up to three myosin heavy chain (MHC) isoforms that differ in their ATPase activity [19]. The MHC protein that moves fastest during electrophoresis on pyrophosphate gels, is the α - α MHC homodimer (designated V1) and has the highest ATPase activity, whereas the slow moving isoform β - β MHC (or V3) has the lowest ATPase activity. The third isoform V2 is a heterodimer composed of one (and one (monomer (α - α MHC), with intermediate ATPase activity.

In Table 1, we noticed that a correlation existed between the type of VF and the respective expression of the cardiac myosin heavy chain (MHC) isoform profile

[20]. Following this comparison we have suggested that:

Transient VF is a feature of mammals with predominant V1 myocardial MHC, which is known to be associated with a high level of SERCA 2a activity, (young and old rats as well as young guinea pigs, rabbits, cats and puppies). Secondly, transient VF is not observed in mammals that express only the cardiac MHC isoform V3, or associated with a very low level of SERCA 2a activity (newborn rats and guinea pigs and adult dogs and pigs). Thirdly, transient VF can be facilitate in mammals with low V1 myocardial MHC (adult guinea pigs, rabbits, cats and young piglets) by treatment with some 'defibrillating' compounds that increase SERCA 2a activity.

How to promote transient VF

It was found that the occurrence of transient VF can be promoted in mammals (adult guinea pigs, rabbits and cats and piglets) by acute treatment with 'defibrillating' compounds such as tricyclic antidepressants (e.g. dibenzepin) [21] that are thought to decrease intracellular Ca^{2+} overload or with other defibrillating compounds like D-sotalol [16] or Tedisamil [17] that likely enhance SERCA 2a activity and decrease $[Ca^{2+}]_i$.

Although the appearance of transient VF in human beings is still a matter of controversy [22], there are reported cases of drug-induced defibrillation in human beings [23]. The question arises whether the occurrence of transient VF in human beings can also been explained by preferential expression of V1 and associated high level of SERCA 2a activity. Support for this comes from the findings of Gorsa *et al.* [24] that the amount of V1 isomyosin differs among human ventricles with a mean value around 33% of total MHC. More over, in some cases, V1 was found to be even the major cardiac isoform [23].

It is obvious that the mechanisms of VF remain a challenge, for both clinicians and basic science cardiologists, and some other new mechanisms might be (re)considered in the future, e.g. inward rectifying potassium current (IK1) [25], interstitial Cajal-like cells [26] or Brugada syndrome [27].

Conclusions

The available findings imply that Ca^{2+} overload is the key event in the appearance and sustaining of VF.

Table 1 Comparison the MHC isoforms and the type of VF found in various mammals at different ages.

	Age	Heart size	VF*	MHC†
Rat	New born	Very small	SVF	V3
	Young	Small	TVF	V1
	Adult ≤ 2 years	Small	TVF	V1 > V3
Guinea Pig	New born	Very small	SVF	V3
	Young < 4 months	Small	TVF	V1 > V3
	Adult	Small	SVF	V3 > V1
Rabbit	Young < 4 months	Small	TVF	V1 > V3
	Adult	Small	SVF	V3 > V1
Cat	Young < 2 years	Medium	TVF	V1 > V3
	Adult	Medium	SVF	V3 > V1
Dog	Puppy 1–5 weeks	Medium	TVF	V1 > V3
	Young > 6 weeks	Medium	SVF	V3 > V1
	Adult	Large	SVF	V3
Pig	Piglet > 4 < 12 days	Medium	SVF	V3 > V1
	Young > 12 days	Large	SVF	V3
	Adult	Large	SVF	V3

*Type of VF, sustained (SVF) or transient (TVF) as examined in our laboratories.

†MHC data according to Lompre *et al.* [20].

Decreasing intracellular Ca²⁺ is likely to decrease the fibrillating rate and set the stage for spontaneous defibrillation. It follows that appropriate antiarrhythmic/ defibrillating compounds must have the ability to decrease [Ca²⁺]_i, e.g. by augmenting SERCA 2a pump activity stimulating Ca²⁺ sequestration. We noticed that a correlation existed between the type of VF and the respective expression of their SERCA 2a activity.

Our experiments and those of others have shown that spontaneous ventricular defibrillation occurs *in vivo* and *ex vivo* and was not limited to animal experiments. There are reported cases of spontaneous or drug induced ventricular defibrillation in human being that, although rare, cannot be considered anecdotal. These findings can encourage research looking for safe and efficient defibrillating antiarrhythmic drugs

for preventing sudden cardiac death due to VF in human beings unprotected by implantable cardioverter defibrillator (ICD). Such drugs can even decrease the number of electrical shocks and significantly improve the quality of life patients with ICD.

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