

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**Worksheet author(s)**

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Date Submitted for review:

4th October 2009Revised: 9th January 2010**Clinical question.**

In adult and pediatric patients with cardiac arrest due to VF (prehospital or in-hospital) (P), does the use of CPR before defibrillation (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Therapy

State if this is a proposed new topic or revision of existing worksheet: Revision W177

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

Chief investigator and first author for study included in this review

Compensated worksheet expert for C2010

Search strategy (including electronic databases searched).

MEDLINE (1950 to Sept 2009)

1	ventricular fibrillation.mp. or Ventricular Fibrillation/	17995 hits
2	electric countershock/ or defibrillation.mp.	12519 hits
3	1 and 2	3878 hits
4	cardiopulmonary resuscitation.mp. or cardiopulmonary resuscitation/	9877 hits
5	3 and 4	741 hits
6	emergency medical service\$.mp. or *emergency medical service\$/	17828 hits
7	5 and 6	125 hits
8	limit 7 to humans	123 hits

EMBASE (1988 to Sept 2009)

1	ventricular fibrillation.mp. or heart ventricle fibrillation/	11951 hits
2	defibrillation.mp. or defibrillation/	7162 hits
3	1 and 2	2798 hits
4	cardiopulmonary resuscitation.mp. or resuscitation/	23023 hits
5	3 and 4	1035 hits
6	emergency medical service\$.mp. or emergency health service\$/	12890 hits
7	5 and 6	132 hits
8	limit 7 to human	127 hits

COCHRANE (Issue 3 – 2009)

1 defibrillation(tw) or
cardiopulmonary resuscitation(tw)

5 hits (Nil relevant)

- State inclusion and exclusion criteria

Excluded:

Animal models; abstracts; conference presentations; non peer reviewed publications

- Number of articles/sources meeting criteria for further review:

After removal of duplicates the abstracts of the remaining 212 papers were reviewed.
Seven papers were identified as relevant to the worksheet question and reviewed in detail.
(LoE I x 3; LoE III x 2; LoE IV x 1; LoE V x 1)
Secondary references of these papers were also checked.

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair	Wik 2003 (A,C,D,E)		Cobb 1999 (C,D)		
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint (1 year survival)
Italics = Animal studies

Evidence Neutral to Clinical question

Good					
Fair	Baker 2008 (A,C) Jacobs 2005 (A,C,E)			Campbell 2007 (A,C,D) Stotz 2003 (A,C,E)	Begue 2005 (A,C)
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint (1 year survival)
Italics = Animal studies

Evidence Opposing Clinical Question

Good					
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The C2005 Consensus on Science statement suggests that a period of 1.5 to 3 minutes of CPR before defibrillation may be considered in adults suffering out of hospital VF or pulseless VT where the EMS response time is greater than 4 to 5 minutes.

Clinical evidence accumulated to date totals three randomized trials (Baker 2008, Jacobs 2005, Wik 2003), two clinical trials using historical comparisons (Stotz 2003, Cobb 1999); one case series (Campbell 2007) and a narrative review (Begue 2005)

Randomised Controlled Trials

Two of the three RCTs (Baker 2008, Jacobs 2005) demonstrated no improvement in ROSC or survival to hospital discharge with a period of CPR before defibrillation. The third RCT (Wik 2003) also demonstrated no statistically significant improvement in either ROSC or survival to hospital discharge overall, although a statistically significant positive benefit in these outcomes was observed where the ambulance response time was greater than 5 minutes.

In each of these studies the intervention arms were slightly different. The studies by Baker and Wik used a period of 3 minutes of CPR prior to defibrillation whereas the study by Jacobs used a CPR period of 90 seconds. Furthermore the Wik study provided for 3 minutes of CPR before each defibrillation attempt whereas the other two RCTs allowed for the intervention to be applied prior to the initial defibrillation attempt only.

Each of these studies were powered to detect an absolute improvement in survival to hospital discharge of at least 10%. All three RCTs did not reach target recruitment and were stopped early for numerous reasons. (Baker – futility; Wik – following interim analysis; Jacobs – trial logistics / funding). As such each of these studies were potentially underpowered to detect clinically meaningful treatment effects. However, based on overall estimates of the treatment effects between the intervention and control group in each study, it is highly unlikely that further recruitment would have yielded a different result.

The effect of ambulance response intervals ≤ 5 minutes or > 5 minutes was assessed in each of these studies. In two studies (Baker 2008; Jacobs 2005) no differences in any of the outcomes were observed however these analyses were undertaken post hoc. In the third study (Wik 2003) improvements were observed in ROSC, survival to hospital discharge and 1 year survival. However, while these subgroups in the Wik study were defined apriori adjustment to the levels of significance (alpha value) to account for the interim analyses was not performed. This will increase the potential for a type one error.

Accordingly each of these RCTs have a number of limitations and as such require caution when interpreting these findings..

Other Clinical Studies

There are three other non randomized clinical studies. Two have used historical comparison groups (Stotz 2003; Cobb 1999) and the third is a case series (Campbell 2007). In the first two of these studies survival to hospital discharge and neurological outcome were observed in the groups where defibrillation was delayed.

While these two studies shared a similar design, delaying defibrillation for 90 seconds of CPR was the specific intervention under investigation in the study by Cobb. Whereas in the study by Stotz clinical outcomes of delayed defibrillation were determined (extrapolated) pre and post introduction of AEDs. The third study (Campbell 2007) was a case series in which outcomes were assessed after stratifying patients based on call to shock times (0-5 mins; 5 to 8 mins > 8 mins). In addition comparisons were made between patients receiving / not receiving bystander CPR as a surrogate for providing CPR before defibrillation. They found no difference in ROSC, survival to hospital discharge or neurological outcome between patients receiving / not receiving bystander CPR.

These studies suffer from the inherent methodological issues, biases and limitations associated with observational studies. This includes maturation effects, other changes in resuscitation protocols unmeasured over the two time periods and selection bias.

The final study (Begue 2005) was a narrative review of the evidence for delaying defibrillation to allow a period of CPR. The review noted the lack of evidence in this regard and cautioned against widespread acceptance of this protocol. This was not a systematic review and thus subject to numerous biases in assembling and interpreting the literature.

Acknowledgements:

ALL CASES

		N	ROSC %	Survival HD %	1 year survival %
Baker 2008	CPR first	97	50.5	10.3	n/a
	Immed. Defib	105	53.3	17.1	n/a
	OR		0.89	0.56	
	95% CI		0.52 to 1.55	0.25 to 1.25	
	p		0.69	0.16	
Jacobs 2005	CPR first	119	9.2	4.2	4.2
	Immed. Defib	137	8.0	5.1	5.1
	OR		1.16	0.81	0.81
	95% CI		0.49 to 2.8	0.25 to 2.64	0.25 to 2.64
	p		0.34	0.47	0.47
Wik 2003	CPR first	104	56	22	20
	Immed. Defib	96	46	15	15
	OR		1.49	1.66	1.48
	95% CI		0.85 to 2.6	0.80 to 3.46	0.71 to 3.11
	p		0.20	0.20	0.35

RESPONSE INTERVAL > 5 MINS

		N	ROSC %	Survival HD %	1 year survival %
Baker 2008	CPR first	81	45.7	7.4	n/a
	Immed. Defib	91	50.6	12.1	n/a
	OR		0.82	0.58	
	95% CI		0.45 to 1.5	0.21 to 1.6	
	p		0.54	0.31	
Jacobs 2005	CPR first	101	n/a	4.9	n/a
	Immed. Defib	113	n/a	3.5	n/a
	OR		n/a	1.41	
	95% CI		n/a	0.37 to 5.43	
	P		n/a	0.74	
Wik 2003	CPR first	40	58	22	20
	Immed. Defib	41	38	4	4
	OR		2.22	7.42	6.67
	95% CI		1.06 to 4.63	1.61 to 34.3	1.42 to 31.4
	p		0.04	0.006	0.01

Citation List

Baker PW, Conway J, et al. Defibrillation or cardiopulmonary resuscitation first for patients with out-of-hospital cardiac arrests found by paramedics to be in ventricular fibrillation? A randomised control trial. Resuscitation 2008;79:424-31.

Comment.

LOE I Quality Fair

RCT of 3 minutes of CPR before defibrillation (n= 97) versus immediate defibrillation (n=105). Out of hospital VF

Randomisation by sequentially numbered opaque envelopes. 37% of VF patients not randomised

All other care same in both groups. Resuscitation guideline change during trial (2006)

Powered for a 5.5 fold increase in survival to hospital discharge from a baseline survival of 3.3% (100 per group) 100% follow-up on all patients

Patient, demographic and clinical characteristics well matched for control and intervention groups.

Non significant differences in ROSC, survival to hospital discharge or CPC. Non significant differences for these outcomes in the ≤ 5 mins or > 5 mins sub groups (post hoc).

This is one of the two out three RCTs that failed to demonstrate a treatment benefit.

Study terminated early for futility.

Begue J, Terndrup T Delaying shock for cardiopulmonary resuscitation: Does it save lives? Current Opinion in Critical Care 2005;11:183-187.

Comment.

LOE V Quality Fair

This is a narrative review of published data relating to delaying defibrillation for CPR. There is no information relating to how the literature was searched or reviewed.

Interesting summary but not taken as a structured systematic review.

Campbell RL, Hess EP, et al. Assessment of a three-phase model of out-of-hospital cardiac arrest in patients with ventricular fibrillation. Resuscitation 2007;73:229-35.

Comment.

LOE IV Quality Fair

A retrospective analysis of VF arrests stratified by call to shock times of 0-5 mins, 5-8 mins and >8 mins. Also analysed by bystander CPR or no bystander CPR.

Data collected between Nov 1990 and December 2004.

Survival and Intact neurological survival significantly better in the 0-5 mins time phase compared with the two other time interval phases.

No differences in ROSC, survival and intact neurological survival observed between bystander and no bystander CPR sub groups in any of the 3 time phases.

Retropective study and concerns of quality of bystander CPR

Cobb LA, Fahrenbruch CE, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation.[see comment]. JAMA 1999;281:1182-8.

Comment.

LOE III Quality Fair

A population based study of 90 seconds of CPR before defibrillation. Historical control group 639 patients in the historical control group; 478 in the intervention period.

AEDs were deployed and used by EMTs more often in the invention period

Overall significantly improved survival in all cases combined and in the bystander witnessed group. Benefit appears greatest where response interval > 4 mins

Response interval comparisons not specified apriori. Unable to control for other changes in cardiac arrest management that may have occurred in the pre and post intervention period.

Jacobs IG, Finn JC, et al. CPR before defibrillation in out-of-hospital cardiac arrest: a randomized trial. *Emergency Medicine Australasia* 2005;17:39-45.

Comment.

LOE I Quality Fair

RCT of 90 seconds of CPR before defibrillation (N= 119) or defibrillate immediately (N= 137) Out of hospital VF only

Randomised by odd / even sequentially computer generated case number. 14% of cases not randomised Powered to detect a 10% absolute improvement in survival from a baseline of 10% 195 patients per group.

Control and intervention groups were well matched. 100% follow-up of participants

All other care as per existing resuscitation guidelines. Service resuscitation guidelines did not allow for paramedics to intubate or give drug therapy

No significant difference between control and intervention groups in either ROSC, survival to hospital discharge or survival at one year.

Neurological outcome (CPC) not assessed.

Study terminated early due to funding. Lower VF survival rates than expected.

Stotz M, Albrecht R, et al. EMS defibrillation-first policy may not improve outcome in out-of-hospital cardiac arrest. *Resuscitation* 2003;58:277-82.

Comment.

LOE IV Quality Fair

Retrospective study of outcomes following the introduction of defibrillation (AEDs) by paramedics.

Pre intervention period N = 76; post intervention period n = 92

No significant change in ROSC, survival to hospital discharge or 1 year survival.

Thus concluded OK to delay defibrillation provided CPR being given

Study underpowered and biased. Historical comparison with the issue of CPR before defibrillation not specifically tested.

Other explanations for the results observed not explicitly considered.

Wik L, Hansen TB, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA* 2003;289:1389-95.

Comment.

LOE I Quality Fair

RCT of 3 mins of CPR before each not just initial defibrillation (n = 104) or immediate defibrillation (n = 96)

Randomised by sealed study envelope. 18% of cases not randomised

Powered for 10% absolute improvement in survival from a baseline of 15%

Baseline characteristics were well matched and 100% follow-up achieved

No difference in overall ROSC, survival to hospital discharge or 1 year survival.

Apriori subgroup analysis showed significant improvements (ROSC, survival to hospital discharge or 1 year survival) in the CPR first group where response interval > 5mins.

Adjustment for interim analysis not done and study did not proceed to full recruitment.