の病院収容までの循環維持の技術と病院選択の問題，さらには非OHCAであっても急変しやすい疾患特性があるため搬送中の安心と安全を確保するには，今後どのようなプレホスピタルケアを構築するのが最善か，消防ならびに救急医療機関双方に改めて問われる時代となった。

謝辞

本研究の一部は，厚生労働科学研究費補助金（課題番号H16-心筋-02：J-PULSE）により行われた。ここに感謝の意を表する。

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心臓突然死の疫学，予知，治療，予防

4. 突然死：プレホスピタルケアと救命率改善に向けて

森田　大*

我が国では病院外心停止傷病者（以下OHCA）の救急医療に対する科学的検証がなされてこなかった．そこで1998年5月以降，蘇生目的で搬送されたOHCAを対象にウツタイン様式に準拠して地域網羅的前向き疫学調査を兼ねた客観的検証を実施した．居住人口約880万人，府域面積1,892 km²の大阪府において，2004年4月までの6年間の調査から，心原性OHCAは人口10万人当たり年間平均29.2の発生数となった．このうち救急隊が接触した時点で心室細動（VF）を確認する割合は11.0％であった．虚脱を市民に目撃された心原性OHCAの最多発生場所は家であるが，VFを確認する割合は職場が最も高い．最多発生時刻は午前9時と午後7時の2峰性をとる．VFは60～69歳に最も多く，次いで50～59歳の男性であった．目撃された心原性VFの1年生存が最も良好で，虚脱から除細動までの時間短縮により1年生存率は改善傾向にあった．一方，府下高槻市（居住人口約36万人，市域面積105 km²）における搬送されたすべてのOHCAの施設別発生頻度を調査したところ，最も高い施設は鉄道駅構内で，次いで病院，ゴルフ場，老人ホーム，競技場の順となった．救命率改善には救急隊員が実施する隊活動の高度化と相まって，地域社会の救命への取り組み意識の向上が期待される．（心電図，2006；26：134～143）

Keywords
- 心原性病院外心停止
- ウツタイン様式
- 心室細動
- 病院外救急医療
- 救命率

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Ⅰ．はじめに

従来，我が国の病院外心停止（out-of-hospital cardiac arrest）傷病者（以下OHCAと略す）の救命率は欧米に比べ低いといわれてきた．しかし，これを説明する科学的根拠はなく，制度的にも欧米のように高度な医療行為を行える救急隊員が養成されていないことが問題となり，1991年に救急救命士法が制定された．米国のパラメディック制度を手本に導入

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されたが，OHCAに対する隊活動内容と実態は大きくかけ離れていたため，期待された救命効果は得られなかった[1]．

制定後10年を迎えるにあたり国家レベルでの検討がなされ，2003年4月から医師の指示を必要としない包括的指示下における除細動実施，2004年7月から実技講習を終了した救急救命士による気管挿管実施，さらに2006年4月からエピネフリンの静注が加わり，救急救命士による隊活動の高度化が図られようとしている[1]．

一方，1991年はOHCAの病院外救急医療に対する科学的検証と評価のための方法論として，国際標準となるウツタイン様式[2]が，欧米の関係学会から発表された年でもあった．救命の連鎖(Chain of Survival)[3]の概念を採り入れることにより，救命率を向上させるためには，地域における救命活動上どの段階(chain)で欠陥が生じているか客観的に明らかにする，つまり，救える生命の質を確保するためのquality controlの一手法である．しかし長年我が国ではこれを導入する地域がなかったため，大阪府において準備を重ね1998年5月から全国に先駆け地域網羅的な前向き疫学調査を兼ねて採用し，検証を開始した．そのデータをもとに本稿では，大阪府におけるOHCAの発生と救命率について概説する．

Ⅱ．対象と方法

1．ウツタイン様式について

OHCAの原因を大きく心原性か非心原性かに分類する．ここでいう心原性とは，外傷，自殺，溺死，薬物中毒，乳児突然死症候群，脳血管障害，大動脈疾患，呼吸器疾患などといった分類枠以外のもので，診断がつかない場合は除外診断に基づく心原性という範疇に含まれる．このことから心原性の割合を過大評価しやすい．地域全体の病院外救急医療の質を検証するうえで，心原性の正確な病名は意味のないものと考えられている．地域間あるいは国際間で比較検討する場合のゴールデンスタンダードとなるのは，居合わせた市民により虚脱するところを目撃された心原性で，かつ心室細動(VF)の傷病者に対するウツタインテンプレートに沿った転帰と，Chain of Survivalの各chainに要した時間の2つの要素である．

2．対象と活動記録票

1998年5月から毎年，大阪府全域(居住人口約880万人，府域面積1,892 km²)で発生し，119番入電後，救急隊員が傷病者接触時に蘇生対象と判断して救急医療機関へ搬送したすべてのOHCAに対する隊活動を前向きに調査した．救急活動記録票はウツタイン様式に準拠した記録事項に，若干の追加項目を盛り込み図1に示したように作成し，大阪府下全消防本部(組合)に配布した．

3．方法

1)救急隊員用の項目と医師用の項目への記入を完成させるために，府下全救急隊員と全救急医療機関の協力を得た．記載済みの個々の活動記録票は，近畿救急医学研究会の下部組織である「心肺蘇生に関する統計基準検討委員会」の管理下におき，1年生存調査と脳機能評価ならびに全身機能評価を実施した．消防本部からの記録票回収率は100％であった．

2)1999～2003年までの5年間に高槻市内(居住人口約36万人，市域面積105 km²)で発生し，搬送されたすべてのOHCAをもとに施設別の年間発生頻度を算出した．施設分類については消防庁への報告事項にある「発生場所別搬送人員調」に基づいた．大分類は住宅，公衆出入場所，仕事場，道路，その他であり，それぞれについて小分類があり，発生がなかった施設については除外した．

Ⅲ．結　　果

1．年次別病院外心停止傷病者の発生数と内訳

表1に示す．家族の要請や救急隊員の判断により搬送しても，二次救命処置の対象となるのは6年間の平均で86％，そのうち推定を含む心原性と考えられる症例は約56％を占め，人口10万人当たり年間29.2の粗発生数となった．その心原性に占めるVF(無脈性VTは原著では別扱いするとされているが，

病院外心肺停止患者記録（大阪版）

①消防機関用

集計No.....

発生記録 core data

発生日 20□□年□□月□□日　事例No.....－

救急車　救急隊名.....　隊長.....

患者　氏名.....　○男　○女　生年月日□□□□年□□月□□日　年齢□□歳（推定□□歳）

初期治療病院.....　引継医.....　ドクターカー出場　○現場　○ドッキング

既往症、治療歴　○あり・心疾患　□心筋梗塞　□狭心症　□その他の心疾患
・冠危険因子　□高血圧　□糖尿病　□高脂血症　□タバコ
・その他　□脳血管　□呼吸器　□悪性腫瘍　□精神病
□その他
○なし　○不　明

普段の生活状態　○良　好　○中等度障害（片麻痺、構語障害等）あるも自立
○重度障害あり要介助（ねたきり）　○植物状態　○不明

現場での傷病判断　○内因性　□前駆症状あり
心停止の前　□数分以内（直前）　□1時間以内
□24時間以内　□それ以前から
□胸痛　□背部痛　□腹痛（心窩部痛）　□頭痛　□冷汗
□呼吸困難　□動悸　□失神　□その他（.....）
□前駆症状なし　□不明
○外因性（□交通事故　□墜落・転落　□縊首　□溺水　□窒息（□餅）
□中毒　□不明）
・その他参考となる状況（.....）

救急救命士乗車　○あり（□□名）　○なし　・□頭指導　○あり（○心臓マッサージのみ）　○なし

救急隊活動状況 core data　core time

心肺停止時刻　○目撃、または音を聞いた.....　□□時□□分
心肺停止の目撃者　□家族　□通行人　□友人　□救急隊員（救急隊到着後の心停止）
□その他（.....）
○既に心肺停止（発見時）

心肺停止場所　○家　○道路上　○職場　○公衆の出入りする場所　○救急車内
○医院内　○老人ホーム　○浴槽内　○その他（.....）

bystander CPR＊1　○あり　○なし

bystander CPRの開始時刻（推定）.....　□□時□□分
覚知時刻.....　□□時□□分
出場時刻.....　□□時□□分
救急車現場到着時刻（現場に停車）.....　□□時□□分
救急隊員が患者の傍に到着時刻＊2.....　□□時□□分

救急隊員によるCPR　○施行　○施行せず　○人工呼吸のみ
○医師による2次救命処置あり
＊CPR開始時刻.....　□□時□□分

装着時心電図　○心室細動　○無脈性心室頻拍　○心静止　○電動収縮解離
○その他　○装着できず
＊モニター装着時刻.....　□□時□□分
＊除細動適応波形確認時刻（心室細動・無脈性心室頻拍）　□□時□□分

除細動　○施行・（回数□□回）＊除細動施行時刻.....　□□時□□分

□包括的指示□二相性○施行できず　理由（.....）

医師の指示　＊指示受け時刻.....　□□時□□分
指示医師（所属病院名.....　医師名.....）
指示内容（.....）

呼吸管理の方法　○人工呼吸器（オートベント・パラパック等）　○バックマスク　○その他

特定行為使用器具　○LM　○食道閉鎖式エアウェイ　○その他（.....）　○なし
＊器具挿入完了時刻.....　□□時□□分

静脈路確保　○施　行　○施行せず　○施行できず

現場より搬送開始時刻.....　□□時□□分
搬送開始時の状態　○心拍再開　○CPR継続　○その他（.....）
病院到着時刻（ドクターカー到着）.....　□□時□□分
病院到着時状況　○心拍再開　○CPR継続　○その他（.....）
病院到着前の心拍再開の有無　○あり　○なし
＊初回心拍再開時刻（病院到着後は記載不要）.....　□□時□□分

＊1 bystander CPR(処置)の内容　○口対口人工呼吸のみ○心臓マッサージ○人工呼吸と心臓マッサージの両方○その他の方法
・処置者　○家族　○知人　○第三者　○医療関係者

＊2 救急隊到着時傷病者状態　○心肺機能停止　○心機能のみ停止
○呼吸機能のみ停止　○すでに心拍再開

死亡徴候　○なし
○あり　□死後硬直　□死斑　□その他

＊特記事項（.....）

初療医師記入欄（記入者氏名.....）

病院到着時状況追加事項　意識：JCS□□□　脈拍：○あり　○なし
呼吸：○あり　○なし　○下顎呼吸

病院到着時モニター心電図　○心室細動　○心室頻拍　○心静止　○電導収縮解離
○洞調律　○心房細動　○房室ブロック　○その他（.....）

二次救命処置　○施　行
非施行の根拠　○施行せず　○屍体反応　○ADL低下（ねたきり、超高齢、るいそう）
○悪性疾患末期（慢性心不全、悪性腫瘍、神経疾患）
○著しい体部の損傷　○家族または本人の希望　○その他

CPAに至った病内 core data

転退院時診断　○内因性　○心原性（○確定　○疑い　○除外診断）
○非心原性（○中枢神経　○呼吸器　○大血管系　○悪性腫瘍末期
○その他）
○外因性
★非心原性と特定できないばあいは除外診断に基づく心原性とする。

転帰（記入者氏名.....）　core data

心拍再開の有無　○あり＜初回心拍再開時刻□□時□□分＞　○なし
病院搬入後　○ICU／病棟入院　○外来処置室で死亡
発症24時間後　○生存　○死亡
発症1週間後　○入院中　○生存退院　○転院　○死亡
発症1か月後　○入院中　○生存退院　○転院　○死亡
発症3か月後　○入院中　○生存退院　○転院　○死亡
発症1年後　○生存　○死亡

一生存退院の場合の確認先
・他院へ　①病院名.....　TEL.....　確認日.....
②病院名.....　TEL.....　確認日.....
・自宅へ　住所.....　TEL.....

一死亡日時.....　20□□年□□月□□日□□時□□分

一機能評価
○発症1か月後　○退院時
・全身機能評価＊3　○1　○2　○3　○4　○5
・脳機能評価＊4　○1　○2　○3　○4　○5
○発症1年後　○退院時
・全身機能評価＊3　○1　○2　○3　○4　○5
・脳機能評価＊4　○1　○2　○3　○4　○5

＊3　1＝良好　2＝中等度障害あるも自立　3＝重度障害あり要介助　4＝植物状態　5＝死亡又は脳死
＊4　1＝良好　2＝中等度障害　3＝重度障害　4＝植物状態　5＝死亡又は脳死

＊特記事項（.....）

図1　ウツタイン様式に準拠した病院外心肺停止患者記録（大阪版）
左の欄が主に救急隊員が記入する項目で，右の欄が主に担当医師が記入する項目．

表1　大阪府における年次別病院外心停止発生数と内訳

	搬送された院外心停止	搬入後二次救命処置対象	前者のうち推定心原性	虚脱時市民に目撃された心原性心停止	前者のうち傷病者接触時の心室細動と割合
1998／5～	5049	4350	2750	914	157 (17.2%)
1999／5～	5090	4389	2750	971	178 (18.3%)
2000／5～	5079	4367	2336	926	152 (16.4%)
2001／5～	5406	4637	2392	971	166 (17.1%)
2002／5～	5759	4994	2563	931	200 (21.5%)
2003／5～ (包括的指示下の除細動)	5173	4521	2625	947	213 (22.5%)

2003年4月以降，包括的指示下における除細動が開始された．すなわち，オンラインで医師の指示を受けなくても救急救命士の裁量で除細動できるようになった．

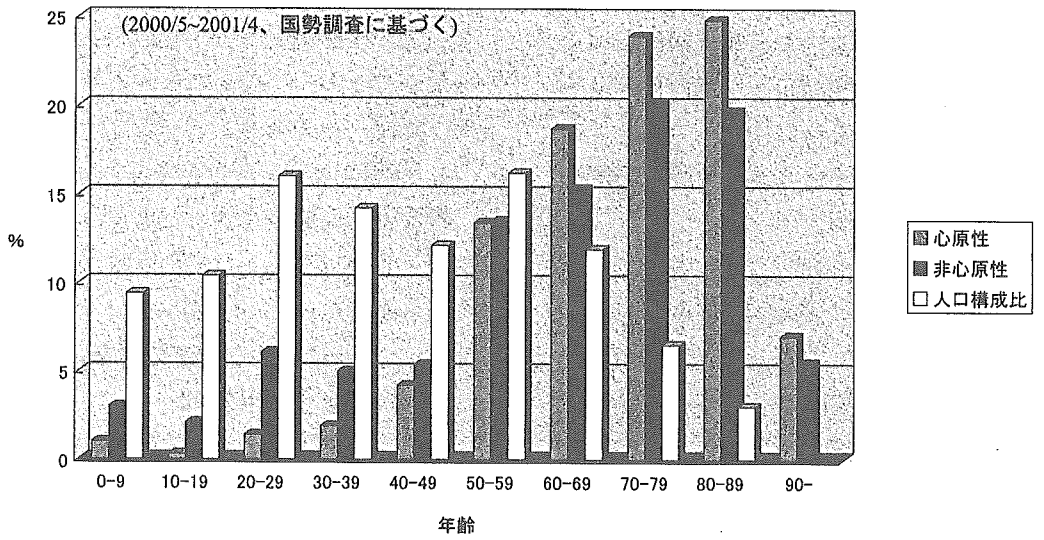

図2　大阪府下の人口構成比と病院外心停止年齢別分布

若年齢層に非心原性が多く，50～59歳より高齢層は心原性が多い．

＊国勢調査に合わせた2000年のみの分布である．人口構成比のうち90歳以上は80～89歳に算入した．

0.3%であったのでまとめてVFとして計上した）は11.0%であった．虚脱するところを市民に目撃されたのは37%で，そのうち救急隊員が傷病者に接触した時点でVFを確認する割合は，1998年の17.2%から2003年の22.5%へと増加傾向にあった．

2．大阪府下の人口構成比と病院外心停止年齢別分布

図2に示す．国勢調査年に合わせた2000年のみの

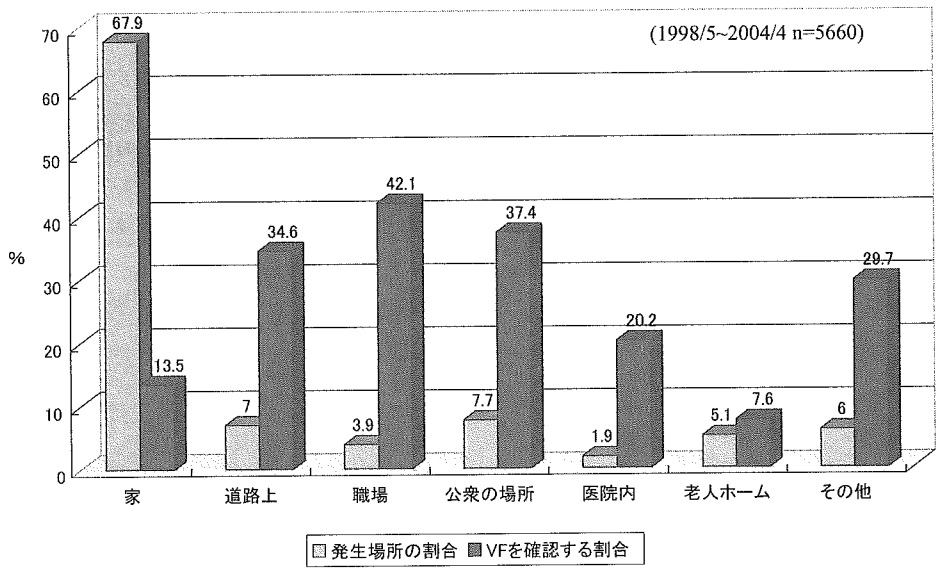

図3　目撃された心原性心停止の発生場所の割合と救急隊が傷病者接触時にVFを確認する割合

家での発生が最も多い．しかし，VFを確認する割合は職場に最も多い．

分布である．OHCAは加齢とともに発生頻度が高くなった．非心原性は若い年齢層に，心原性は50～59歳を境に中高年齢層に多くみられた．

3．目撃された心原性心停止の発生場所と傷病者接触時にVFを示す割合

家での発生が最も多くを占めた(図3)．しかし，救急隊員が傷病者に接触した時点でVFを確認する割合は職場が最も高かった．ちなみに，居合わせた人(bystander)によるCPR実施率は家28％に対し職場31％であった．虚脱から傷病者接触までの時間は家が平均値11.4 ± 10.9分，中央値9分に対し，職場が平均値9.2 ± 5.2分，中央値9分となった．平均年齢は家が70歳に対し，職場では54歳，かつ男性の割合は家では61％，職場が90％であった．

4．目撃された心原性心停止の発生時刻

午前9時と午後7時に発生数が多くなる2峰性を示した(図4)．家での発生時刻においてもその傾向がみられた．

5．目撃された心原性心停止の年齢別VF発生数

救急隊員が傷病者接触時に装着した心電図モニターでVFを確認するのは女性より男性に多く，年齢別では60～69歳において発生数が最も高く，次いで50～59歳が続いた(図5)．

6．目撃された心原性心停止の経時的VFの割合

虚脱後，時間の経過とともにVFを確認する割合が低下した(図6)．心停止直後の正確なVFの割合は明らかでない．0～3分より4～7分のほうが高いのは，bystander CPR実施の影響が示唆された．

7．心原性心停止の転帰

簡略化したウツタインテンプレートを用いての転帰調査は，目撃されたVFを呈する傷病者においては1年生存が最も良好であった(図7)．

8．目撃された心原性心停止VF例の年次別病院外救急医療活動と転帰

表2に示す．119番通報から傷病者接触までの時間，ならびにbystander CPR実施率の改善はみられなかったが，虚脱から除細動実施までの時間短縮とともに1年生存率は改善される傾向にあった．2002年の1年生存率が21.7％と極端に高い理由は，今後の検証が待たれる．

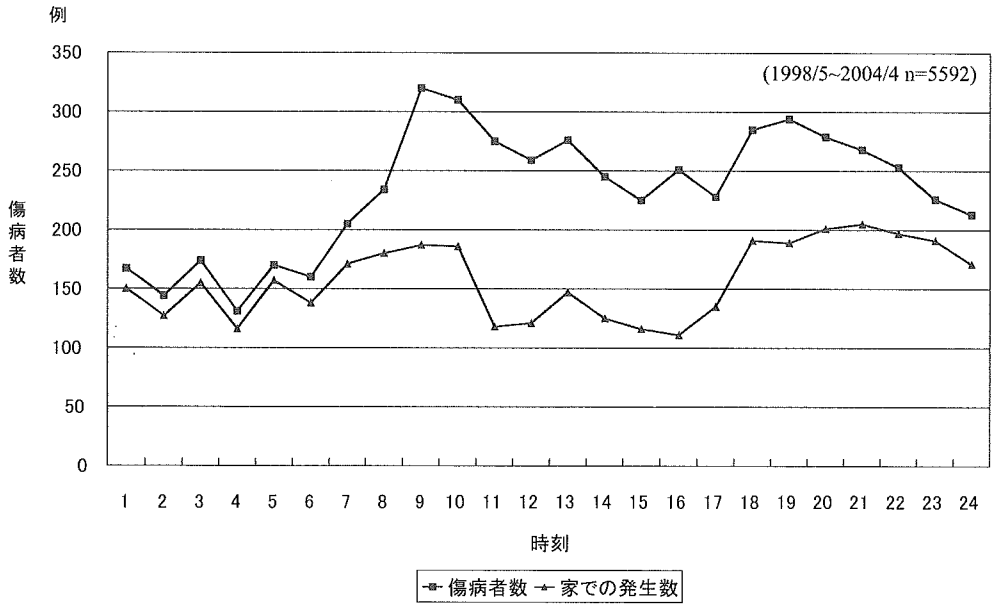

図4　目撃された心原性心停止の発生時刻

午前9時と午後7時に発生が多い．家での発生もこれに類似する．

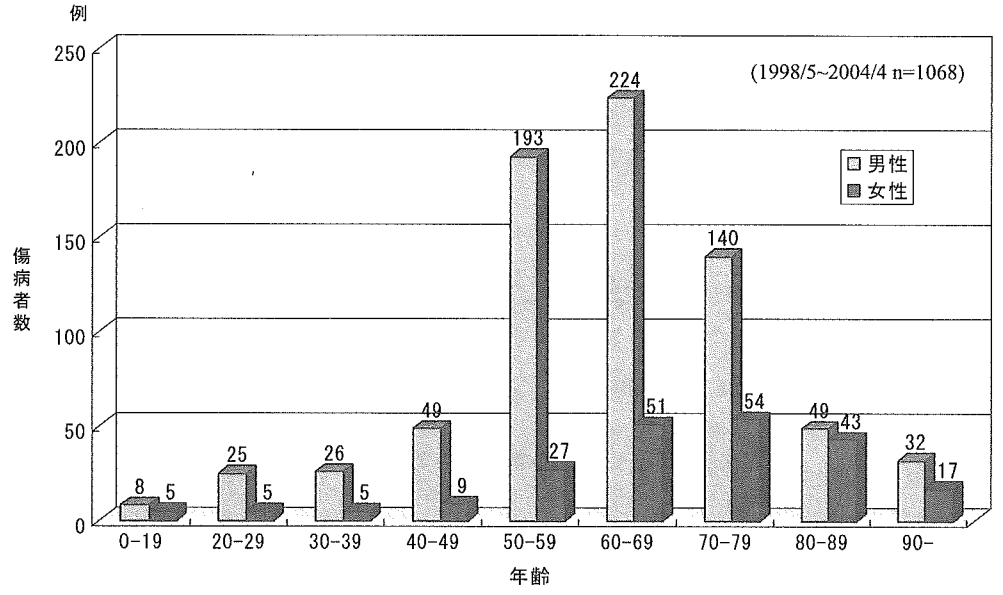

図5　目撃された心原性心停止の年齢別VF発生数

男性に圧倒的に多く，60～69歳が最多で，次いで50～59歳と続く．

9．高槻市で発生した病院外心停止の施設別発生頻度

図8に示すように，最も発生頻度の高い施設から鉄道駅構内，病院，ゴルフ場，老人ホーム，競技場の順となった．病院からの搬送依頼は精神科単科病院が多くを占めた．

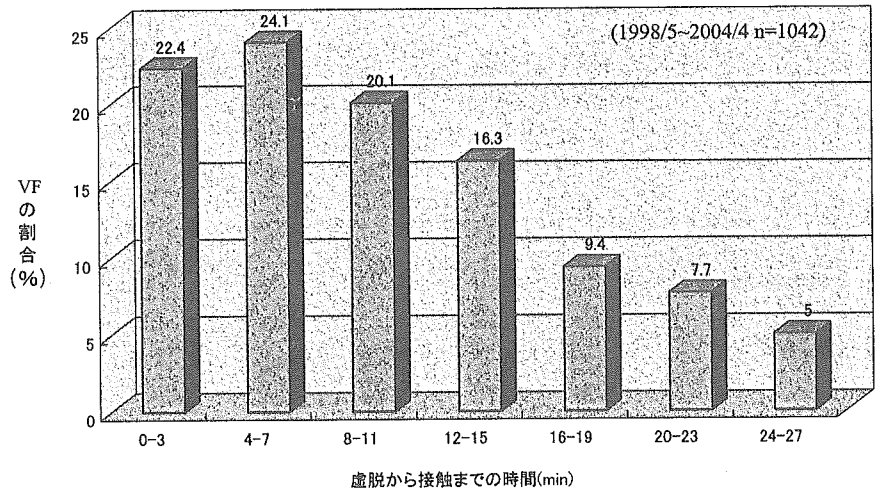

図6　目撃された心原性心停止の経時的VFの割合

時間とともにVFが消滅していくが，発生時点での正確なVFの割合は不明である．

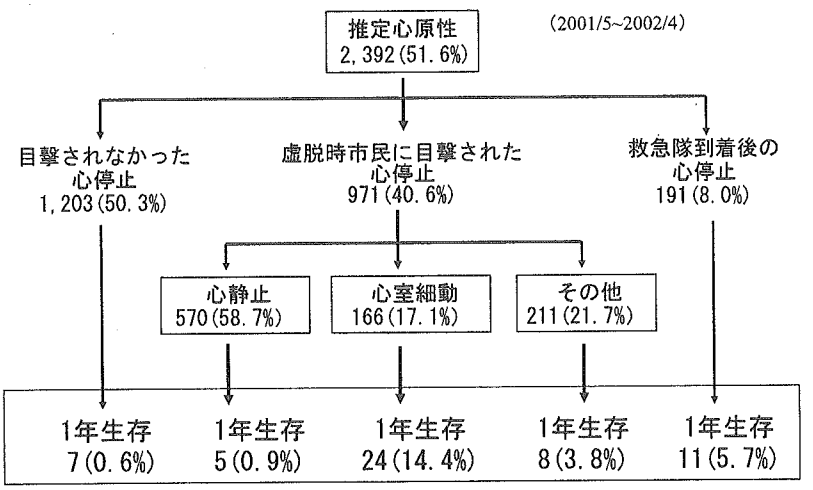

図7　簡略化したウツタインテンプレートを用いた心原性心停止の転帰

目撃された心原性VFが最も救命されやすい．

＊2001年5月から2002年4月までの1年間を代表して提示した．

Ⅳ．考　　察

我が国におけるOHCAにかかわる全国的な疫学調査はいままで行われたことがなく，その実態を把握することは不可能に近い．多くの府県単位で実施されていないとはいえ，地域差が予想されるため大阪府の調査結果が我が国を代表するとはいえない．幸いにして2005年1月から総務省消防庁は，救命効果を科学的に評価検証するための国家戦略として，ウツタイン様式に準じた隊活動記録と1ヵ月転帰調査を全国一斉に開始した．これは世界でも初めての試みである．これにより病院外救急医療における問題の所在が浮き彫りにされ，救命率改善への取り組みが期待される．

救急隊員が搬送するのは蘇生の対象と判断された傷病者のみであって，死体現象が認められる場合に

表2　目撃された心原性心停止VF例の年次別病院外救急医療活動と転帰

	1998/5~	1999/5 ~	2000/5~	2001/5~	2002/5~	2003/5~
目撃された心原性のうちVFの割合(%)	17.2	18.3	16.4	17.1	21.5	22.5
119番通報～傷病者接触までの時間(中央値:分)	6	6	6	6	6	6
虚脱～除細動までの時間(中央値:分)	20	18.5	15	16	14	11
Bystander CPR実施率(%)	34.8	38.7	38.7	39.1	38.4	38.0
1年生存率(%)	6.3	7.8	14.5	14.4	21.7	13.1

は不搬送傷病者として取り扱われている．そのために実態を過小評価している可能性が否定できない．大阪府では，病院へ不搬送となり検死される割合は全OHCAの43％に上る[4]．そのために，心原性OHCAの正確な発生数は，二次救命処置を受けた傷病者から算出した発生数より増加するはずであるが，推計は困難を伴う[4]．

救急隊員は，傷病者に接触後直ちに心肺蘇生の開始とともに心電図モニターを装着し，VF，無脈性VT，心静止，または無脈性電気活動のどの調律に属するか分類する．VFあるいは無脈性VTを確認する頻度は，欧米に比しきわめて低いとされている[5]．その要因については致死的不整脈発生原因疾患の罹病率，発症年齢，性差，虚脱時の目撃の有無，bystander CPRの実施率，心停止から傷病者接触までの時間などが関係すると思われるが，本研究から明らかにすることはできない．心原性OHCAの発生時刻は，急性心筋梗塞の発症する日内変動と類似性があり[6]，中高年齢層が多くを占めることから虚血性心疾患を原因とする可能性が示唆された．

簡略型のウツタインテンプレートに沿った転帰調査では無脈性VTを含むVFの1年生存が最も良好であった．なかでもbystander CPRが実施されていればより救命率は高くなる[4]．ちなみに，救急医療体制に差異のあることを承知のうえで国際比較すれば，大阪府の救命率はLos Angeles，New York，Chicagoよりよく，SeattleやMiamiに劣るもののOntarioと同等であった[7]．VFならびに無脈性VTは，除細動器が手元にあれば現場で蘇生できる唯一救命効果の高い調律である．しかも，早ければ早いほど脳への後遺症を残さずに完全社会復帰できる可能性が高くなるので，一般市民を巻き込んだ地域社会の救命への取り組み意識が試されると考えてよい．

救急隊員による隊活動の高度化が進むなかで，虚脱から除細動実施までの時間が短縮されるにつれて，1年生存率も6.3％から13.1％へと改善する傾向にあった．AHA心肺蘇生と救急心血管治療のための国際ガイドライン2000[8]では，心原性OHCAへの除細動は通報を受けてから5分以内が推奨されている．現実には119番通報から傷病者接触までの時間は中央値で6分を要している(表2)ことから，病院外救急医療に対する社会基盤の整備がより強化されねばならない．さらに，除細動後自己心拍が戻った傷病者に，病院到着までの間バイタルを安定させるための治療を誰が行うのかが今後問われると思われる[1]．また，International Liaison Committee on Resuscitation(ILCOR)は，心拍再開後も意識が回復しない目撃された心原性OHCAのVF例に対して，脳低温療法の導入を勧めている[9]．したがって，この療法が常時可能な救急医療機関選別のために医療内容の公開が重要となってくるであろう．

社会基盤整備の一環として，OHCAの発生施設を

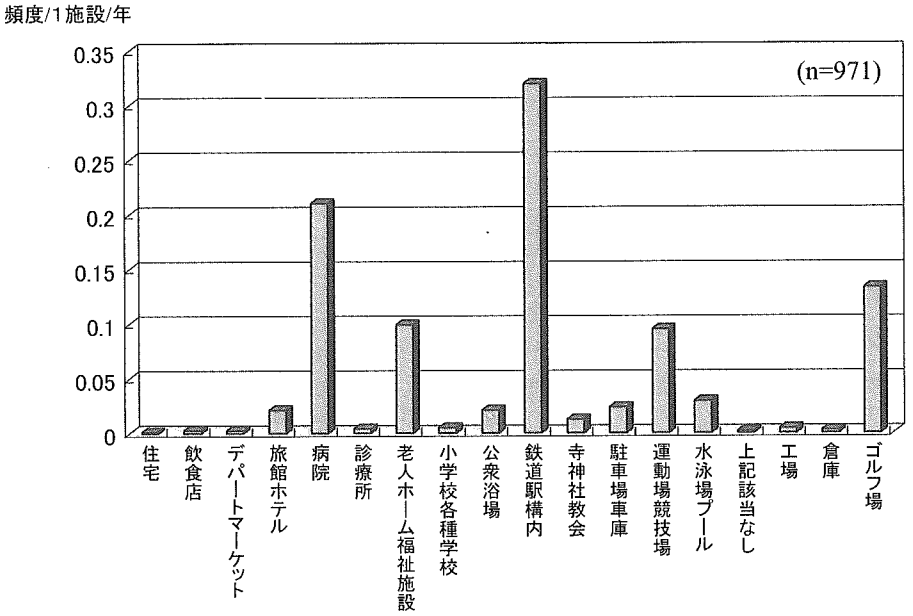

図8　高槻市で発生した病院外心停止の施設別発生頻度

発生のない施設は除外してある．病院からの搬送要請の多くは精神科単科病院であった．

＊縦軸は，1施設当たりの平均年間発生頻度を示す．

調査することにより，効率的な対策が立てられる．まず，図8に示した発生頻度の高い施設から自動体外式除細動器の設置を推奨する．Cobbらのグループ[10]は1施設当たり年間平均発生頻度が0.03以上を高頻度施設，0.01以下を低頻度施設としている．1施設当たりの年間発生頻度は高くないが，生徒数が多く安全が求められる学校に対しても積極的に普及を図るべきであろう．

V．ま と め

大阪府下で発生したOHCAの病院外救急医療の評価検証をウツタイン様式に準じて地域網羅的な前向き研究として実施してきた．

蘇生対象となった心原性OHCAの発生数，虚脱を目撃された心原性心停止の発生時刻，発生場所，VFの割合，VFの年齢分布，VFに対する病院外救急医療状況，年次別の転帰，ならびに府下一市域におけるOHCAの1施設当たり平均年間発生頻度についての実態把握を行った．

心肺蘇生に関する統計基準検討委員会委員(2005年10月現在)

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謝辞

本研究の一部は，厚生労働科学研究費補助金(課題番号H16-心筋-02：J-PULSE)により行われた．ここに感謝の意を表する．

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Circ J 2006; **70:** 442–446

Comparison of Nifekalant and Lidocaine for the Treatment of Shock-Refractory Ventricular Fibrillation

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Background Although nifekalant is a class III antiarrhythmic agent without negative inotropic activity, its effect in patients with shock-refractory ventricular fibrillation remains unclear.

Methods and Results Patients who had an out-of-hospital cardiac arrest with ventricular fibrillation that persisted after 3 shocks from an external defibrillator, intravenous epinephrine, and another shock were retrospectively studied. The patients received lidocaine from January 1997 through June 2001 and nifekalant from July 2001 through December 2004. Short-term survival rates (survival to hospital admission and 24-h survival) were compared between the groups. The study group comprised 120 patients (mean age: 62±16 years): 55 received nifekalant and 65 received lidocaine. Age, sex, history of ischemic heart disease, whether arrest was witnessed or not and time to arrival at the hospital did not differ significantly between the groups. As compared with lidocaine, nifekalant was associated with significantly higher rates of survival to hospital admission (67% vs 37%, $p<0.001$) and 24-h survival (53% vs 31%, $p=0.01$). Multivariate analysis showed that treatment with nifekalant and early initiation of cardiopulmonary resuscitation were independent predictors of 24-h survival.

Conclusions As compared with lidocaine, nifekalant may improve short-term survival in patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation. (*Circ J* 2006; **70:** 442–446)

Key Words: Antiarrhythmic agents; Cardiac arrest; Cardiopulmonary resuscitation; Emergency care; Ventricular fibrillation

In the United States of America, sudden death occurs in more than 400,000 adults each year. Ninety per cent of such deaths are attributed to heart disease. Ventricular fibrillation accounts for 80% of all cases of sudden cardiac arrest[1,2] In Japan, ventricular fibrillation is suspected to occur in 63% of all cases of cardiac arrest, but has been documented on the scene in only 15% of cases[3] This difference is attributed to a low rate of bystander cardiopulmonary resuscitation (CPR) and a long time interval from the onset of ventricular fibrillation to the initial recording of electrocardiograms (ECG) by emergency medical service (EMS) personnel. The rate of ventricular fibrillation documented on the scene will probably increase with improvements in EMS and health care systems.

Since publication of the American Heart Association (AHA) guidelines for CPR and emergency cardiac care in 2000, interest has focused on the role of CPR in the prevention of sudden death from cardiac arrest[4] Early detection of ventricular fibrillation and effective defibrillation have been acknowledged as important determinants of the rate of survival to hospital discharge. Patients in whom spontaneous circulation is restored using defibrillation promptly after the onset of ventricular fibrillation generally have a good prognosis, whereas those with persistent ventricular fibrillation have a poor prognosis[5–8] Adjunctive therapies that promote the return of spontaneous circulation in patients with ventricular fibrillation refractory to defibrillation are therefore needed.

The Amiodarone versus Lidocaine in Pre-hospital Ventricular Fibrillation Evaluation (ALIVE) trial compared amiodarone with lidocaine in patients with ventricular fibrillation persisting after shocks from an external defibrillator (shock-refractory ventricular fibrillation). The rate of survival to hospital admission was significantly higher in patients given intravenous amiodarone (22.8%) than in those given intravenous lidocaine (12.0%)[9] Intravenous amiodarone is recommended for antiarrhythmic therapy in patients with shock-refractory ventricular fibrillation by the 2000 AHA guidelines, but it is not approved in Japan.

Nifekalant is a class III antiarrhythmic agent according to the Vaughan Williams classification, similar to amiodarone. This drug has been developed and approved for clinical use in Japan. As compared with amiodarone, nifekalant is considered to have several advantages when used in patients who require CPR, such as lowering the threshold for ventricular defibrillation and having no effect or a mild positive inotropic effect on myocardial contractility[10] Several studies have reported that nifekalant is effective for the management of ventricular arrhythmias refractory to treatment with other drugs[11,12] Nifekalant is expected to be an effective adjunctive treatment for refractory ventricular fibrillation, but this remains to be confirmed clinically. We retrospectively compared intravenous nifekalant with intravenous lidocaine in patients who had refractory ventricular fibrillation with no return of spontaneous circulation after 3

(Received September 15, 2005; revised manuscript received January 17, 2006; accepted January 31, 2006)

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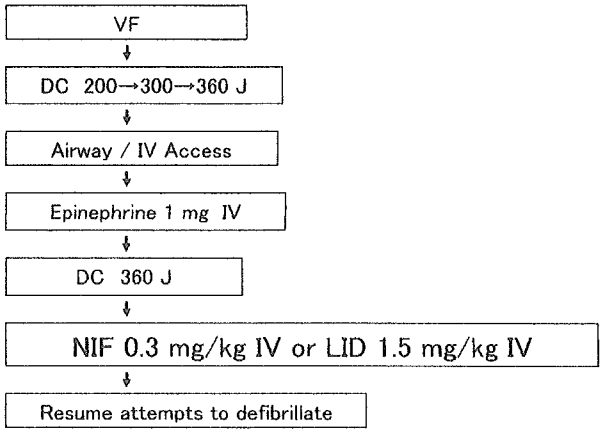

Fig 1. Nifekalant (2001-2004) vs Lidocaine (1997-2001): Observational Study. Patients were treated with nifekalant or lidocaine if they had out-of-hospital ventricular fibrillation resistant to 3 shocks, intravenous epinephrine, and further shock. The drugs were administered by hospital personnel after arrival. VF, ventricular fibrillation; DC, direct-current shock; IV, intravenous; NIF, nifekalant; LID, lidocaine.

shocks from an external defibrillator, as recommended by the 2000 AHA guidelines.

Methods

We studied patients who had out-of-hospital cardiac arrest with ventricular fibrillation and were transferred to our hospital from January 1997 through December 2004. In all patients, ventricular fibrillation persisted after 3 shocks from an external defibrillator used by emergency medical personnel, followed by an intravenous dose of epinephrine and another shock given by hospital personnel after arrival at the hospital. The mean age of the patients was 62±16 years. Of the patients, 80% were men.

Patients treated from January 1997 though June 2001 were given intravenous lidocaine. Those treated from July 2001 though December 2004 were given intravenous nifekalant. The rates of short-term survival (survival to hospital admission and 24-h survival), survival to hospital discharge and return to independent living or their former employment were compared between the groups. Treatment algorithms for ventricular fibrillation in the 2000 AHA guidelines recommend that patients with sudden cardiac arrest due to ventricular fibrillation initially receive 3 shocks from an external defibrillator. Patients who are not successfully resuscitated should be intubated for airway protection, and intravenous access should be established to permit drug administration. A 1-mg dose of epinephrine should be given intravenously, followed by another shock. Patients with persistent or recurrent ventricular fibrillation should be intravenously given antiarrhythmic agents (amiodarone, lidocaine, magnesium sulfate or procainamide), followed by one or more precordial shocks.[4]

Fig 1 shows our protocol, which was similar to the 2000 AHA guidelines. Intravenous nifekalant (0.3 mg/kg) and intravenous lidocaine (1.5 mg/kg) were used as antiarrhythmic therapies. All patients received epinephrine and artificial ventilation in the hospital, and hospital personnel started intravenous infusion. Spontaneous circulation was not successfully restored by a single intravenous dose of nifekalant or lidocaine in any patient. If an additional shock failed to restore spontaneous circulation after a bolus of nifekalant or lidocaine, a continuous infusion of nifekalant ($0.4\,mg\cdot kg^{-1}\cdot h^{-1}$) or lidocaine ($1\,mg\cdot kg^{-1}\cdot h^{-1}$) was started; thereafter, shocks were delivered every minute. After hospital admission, a 12-lead ECG was recorded and corrected QT (QTc) intervals were evaluated to adjust the infusion dose.

Table 1 Clinical Characteristics of Patients and Course of Resuscitation Before Administration of Nifekalant or Lidocaine.

	NIF (N=55)	*LID (N=65)*	*p value*
Age (years)	*63±15*	*61±16*	*0.39*
Male sex (%)	*86*	*77*	*0.22*
Coronary artery disease (%)	*69*	*63*	*0.46*
Witnessed arrest (%)	*58*	*59*	*0.93*
CPR by bystander (%)	*42*	*39*	*0.70*
Time to CPR start (min)	*7±5*	*7±6*	*0.80*
Time to arrival at the hospital (min)	*26±8*	*27±10*	*0.88*
Time to study drug administration (min)	*34±7*	*35±9*	*0.79*
Total number of DC shocks	*9±4*	*10±4*	*0.92*
Total dose of epinephrine (mg)	*6±3*	*8±5*	*0.01*

NIF, nifekalant; LID, lidocaine; CPR, cardiopulmonary resuscitation; DC shock, direct-current shock.

Endpoints

The primary endpoints were the rates of survival to hospital admission and 24-h survival. Patients with resolution of ventricular fibrillation who had a transient but unsustained return of spontaneous circulation and died in the emergency room were not considered to have survived to hospital admission. The secondary endpoint was the rate of survival to hospital discharge. The most important goal of CPR was an absence of neurologic deficits during convalescence. The rates of return to independent living or former employment–that is, intact neurologic function–were also compared between the groups. The study protocol was approved by the Ethics Committee of Yokohama City University Medical Center.

Statistical Analysis

The results are expressed as means±SD, and p values were calculated with Student's t-test. Means (±SD) were compared between the groups with use of the chi-square test. A multivariate logistic regression analysis was used to identify clinical predictors of 24-h survival among the variables associated ($p<0.1$) on univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. P values of less than 0.05 were considered to indicate statistical significance. All analyses were performed using SPSS 11J (SPSS Inc, Chicago).

Results

Of the 2,221 patients with out-of-hospital cardiac arrest treated at our hospital from January 1997 through December 2004, 12% of the patients had ventricular fibrillation and 120 (5%) met the inclusion criteria and were included in the study. Fifty-five patients received nifekalant, and 65 received lidocaine (Table 1). Age, sex, history of ischemic heart disease, whether the arrest was witnessed, whether a bystander initiated CPR, time to initiation of CPR, time to arrival at the hospital, time to study drug administration and

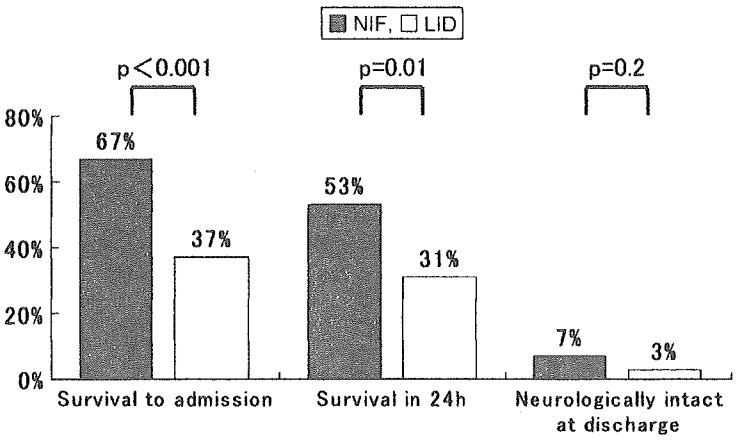

Fig 2. Effect of treatment with nifekalant or lidocaine on the rate of survival. Intravenous nifekalant was effective in increasing the rates of survival to hospital admission and 24-h survival. NIF, nifekalant; LID, lidocaine.

Table 2 Multivariate Predictors of 24-h Survival

Factor	*Odds ratio (95%CI)*	*p value*
Age (per additional year)	*0.98 (0.96–1.01)*	*0.21*
Sex (male vs female)	*2.11 (0.69–6.44)*	*0.19*
Witnessed arrest (yes vs no)	*1.42 (0.60–3.36)*	*0.43*
Time to CPR start <5 min (yes vs no)	*3.57 (1.43–8.94)*	*<0.01*
Time to drug administration (per additional min)	*0.97 (0.93–1.02)*	*0.25*
Treatment assignment (nifekalant vs lidocaine)	*3.16 (1.40–7.17)*	*<0.01*

CI, confidence interval; CPR, cardiopulmonary resuscitation.

the total number of shocks delivered did not differ significantly between the groups. The total dose of epinephrine was greater in patients given lidocaine than in those given nifekalant. Fig 2 shows the effects of nifekalant and lidocaine. As compared with patients given lidocaine, patients given nifekalant had significantly higher rates of survival to hospital admission (67% vs 37%, p<0.001) and 24-h survival (53% vs 31%, p=0.01). The rates of survival to hospital discharge (26% vs 22%, p=0.6) and intact neurologic function at discharge (7% vs 3%, p=0.2) were slightly but not significantly higher in patients given nifekalant than in those given lidocaine. At 24 h, survivors (n=49) differed significantly from non-survivors (n=71) with respect to age (58.8±15.7 years vs 63.5±15.5 years, p=0.09), being male (89% vs 75%, p=0.05), having the initial arrest witnessed (70% vs 51%, p=0.03), time to the start of CPR (<5 min) (53% vs 23%, p<0.01), time to arrival at the hospital (24.2± 9.6 min vs 27.6±8.6 min, p=0.03), time to study drug administration (34.1±9.2 min vs 37.4±8.4 min, p=0.03) and whether nifekalant or lidocaine was administered (55% vs 33%, p=0.01).[13] Table 2 shows the results of multivariate analysis designed to identify baseline predictors of 24-h survival. The independent variables included in analysis were age, sex, treatment assignment (nifekalant or lidocaine), whether arrest was witnessed, time to CPR start (<5 min) and time to drug administration. Treatment with nifekalant (OR, 3.16; 95% CI, 1.40 to 7.17; p<0.01) and time to CPR start (<5 min) (OR, 3.57; 95% CI, 1.43 to 8.94; p<0.01) were found to be independent predictors of 24-h survival.

Discussion

In the present study of patients with cardiac arrest due to shock-refractory ventricular fibrillation, the rates of survival to hospital admission and 24-h survival were higher in patients given intravenous nifekalant than in those given intravenous lidocaine. Multivariate analysis showed nifekalant is an independent factor of 24-h survival. Our results suggest that nifekalant is therapeutically useful in patients undergoing defibrillation for ventricular fibrillation.

The optimal use of antiarrhythmic drugs for CPR remains poorly defined. The 2000 AHA guidelines recommend antiarrhythmic treatment with amiodarone, lidocaine and procainamide at the time of external defibrillation in patients with refractory ventricular fibrillation. The guidelines now classify amiodarone and procainamide as class IIb drugs ("acceptable and useful") and lidocaine as a class indeterminate drug ("no harm but no benefit").[4] Procainamide is currently listed as a class IIb drug for ventricular fibrillation unresponsive to other antiarrhythmic agents, but it is not considered a first-line drug. Lidocaine has conventionally been used to treat patients with out-of-hospital cardiac arrest due to refractory ventricular fibrillation. To our knowledge, however, no large clinical study has verified its effectiveness. The Amiodarone for Resuscitation After Out-of-hospital Cardiac Arrest due to Ventricular Fibrillation (ARREST) study, comparing amiodarone with placebo,[14] and the ALIVE study, comparing amiodarone with lidocaine, have focused attention on amiodarone as a potential drug of choice for the treatment of out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation.[9] However, amiodarone can cause adverse reactions such as hypotension and bradycardia.[15] These reactions are attributed to the fact that amiodarone is a multiple-channel blocker with complex pharmacologic properties, affecting β-adrenergic receptors, calcium channels, sodium channels, as well as potassium channels. Patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation are likely to have cardiac dysfunction. Antiarrhythmic drugs with negative inotropic activity can negatively affect the outcome of CPR in such patients.

Nifekalant is a pure potassium-channel blocker effective for the management of out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation;[10] its advantages include no negative inotropic effects[16–18] and a lowering of the defibrillation threshold.[19–21] Even if adverse reactions develop, they are transient because nifekalant has a short

half-life![10] In the present study, the period of continuous infusion of antiarrhythmic agents was 3 days on average. In patients with excessive QTc prolongation (>0.55), the infusion dose was reduced. Consequently, there were no side effects, including torsades de pointes and sinus arrest, during the study period. However, concurrent use of nifekalant and lidocaine should be avoided because interactions between these drugs can cause sinus-node suppression![11] Ischemic myocardium during acute myocardial infarction is characterized by decreased intracellular ATP levels and opening of ATP-sensitive potassium channels, leading to non-uniform shortening of the action potential and refractory period, increasing the risk of reentry. Nifekalant blocks the delayed rectifier potassium (IKr) current and has strong antiarrhythmic activity against reentrant tachycardias. Its pharmacologic characteristics are considered particularly effective against ventricular arrhythmias occurring after the onset of acute myocardial infarction![22]

In the present study, the rates of survival to hospital admission and 24-h survival were higher in patients given intravenous nifekalant than in those given intravenous lidocaine; however, the rate of survival to hospital discharge did not differ significantly between the groups. The lack of a difference in survival to discharge is most likely related to the time to the return of spontaneous circulation![23] Differences in survival rates between the ALIVE study and the present study may be ascribed to differences between the rate of bystander initiated CPR (average 27% vs 40%) or differences in the underlying disease severity among patients with ventricular fibrillation![9] Albeit such differences exist, the rate of survival to hospital admission was 1.9 times higher in the amiodarone group than in the lidocaine group in the ALIVE study, as compared with 1.8 times higher in the nifekalant group than in the lidocaine group in the present study. These results suggest that nifekalant and amiodarone are similarly effective.

Ventricular fibrillation becomes refractory to treatment with the passage of time; early detection of cardiac arrest due to ventricular fibrillation and early defibrillation are thus important determinants of outcome in patients with out-of-hospital cardiac arrest![24] Furthermore, awareness of the importance of CPR should be widely disseminated among the general public![25] In addition to CPR, improvement in survival with intact neurologic function among patients with cardiac arrest requires increased emphasis on cerebral-CPR after hospital admission. Improved patient care, including techniques for brain hypothermia, are essential![26,27] More aggressive policies for resuscitation in conjunction with the use of intravenous nifekalant may contribute to higher rates of survival to hospital admission and survival with intact neurologic function.

Study Limitations

This was a retrospective study performed at a single center, not a randomized trial. Patients who had previously received lidocaine served as control. The baseline clinical characteristics of the 2 treatment groups were similar, except for a lower dose of epinephrine in the nifekalant group. This lower dose may be attributed to the fact that spontaneous circulation was regained without the need for additional epinephrine in a higher proportion of patients in the nifekalant group. In the lidocaine group, ventricular fibrillation most likely led to cardiac arrest during CPR in a substantial proportion of patients; additional epinephrine was therefore given and CPR continued. The difference in the dose of epinephrine suggests that nifekalant was more useful than lidocaine for the treatment of cardiac arrest due to ventricular fibrillation. However, lidocaine and nifekalant were used during different periods. Our outcomes may therefore have been affected by factors such as technical advances and improved medical care in addition to differences in drug efficacy. Another important limitation of the present study was that nifekalant was not compared with intravenous amiodarone, most commonly used for the management of shock-refractory ventricular fibrillation in Western countries but not available in Japan.

Conclusions

Our results show that nifekalant improves short-term survival; that is, the rates of survival to hospital admission and 24-h survival, as compared with lidocaine in patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation. However, our findings are preliminary and must be confirmed by further clinical studies.

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