Review article

Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review

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A R T I C L E   I N F O

Article history:
Received 26 July 2011
Received in revised form 19 January 2012
Accepted 27 January 2012

Keywords:
Cardiopulmonary Resuscitation
Ventricular fibrillation
Beta-blockade
Beta-blockers
Advanced Life Support

A B S T R A C T

Introduction: Advanced Life Support guidelines recommend the use of epinephrine during Cardiopulmonary Resuscitation (CPR), as to increase coronary blood flow and perfusion pressure through its alpha-adrenergic peripheral vasoconstriction, allowing minimal rises in coronary perfusion pressure to make defibrillation possible. Contrasting to these alpha-adrenergic effects, epinephrine's beta-stimulation may have deleterious effects through an increase in myocardial oxygen consumption and a reduction of subendocardial perfusion, leading to postresuscitation cardiac dysfunction.

Objective: The present paper consists of a systematic review of the literature regarding the use of beta-blockade in cardiac arrest due to ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT).

Methods: Studies were identified through MEDLINE electronic databases research and were included those regarding the use of beta-blockade during CPR.

Results: Beta-blockade has been extensively studied in animal models of CPR. These studies not only suggest that beta-blockade could reduce myocardial oxygen requirements and the number of shocks necessary for defibrillation, but also improve postresuscitation myocardial function, diminish arrhythmia recurrences and prolong survival. A few case reports described successful beta-blockade use in patients, along with two prospective human studies, suggesting that it could be safe and effectively used during cardiac arrest in humans.

Conclusion: Even though the existing literature points toward a beneficial effect of beta-blockade in patients presenting with cardiac arrest due to VF/pulseless VT, high quality human trials are still lacking to answer this question definitely.

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1. Introduction

Ventricular fibrillation (VF) is the rhythm most frequently associated with out-of-hospital cardiac arrest, detected in approximately 40% of cases. VF also represents, along with pulseless ventricular tachycardia (VT), the group of arrhythmias subject to a therapeutic defibrillatory shock.

Mortality rates associated with sudden cardiac arrest are elevated even if basic or Advanced Life Support procedures are correctly applied.1,2 Even though approximately 40% of the victims are effectively resuscitated, the majority of them does not survive for the first 72 h, usually due to a new cardiac arrest or acute heart failure.1,4–6 Thus, the actual survival rate to hospital discharge is low in different centers.1,4–6

The most recent Advanced Life Support (ALS) guidelines for the treatment of cardiac arrest due to VF recommend the administration of either epinephrine or vasopressin as the first drug used after the first or second defibrillatory shocks.1 Even though its use is supported by experimental studies rather than clinical trials, the rational for epinephrine’s administration during Cardiopulmonary Resuscitation (CPR) states that selective peripheral vasoconstriction would favor the perfusion of vital organs such as the heart, kidneys and the brain.7,8

Epinephrine’s selective vasoconstriction occurs due to its actions on α2-adrenergic receptors present in the peripheral vasculature. However, experimental studies suggest that, in spite of the rise in coronary perfusion pressure (CPP) after its use, epinephrine’s actions on α1- and β-adrenergic receptors, found in the heart and coronary vessels, would produce adverse effects, leading to myocardial dysfunction and development of new arrhythmias.9,10

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That could be the reason why a rise in survival rates has not been observed with higher doses of epinephrine.\textsuperscript{11}

During cardiac arrest and CPR, coronary blood flow may be reduced to levels as low as 20–40% resting values.\textsuperscript{12} On the other hand, myocardial oxygen consumption during VF is disproportionately increased to more than 4-fold of resting values.\textsuperscript{13,14} This rise in myocardial demand, along with the reduced blood flow present during CPR, results in a situation of severe global ischemia, to a certain extent responsible for the postresuscitation cardiac dysfunction associated with the high rates of recurrence and mortality amongst those patients successfully resuscitated.

While epinephrine does increase the CPP, elevating the oxygen availability to the myocardium, activation of β-adrenergoreceptors causes an increase in myocardial oxygen consumption through its positive inotropic and chronotropic effects.\textsuperscript{10} This disequilibrium between oxygen supply and demand in the fibrillating heart seems to promote the main deleterious effects of epinephrine in cardiac arrest, leading to severe myocardial dysfunction and development of new reentrant ventricular arrhythmias.\textsuperscript{15,16} Epinephrines β1-stimulation also promotes hyperphosphorylation of Ryandine Receptor 2 (RyR2) in the myocardium, leading to excessive calcium influx from the sarcoplasmic reticulum into the cytoplasm what could contribute to augmented electrical instability, triggering of arrhythmias and sudden cardiac death.\textsuperscript{17,18} Additionally, it seems that epinephrine acts in the pulmonary circulation, producing an increase in right-to-left blood shunt and alveolar dead-space ventilation,\textsuperscript{19} worsening the degree of ischemia as cardiac arrest remains untreated or unresolved.

Different β-blockers have distinct pharmacological properties, and thus may differently affect myocardial function during CPR. For example, while propranolol has no receptor-selectivity and is highly lipophilic, with a half-life of 3–4 h, esmolol is β1-specific and has very low lipophilicity, with the fastest onset of action and the shorter half-life of all beta-blockers (9 min).\textsuperscript{19,20} Atenolol too is β1-specific, but with high lipophilicity and a longer half-life (6–9 h). While carvedilol has a similar half-life, it has high lipophilicity and is the only available β-blocker with associated α1-blockade action.\textsuperscript{19,20}

Since the deleterious effects of epinephrine seem to be associated with its actions in α1- and β-adrenergic receptors, many authors have suggested the use of specific antagonists to selectively block the actions of the catecholamines on these receptors, thus improving epinephrine’s actions in the fibrillating heart. In this context, the present paper intends to review the available literature systematically to summarize the evidences regarding the use of β-blockade in the acute management of cardiac arrest due to VF/pulseless VT.

2. Methods

Studies were identified through electronic search over MEDLINE databases. We looked for clinical trials, case reports, case series and experimental studies published until February 2011. The MESH terms and search strategy used were as follows: [“tachycardia, ventricular” OR “ventricular fibrillation” OR “resuscitation”] AND “adrenergic beta-antagonists”), with 1153 articles found. The following keywords were also used without subject headings: “beta-blocker”, “beta-adrenergic blockade”, “resuscitation”, “Cardiopulmonary Resuscitation” and ‘cardiac arrest’. Article selection was discussed between the authors, with inclusion of the ones which there was a consensus. Only articles dealing with the use of β-adrenergic blockade during CPR or immediately before VF induction were included. Studies that did not evaluate the use of β-blockade in the acute management of cardiac arrest due to VF/pulseless VT were excluded. The references of the most relevant articles included were also screened and submitted to the same selection criteria. Papers which neither the full text nor the abstract were available were not included. These steps followed the PRISMA Statement reporting guidelines for systematic reviews,\textsuperscript{21} as summarized in Fig. 1.

Accordingly, the abstracts from the 94 initially selected papers were then read, with exclusion of 71 for various reasons, such as the use of beta-blockers for secondary prevention of sudden death or β-blocker chronic administration in the post-myocardial infarction setting. Three other papers were excluded after full text evaluation because they were review articles. Another 4 articles were added to the analysis after reference screening of the selected papers.

3. Results

After the database research and application of inclusion and exclusion criteria, 12 animal studies, 10 case reports and 2 human clinical papers were analyzed.

3.1. Animal studies

3.1.1. Propranolol in CPR

Ditchez and colleagues conducted the first few experiments on the effects of beta-blockade during CPR in 1994. At first, dogs were pre-treated with propranolol before induction of VF and CPR,\textsuperscript{22} which resulted in greater CPP even though there was no difference in myocardial performance parameters. However, when propranolol was maintained or introduced after return of spontaneous circulation (ROSC), there were improvements in echocardiographic parameters. This suggested a beneficial effect on myocardial function during CPR, possibly due to a reduction in postresuscitation compensatory sympathetic stimulation.\textsuperscript{22} There was no exogenous epinephrine administration in these experiments.

In another experiment, Ditchez et al. used a canine cardiac arrest model to test epinephrine against phenylephrine (α-adrenergic agonist) and phenylephrine-plus-propranolol, with a compressions-only control group.\textsuperscript{23} The authors did not reproduce a perfect clinical CPR model, with CPR procedures and drug

![Fig. 1. Database research process and article selection.](image-url)
administration at the very moment which VF was diagnosed. Even so, in spite of a higher CPP in all 3 study groups (without statistically significant difference between them) compared to the control group, those values were better sustained over time only in the phenylephrine-plus-propranolol group. Additionally, myocardial ATP concentration was significantly higher and myocardial lactate concentration tended to be lower in the phenylephrine-plus-propranolol group than in the control group, which had surprisingly lower lactate levels than epinephrine-treated dogs, in spite of a slightly greater CPP in this last group.23

Vasopressin was introduced in human CPR protocols as a non-adrenergic alternative vasoconstrictor after studies demonstrating increases in both coronary and cerebral blood flows during CPR while avoiding inotropic and chronotropic beta-adrenergic actions of epinephrine.1,2,4,25 Pellis et al., in 2003, used a porcine model to compare the effects of epinephrine, epinephrine after α1- and β-adrenergic blockade (through pre-arrest prazosin and propranolol), and vasopressin on postresuscitation myocardial function, troponin I release, and neurological outcomes.5 Increases in troponin I concentrations observed in both epinephrine and vasopressin groups after resuscitation contrasted with the animals receiving α1- and β-adrenergic blockade, which maintained near baseline values, suggesting that this treatment, and not vasopressin, was able to diminish the ischemic damage caused by epinephrine.6 That is in accordance to what had already been described by Ditchey.7 However, even though all animals showed a reduced postresuscitation cardiac output, relatively rapid recovery over the ensuing 4 h to near baseline values was observed only in the prazosin-plus-propranolol pre-treated group.8 Epinephrine alone and vasopressin demonstrated an approximately equal incidence of ventricular dysrhythmias, which were minimized after α1- and β-blockade. Nevertheless, no statistically significant differences in 72-h survival were documented.8

Hilwig et al., however, failed to demonstrate any difference on ROSC, survival rates or hemodynamic parameters between epinephrine, propranolol-plus-epinephrine or propranolol-plus-phenylephrine during CPR in his swine model.11

3.1.2. Esmolol in CPR

Both Tang et al. and Theochari et al. demonstrated better resuscitation rates when rats were treated with epinephrine-plus-epinephrine as opposed to placebo or epinephrine-alone.15,26 Not only that, esmolol association led to smaller energy requirements for successful defibrillation, along with shorter resuscitation times and longer post-ROSC survival.15,26 Even though Tang found a significant decrease in myocardial contractility in all study groups after ROSC, the greatest impairment was seen in the epinephrine group and, most importantly, esmolol administration was associated with the best results,15 consistent with previous reports.22,23 Tang’s experiments had also a phenylephrine-alone group, which had resuscitation and survival rates comparable to those of esmolol, but with intermediate myocardial function results.15

Killingsworth et al. tested a swine model of cardiac arrest in which esmolol or placebo were given at the start of CPR procedures, followed by epinephrine administration and defibrillation shocks, since β-blockade could be beneficial from the very beginning in order to counterbalance endogenous catecholamines.27 No significant difference in the CPR time or CPP was observed between the groups, but the esmolol group had a better 4-h post-ROSC survival, along with a lower maximum systolic arterial pressure. There were no differences in systolic or diastolic function between pre-arrest and 4-h post CPR in esmolol treated animals, suggesting it did not have a long-term effect on postresuscitation cardiac function in these animals,27 possibly due to its short half-life.

Most recently, Jingjun et al. demonstrated that, even though there were no differences in ROSC or CPR time between pigs treated with esmolol or placebo during CPR with epinephrine, the esmolol group needed less shocks to revert VF, had no VF recurrences, and presented a significantly higher survival rate than the placebo group.28 Esmolol blunted transiently and reversibly the hemodynamic response to epinephrine, including heart rate and mean blood pressure, without affecting negatively the percentage of survivors and post-resuscitation survival.28 Jingjun also demonstrated that esmolol proved effective in suppressing hyperphosphorylation of the RyR2,28 thus inhibiting an excessive calcium influx that could otherwise promote electrical instability and trigger arrhythmias.7,18 Their analysis of action potential restitution curves showed accordingly that esmolol seemed to block epinephrine’s effect on the electrical restitution, thus making the myocardium electrically stable.28

Cammarata et al. injected placebo or esmolol alone during CPR after VF in rats, this time with no epinephrine.29 No difference in CPP was observed between groups. However, all esmolol-treated animals were successfully defibrillated whereas only half of control animals were resuscitated, with significantly prolonged postresuscitation survival in esmolol-treated animals. Left ventricle function tests demonstrated better postresuscitation contractile function also with better myocardial lusitropic function in the treatment group.29

Since the main benefits of beta-blockade during CPR seemed to come from its effects on myocardial oxygen supply and consumption, Strohmenger et al. assessed whether the use of the bradycardic agent zatebradine would have a similar or better outcome than esmolol in a swine model of CPR.30 Both drugs were tested in combination with epinephrine against a placebo plus-epinephrine group. Accordingly, zatebradine resulted in a significant reduction in both heart rate and number of premature ventricular contractions after ROSC, without compromising myocardial perfusion and contractility.28 Although esmolol was associated with worse myocardial performance in most of the parameters studied when compared to both zatebradine and placebo, ROSC rates as well as the number of shocks and organ perfusion did not differ between groups.30

3.1.3. Other beta-blockers in CPR

Bassiaiou et al. demonstrated, in a swine model, that atenolol may also be used as an adrenergic-blockage option when used before epinephrine administration and electrical defibrillation attempts.31 Their results showed greater successful resuscitation rates, along with greater systolic and diastolic pressures and a reduction in ventricular ectopy with atenolol.31

Since some studies had suggested epinephrine’s α1 actions may also be detrimental, possibly causing coronary vasoconstriction in spite of a greater CPP, Huang et al. tested carvedilol, a nonselective-β and α1-selective adrenergic receptor-blocking agent, to turn epinephrine into a selective specific α2-agonist.32 They tested carvedilol pretreatment with or without CPR administration of epinephrine. Carvedilol-plus-epinephrine treatment reduced early postresuscitation ventricular ectopy and minimized increases in arterial blood lactate at 5 min after ROSC, with longer post-resuscitation survival and less neurologic deficit.32 Even though equivalent increases in CPP were observed after epinephrine injection independently of carvedilol pretreatment, left ventricular diastolic pressures were decreased in the carvedilol-plus-epinephrine group.32

Animal studies are summarized in Table 1.
<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Start of CP</th>
<th>Drug admin.</th>
<th>Groups</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditche et al.22</td>
<td>Random-source dogs</td>
<td>At the onset</td>
<td>Pre-treatment</td>
<td>(a) Placebo (b) Propranolol (2 mg/kg)</td>
<td>ROSC: 6/11, 9/11</td>
<td>No difference in myocardial performance parameters Epinephrine (0.015 mg/kg) was given to both groups</td>
</tr>
<tr>
<td>Ditche et al.23</td>
<td>Random-source dogs</td>
<td>At the onset</td>
<td>0 min and 5 min</td>
<td>(a) Compressions only (b) Epinephrine (0.2 mg/kg) (c) Phenylephrine (0.4 mg/kg) (d) Phenylephrine plus propranolol (1 mg/kg)</td>
<td>Group (d) had higher ATP levels, lower lactate levels, and sustained greater CPP for a longer period</td>
<td>No defibrillation was attempted</td>
</tr>
<tr>
<td>Tang et al.19</td>
<td>Sprague-Dawley rats</td>
<td>Group 1: 4 min after VF</td>
<td>Group 1: 8 min after VF</td>
<td>(a) Placebo (b) Epinephrine (30 μg/kg) (c) Phenylephrine (300 μg/kg) (d) Epinephrine plus esmolol (30 μg + 300 μg/kg)</td>
<td>ROSC – survival (h) Number of shocks Group 1: 4/5 – 12 ± 11 – 12 ± 9 Group 2: 3/5 – 2.5 ± 1 – 16 ± 10</td>
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<tr>
<td>Theochari et al.26</td>
<td>Pigs</td>
<td>5 min after VF</td>
<td>Group 1: 8 min after VF</td>
<td>(a) Placebo (b) Esmolol (0.4 mg/kg) (c) Esmolol (30 μg + 300 μg/kg)</td>
<td>ROSC – CPR duration</td>
<td>Esmolol increased CPP from the sixth minute on during CPR</td>
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<tr>
<td>Strohmenger et al.30</td>
<td>Domestic pigs</td>
<td>4 min after VF</td>
<td>7 min after VF</td>
<td>(a) Placebo (b) Zatebradine (0.5 mg/kg) (c) Esmolol (1 mg/kg)</td>
<td>ROSC – Zatebradine</td>
<td>All animals received epinephrine</td>
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</table>

*Table 1*  
Animal studies regarding beta-blockade during cardiac arrest due to VF.4
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Start of CPR</th>
<th>Drug admin.</th>
<th>Groups</th>
<th>Results</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Hilwig et al.(^{11})</td>
<td>Domestic swine</td>
<td>1 min after VF</td>
<td>Epineph. = 8, 11, 14 min</td>
<td>(a) Epinephrine (0.02 mg/kg)</td>
<td>10/12 – 9/12</td>
<td>100% oxygen and other ACLS techniques only after 7 min of VF</td>
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<td>(b) Epinephrine (0.02 mg/kg) + propranolol (0.04 mg/kg)</td>
<td>10/12 – 10/12</td>
<td>high dose epinephrine group did not correlate with better</td>
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<td></td>
<td>(c) Ep. “high dose”(0.2 mg/kg) + propranolol (0.04 mg/kg)</td>
<td>5/10 – 4/10</td>
<td>post-CPR outcomes</td>
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<td>(d) Phenylephrine (0.4 mg/kg) + propranolol (0.04 mg/kg)</td>
<td>9/10 – 9/10</td>
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<tr>
<td>Pellis et al.(^{8})</td>
<td>Yorkshire-cross domestic pigs</td>
<td>7 min after VF</td>
<td>Epinephrine or Vasopressin = 9 min after VF</td>
<td>(a) Epinephrine (20 (\mu)g/kg)</td>
<td>4/5 – 6.6 ± 1.8 – 41 ± 15 (\mu)g/ml</td>
<td>OBS: Group (b) had significantly lower number of ventricular</td>
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<td>(b) Pretreatment propranolol + prazosin (1 mg/kg + 0.5 (\mu)g/kg) + Epinephrine (0.4 U/kg)</td>
<td>5/5 – 1.6 ± 0.9 – 3 ± 2 (\mu)g/ml</td>
<td>ectopies, and VF recurrences. No differences in 72-h survival</td>
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<td></td>
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<td></td>
<td>5/5 – 1.6 ± 0.9 – 36 ± 14 (\mu)g/ml</td>
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<tr>
<td>Killingsworth et al.(^{27})</td>
<td>Mixed-breed pigs</td>
<td>8 min after VF</td>
<td>8 min after VF</td>
<td>(a) Placebo</td>
<td>3/8 – 3/8 – 10 ± 8</td>
<td>OBS: Epinephrine (0.01 mg/kg) administered only after ROSC if</td>
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<td></td>
<td>(b) Esmolol (0.1 mg/kg)</td>
<td>7/8 – 7/8 – 5 ± 4</td>
<td>systolic BP &lt; 50 mmHg. Authors also realized other important in vitro experiments</td>
</tr>
</tbody>
</table>
Cammarata et al.\textsuperscript{29} Sprague-Dawley rats 6 min after VF 8 min after VF (a) Placebo (b) Esmolol (300 μg/kg) ROSC – Survival (h) – Number of shocks 5/9 – 20 ± 11 – 14 ± 6 9/9 – 50 ± 25 – 7 ± 4 OBS: No exogenous epinephrine administration in either group. Better postresuscitation contractile andlusinotropic in group (b)

Huang\textsuperscript{32} Sprague-Dawley rats 8 min after VF Carvedilol (50 μg/kg) = 15 min before VF Epinephrine (30 μg/kg) = 10 min after VF (a) Placebo + Placebo (b) Placebo + Epinephrine (c) Carvedilol + Epinephrine (d) Carvedilol + Placebo Group (c) treatment reduced ventricular ectopy and minimized increases in arterial blood lactate at 5 min after ROSC, with longer post-resuscitation survival and less neurological deficit Equivalent increases in coronary perfusion pressure were observed after the injection of epinephrine independently of carvedilol pretreatment

Bassiaikou et al.\textsuperscript{31} Landrace/Large White piglets 8 min after VF 8 min after VF (a) Epinephrine (0.02 mg/kg) (b) Atenolol (0.05 mg/kg) + Epinephrine (0.02 mg/kg) ROSC – PVC\textsuperscript{3} – VF recurrence 4/10 – 45 ± 30 – 18 ± 6 9/10 – 80 ± 27 – 2 ± 1 OBS: HR in group (a) > group (b) (in the first 10 min postresuscitation) Lower HR, BP, and CPP were seen within 30 min post-resuscitation in group (b) Also realized other important in vitro experiments

Jingjun et al.\textsuperscript{28} Yorkshire-cross domestic pigs 4 min after VF 8 min after VF (a) Placebo (b) Esmolol (0.5 mg/kg) ROSC – Number of shocks – VF recurrence 18/20 – 3.5 ± 2.5 – 5/18 17/20 – 1.5 ± 0.5 – 0/17 OBS: All animals received epinephrine at 4 and 5 min after VF Animals were randomized to drug treatments only after failure of the first defibrillation attempt (at 6 min) Lower HR, BP, and CPP were seen within 30 min post-resuscitation in group (b) Also realized other important in vitro experiments

\textsuperscript{a} Modified from Bourque et al.\textsuperscript{33}
3.2. Human studies

Little evidence exists regarding the use of β-blockade in humans. Most of the literature consists of case reports and case series; in fact, only two clinical prospective human studies tested the effects of β-blockade against regular therapy in patients presenting with electrical storm (ES).34,35 Many of the case reports were published in the 1960s, with the majority of patients developing VF after myocardial infarction.36–45 In general, β-blockade was attempted as a last resource to revert refractory VF resistant to defibrillatory shocks and usual pharmacologic therapy. It is noteworthy that resuscitation guidelines were quite different in that period with propranolol as a second choice and procainamide as the first choice drug. In most cases, β-blockade, through propranolol or esmolol, successfully reverted VF, with the majority of patients surviving to hospital discharge.36–45 Over time, there was a tendency to lower β-blocker doses, since high doses correlated with serious adverse effects (such as hypotension and atrioventricular block). Table 2 summarizes these case reports.

The first comparative prospective study analyzed the efficacy of β-blockade in reverting shock-refractory VF. Nademanee et al. studied 49 patients who developed ES, defined as over 20 VF/VT episodes per day or over 4VF/VT episodes per hour, after a recent history of myocardial infarction (within 72 h to 3 months before VF onset).34 Subjects were divided into 2 groups; the first (n = 22) received conventional ALS-guided therapy throughout treatment approaches, whereas the other group (n = 27) received sympathetic blockade treatment within 1 h after discontinuation of all antidysrhythmic medications initiated during CPR. Of these patients, 6 were treated with Left Stellate Ganglion Blockade, 7 with esmolol and 14 with propranolol, determined by physician preference and predilection for each strategy.34

After sympathetic blockade therapy was initiated, the mean number of VF episodes declined from over 20 to 2.6 ± 1.7 per day (P < 0.01). In contrast, 91% of patients in the other group continued to have VF episodes.34 The short-term outcome was much better in patients treated with sympathetic blockade: 82% vs. 22% 1-week survival rate between groups.34 In 1 year follow-up, two out of the four ALS–group patients who had survived the first week developed recurrent VF and died. At the end of the first year, 18/27 patients in the β-blockade group were still alive, compared with 1/22 in the other group.34

The other human clinical trial available, conducted by Miwa et al. in 2010, evaluated the effect of landiolol, a fast-acting β1-selective blocker, on refractory ES.35 Forty-two consecutive patients who presented with ES refractory to regular ALS therapy were submitted to the study protocol which consisted of intravenous landiolol administration in increasing doses (starting at 2.5 μg/kg/min; maximum dose was 80 μg/kg/min) up to the minimum dose required for arrhythmia control.35 The study protocol was ineffective in 9 patients (21%), who did not receive any other treatment beyond β-blockade and died of arrhythmia. From the 33 patients who responded to landiolol, 21 received carvedilol and 12 were started on bisoprolol, with oral β-blocker administration immediately after patient stabilization. Even so, 8 of these 33 patients (19%) died afterwards from causes such as severe multiple organ failure or infection. Of the 25 survivors (60% of the initial 42 patients), 24 could walk by themselves at discharge.35

Group analysis demonstrated a few important differences. The age was significantly lower in responders to landiolol compared with non-responders (62 ± 16 years vs. 74 ± 12 years), also with lower APACHE II scores in the first group (17 ± 9 vs. 26 ± 12).35 This same pattern was seen between survivors and non-survivors (age = 60 ± 16 years vs. 72 ± 11 years; p = 0.01; APACHE II = 15 ± 9 vs. 24 ± 11; p = 0.01). Ischemic heart disease was present in 25 (60%) of patients, but the group of survivors had more Killip I (16 vs. 4) and fewer Killip IV (8 vs. 11) patients compared to the non-survivors group (p = 0.02).35

Table 3 summarizes these 2 human prospective studies.

4. Discussion

Cardiac arrest due to VF is a situation of extreme stress in which the interruption of blood flow combine with an increase of as much as 4-fold baseline oxygen consumption to produce profound myocardial ischemia.1,13,14 ALS guidelines recommend the use of epinephrine as the vasoactive drug of choice during CPR, in an attempt to increase coronary blood flow and CPR during resuscitation.1 The actions of epinephrine are associated to its α-adrenergic peripheral vasoconstriction and seem very important in order to obtain minimum levels of CPP necessary for successful defibrillation.46,47 In contrast, β-stimulation may have deleterious effects through an increase in oxygen consumption of the fibrillating myocardium, reduction of subendocardial perfusion (due to its inotropic action), and worsening of the intrapulmonary shunting caused by hypoxic pulmonary vasoconstriction.9,10 All this contribute to cardiac ischemia, in spite of the higher CPP, leading to poorer postresuscitation myocardial function.

Increasing evidence indicates that, despite exogenous epinephrine administration, CPR consists of an extremely stressful situation in which high levels of endogenous catecholamines should be expected, independently of exogenous administration of epinephrine.48,49 Killingsworth et al. demonstrated that concentration of catecholamines in the cardiac interstitial fluid mounted to levels as high as 170 times baseline (pre-arrest) levels, with a significant increase also after defibrillation47 (indicating that CPR procedures may have themselves a part in post-resuscitation myocardial dysfunction). Since there is no blood flow during VF, it is likely that local release of catecholamines occur, possibly through sympathetic cardiac nerves.27 These results are also in accordance with other studies that show extremely high levels of catecholamines even before CPR procedures and exogenous epinephrine administration.48,49

Considering all the ethical aspects involving research in the field of CPR in humans, most of the evidence available comes from animal studies. Use of β-blockade has been extensively studied in animal models of cardiac arrest. Swine, canine and murine models have shown that β-blockade can reduce the number of shocks necessary for defibrillation,9 diminish cardiac ischemia by lowering myocardial oxygen requirements,15,22 improve postresuscitation myocardial function,23,26 reduce recurrences of arrhythmias28 and prolong survival.27 Analysis of action potential restitution curves and RyR2 phosphorylation by Jingjung et al. showed that esmolol seemed to suppress epinephrine’s mediated hyperphosphorylation of RyR2, inhibiting excessive myocardial calcium influx, blocking epinephrine’s effect on the electrical restitution and thus making the myocardium electrically stable.28

Propranolol has been tested in cardiac arrest since 1994, when Ditchey et al. demonstrated that it may have facilitated peripheral vasoconstriction by allowing unopposed α-adrenergic stimulation, especially since the use of the α-agonist phentylephrine alone did not have the same effect.23 Their data also suggested that while epinephrine promotes greater CPP, it may have an adverse effect on cardiac ischemic injury through its beta-adrenergic actions, possibly increasing myocardial oxygen requirements beyond this rise in CPP. Both Ditchey23 and Pells8 successfully reduced myocardial damage attributed to epinephrine with propranolol treatment, demonstrated by lower lactate levels.8,23 Moreover, in this later study, propranolol beta-blockade (associated with prazosin alpha-blockade), and not vasopressin, promoted faster recovery of inotropic function to near pre-arrest values, even
Table 2
Case reports.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population size</th>
<th>Age median</th>
<th>β-Blocker</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besterman²⁶,²⁹</td>
<td>n = 1</td>
<td>60</td>
<td>Propranolol (60 mg)</td>
<td>The Adams–Stokes attacks diminished in frequency and finally ceased</td>
<td>The first 10 mg were given IV</td>
</tr>
<tr>
<td>Sloman²⁷</td>
<td>n = 3</td>
<td>44</td>
<td>Propranolol (15–22 mg)</td>
<td>VF ceased in all cases, but 2 patients died:</td>
<td>Except for the patient with heart failure, the other two had a recent myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– One developed circulatory failure because VF episodes</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>occurred for 30 h before propranolol administration and consequent VF termination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– The other evolved with hypoxemia and asystole after VF termination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>propranolol; she had heart failure</td>
<td></td>
</tr>
<tr>
<td>Iwatsuki²⁸</td>
<td>n = 1</td>
<td>22</td>
<td>Propranolol (4 mg)</td>
<td>Propranolol 4 mg given intravenously completely suppressed the recurrent attacks after other drugs had failed.</td>
<td>The patient was suspected to have a certain localized myocarditis that triggered the VF episodes.</td>
</tr>
<tr>
<td>Ikram²⁹</td>
<td>n = 4</td>
<td>58</td>
<td>Propranolol (1 mg)</td>
<td>Successful control of persistent ventricular fibrillation in all 4 patients.</td>
<td>Except for a 73 years old lady, with massive IV MI, all patients survived to hospital discharge</td>
</tr>
<tr>
<td>Rothfeld⁴⁰</td>
<td>n = 1</td>
<td>64</td>
<td>Propranolol (5 mg)</td>
<td>The patient survived to discharged; He had had a MI that evolved with recurrent VF Propranolol reverted to sinus rhythm after large doses of lidocaine and procainamide had failed.</td>
<td>Propranolol was administered immediately after sinus rhythm was restored by a direct current electric shock</td>
</tr>
<tr>
<td>Mason⁴¹</td>
<td>n = 3</td>
<td>59</td>
<td>Propranolol (2–5 mg)</td>
<td>Successful termination of VF and survival to hospital discharge 2 patients had a MI preceding the VF episodes</td>
<td>Propranolol was used after lidocaine and procainamide had failed to revert VF</td>
</tr>
<tr>
<td>Van Dantzig⁴²</td>
<td>n = 1</td>
<td>23</td>
<td>Esmolol (500 μg/kg)</td>
<td>Complex ectopic ventricular activity was completely suppressed together with a reduction in heart rate and a significant decrease of ST segment elevation. The patient survived to discharge</td>
<td>The patient had a acute transmural anteroseptal ischemia after a cardiac surgery</td>
</tr>
<tr>
<td>Schmidt⁴³</td>
<td>n = 1</td>
<td>18</td>
<td>Metoprolol (5 mg)</td>
<td>The patient responded almost immediately with resolution of the VF and no recurrence</td>
<td>Electrical storm occurred after liver transplant for fulminant Wilson’s disease</td>
</tr>
<tr>
<td>Srivatsa²⁴,²⁵</td>
<td>n = 1</td>
<td>20</td>
<td>Esmolol</td>
<td>The VF episodes ceased immediately after esmolol administration. The patient survived to discharge and referred to psychiatric care</td>
<td>The episodes were precipitated by synephrine overdose</td>
</tr>
<tr>
<td>Tsagalou²⁶</td>
<td>n = 1</td>
<td>60</td>
<td>Propranolol (0.5 mg)</td>
<td>VF immediately subsided and was replaced by a ventricular paced rhythm</td>
<td>The therapeutic effect of propranolol was not sustained in absence of amiodarone (after hospital discharge)</td>
</tr>
</tbody>
</table>

* The only cases summarized here are the ones involving the use of β-blockers for the treatment of VF. Cases unrelated to this subjected were not listed in spite of being reported in the same paper.

though no statistically significant differences in 72-h survival were documented.⁸ Even though vasopressin may have smaller adverse effects than exogenous epinephrine, it did not block the β-actions of endogenous catecholamines, what possibly accounts for lower post-resuscitation parameters than pre-treatment with propranolol and prazosin.⁸

Compared to propranolol, esmolol may be a better option for beta-blockade in CPR due to its faster onset of action and shorter half-life. Several studies¹⁵,²⁶–²⁸ demonstrated that esmolol administration alone improved post-ROSC survival and reduced shock requirements, in spite of similar CPP when compared to epinephrine alone, even though only Tang,¹⁵ Theochari,²⁶ and Cammarata²⁹ reported higher resuscitation rates.

Similarly, both atenolol and carvedilol have been tested in cardiac arrest with good results in Bassiakou et al. and Huang et al. reports respectively.³¹,³² Pre-arrest β- and x₁-adrenergic blockade with carvedilol seemed to yield better postresuscitation myocardial and neurologic functions in addition to the increase in postresuscitation survival.³⁸

There are several differences in β-receptors between species, as well as cardiac function and response to CPR procedures.⁵⁰ There are marked differences, for example, among the proportion of β₁ and β₂-receptors,⁵¹,⁵² which could account for diverging results in some of the studies cited, namely in the reports from Strohmenger et al.³⁰ and Hilwig et al.¹¹ It is noteworthy that, even though these studies failed to show a benefit on the use of beta-blockers
during CPR, both of them indicate that it is a safe strategy and seem not to change the outcome of CPR.\textsuperscript{11,30} Even so, many evidences have been accumulating over the years, with elucidation of many mechanisms behind the benefits of β-blockade during CPR. Thus, it seems reasonable to believe that some of these results can be extrapolated to human clinical situations.

A few case series report the use of β-blockade in human patients, mostly patients with refractory VF after myocardial infarction.\textsuperscript{34–45} In the majority of cases, β-blockers in low doses were the only strategy capable of reverting VF to sinus rhythm and avoid recurrences, even though many patients did not have a long survival due to underlying disease.\textsuperscript{36–45} Along with the results in the human studies available in the literature regarding β-blockade in patients with VF during ES,\textsuperscript{34,35} these data suggest that there are situations in which β-blockade can be effectively and safely used during cardiac arrest. Studies with other commonly used drugs that have themselves some β-blocking actions, such as amiodarone\textsuperscript{34} and sotalol,\textsuperscript{34} could also indicate a benefit of β-blockade in human CPR. In fact, it could be that the beneficial effects of these drugs on resuscitation result from their β-blocking actions rather than solely from its antiarrhythmic properties.

Despite their importance, both human studies had limitations. In the one by Nademanee et al., patients could not be randomly assigned to a treatment arm and treatment selection (either sympathetic blockade or ALS-guided therapy) was determined by physician preference, who could not therefore be blinded.\textsuperscript{34} After the initial acute sympathetic blockade treatment, all patients who were able to take oral drugs were also given oral amiodarone. Since most patients in the ALS group died or kept having VF episodes, they had to remain under endotracheal anesthesia for multiple cardioversions and could not switch to oral antiarrhythmics. This contrasted with the drastic reduction of the number of VF episodes observed in the β-blocking group, allowing for ventilator withdrawal and oral drug administration.\textsuperscript{34}

Miwa et al. conducted a well-designed study pointing toward real benefit favoring β-blockade use in the acute management of refractory ES.\textsuperscript{35} However, the authors suggest that the effectiveness of lanidoliol over amiodarone or nifekalant (anti-arrhythmics used before lanidoliol administration) in controlling refractory ES could be due to a difference in the arrhythmia mechanism, with predominance of automatism over reentry in these selected patients, thus explaining why β-blockade was the only effective strategy.\textsuperscript{35} Thus, it needs to be assessed whether this strategy would work in all patients instead of just those with refractory ES.

Many aspects must still be investigated. Beyond clarifying the mechanisms through which β-blockade affects the fibrillating heart, its efficacy and safety in humans must be carefully assessed before put into use. Beta-blockers could perhaps be safely tested during electrophysiological studies in patients evaluated for implantable cardioverters placement, when there is constant and careful monitoring.

5. Conclusion

Even though prospective human studies point toward a beneficial effect of β-blockade in patients presenting with cardiac arrest due to VF/pulseless VT, in accordance with the results from the majority of the case reports and animal experimental studies, high quality human trials are still lacking and necessary to approach this matter and answer definitively this question.

Conflicts of interest

None.

References
