

A Systematic Review with Meta-Analysis Investigating the Impact of Targeted Perfusion Parameters during Extracorporeal Cardiopulmonary Resuscitation in Out-of-Hospital and Inhospital Cardiac Arrest

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Abstract: Evidence regarding perfusion conditions during extracorporeal cardiopulmonary resuscitation (ECPR) is rare. Therefore, we investigated the impact of perfusion parameters on neurologic outcome and survival in patients with in- or out-of-hospital cardiac arrest (IHCA; OHCA) treated with ECPR. We performed a systematic review with meta-analysis. The focus was set on perfusion parameters and their impact on survival and a goal neurological outcome using the cerebral performance category score of 1–2. We conducted random- and mixed-effects meta-analyses and computed pooled estimates and 95% confidence intervals (CI). We included a total of $n = 1,282$ ECPR (100%) patients from 20 ECPR studies. The target values of flow and mean arterial pressure (MAP) were frequently available. We transferred flow and MAP target values to high, medium, and low categories. The meta-analysis could not demonstrate a single effect of flow or MAP on outcome

variables. In a second mixed-effects model, the combined occurrence of targeted flow and MAP as medium and high showed a significant effect on survival (OHCA: 52%, 95% CI: 29%, 74%; IHCA: 60%, 95% CI: 35%, 85%) and on neurological outcomes (OHCA: 53%, 95% CI: 27%, 78%; IHCA: 62%, 95% CI: 38%, 86%). Random-effects analysis showed also that IHCA led to a significant 11% ($p = 0.006$; 95% CI: 3%, 18%) improvement in survival and 12% ($p = .005$; 95% CI: 4%, 21%) improvement in neurological outcomes compared to OHCA. A combination of medium flow and high MAP showed advantages in survival and for neurological outcomes. We also identified improved outcomes for IHCA. **Keywords:** cardiac arrest, cardiopulmonary resuscitation, extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, meta-analysis, venoarterial ECMO. *J Extra Corpor Technol. 2022;54:191–202*

Extracorporeal cardiopulmonary resuscitation (ECPR) is increasingly applied for both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). Despite

the potential superiority of ECPR compared to conventional cardiopulmonary resuscitation (CPR), the corresponding outcome in these patients remains heterogeneous (1). Consequently, numerous groups have been investigating the topic of ECPR recently, focusing on various clinical and experimental attempts to improve the survival and neurological outcomes of patients treated with ECPR (2). Several reviews and meta-analyses have investigated the effect of confounding factors such as time from cardiac arrest (CA) to resuscitation (3), the influence of bystander CPR (4), the difference in outcomes between OHCA and IHCA (5), and the impact of age

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(6). Nevertheless, despite great efforts, the results remain unsatisfactory.

Instead of confounding factors, the core procedure of ECPR treatment is the reperfusion of the body by venoarterial extracorporeal membrane oxygenation (VA-ECMO). However, from other fields like cardiovascular and neurological medicine, it is known that the perfusion strategy following ischemia could be crucial for the recovery and subsequent maintenance of tissue viability (7–11). Although perfusion parameters are fundamental factors of reperfusion by VA-ECMO after CA, their impact on neurological outcomes and survival in IHCA and OHCA has not been comprehensively investigated. To fill this knowledge gap, we performed a systematic review and meta-analysis to compare the effect of differently targeted circulatory perfusion parameters on neurological outcomes and survival in IHCA and OHCA.

METHODS

Study Design

We conducted a systematic review of the literature and a meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (12). We described the detailed search strategy and review process in our previously published protocol (13). In contrast to the published protocol referring to a scoping review, we included statistical analyses in the present research work. Although the research question did not change, the current review is more comprehensive than a scoping review, including more details on methodological study items and effect measure. We assessed the methodological quality of studies using the National Institutes of Health Quality Assessment (14).

Eligibility Criteria

We included all clinical ECPR studies for patients who were at least 18 years of age that clearly distinguished between IHCA and OHCA, stated perfusion parameters and respective target values, and gave the survival rate and neurological outcomes at hospital discharge. Studies that included patients with CA secondary to extracardiac causes, e.g., pulmonary-respiratory origin, case studies, or studies written in languages other than English or German, were excluded.

Information Sources and Systematic Search

We searched the electronic databases PubMed via Medline, Social Science Citation Index via Web of Science, Social Science Citation Index Expanded, and the Cochrane library from the beginning of the ECPR literature until September 13, 2019.

The final search strategy was developed with an expert medical sciences librarian and is described in detail in the published protocol (13). We performed forward citation tracking and checked references of relevant articles. Contacting authors of relevant articles was not necessary. The following search items were predefined to guarantee a broad search strategy: “eCPR,” “VA-ECMO,” “ECMO CA resuscitation,” and “ECLS.”

Study Selection

Title and abstract screening and full-text reading were performed independently by two reviewers. Disagreement was solved by discussion and moderated by a third reviewer.

Data Collection Process

Before data extraction was started, we performed a pilot test with five citations. Data extraction was performed independently by two reviewers. Dissent was resolved by consensus moderated by a third reviewer.

Data Items

We extracted data based on perfusion parameters, outcome, and patient characteristics. We performed the data extraction manually. The data were documented in MS Excel. Then, the data was imported into the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) (15) to be analyzed. We documented all target values of perfusion parameters, time from CA to the beginning of ECPR, location of CA and of ECPR as in-hospital or out-of-hospital, survival rate and neurological outcomes at hospital discharge, total number of subjects per study, digital object identifier, year of publication, and country of study. We presented outcome parameters as number of events. Accordingly, neurological outcome was transferred to number of patients with a favorable neurological outcome, defined as a score of 1–2 based on the numerical five-value scale of the cerebral performance category (CPC) (16). A score of CPC 1–2 describes good cerebral performance to moderate cerebral disability, including consciousness and sufficient cerebral function for independent activities of daily life (16). Differing information on neurological outcomes were transferred to CPC or the study was excluded if transfer of the outcome scale was not possible. If necessary and possible, outcome parameters were calculated from the given information, e.g., when patients on ECPR were presented as a subgroup of a whole cohort, including all VA-ECMO cases from one hospital. All data items were listed in tabular format. The data item table was imported into the statistical software R (15).

Due to the limited number of studies that provided sufficient information and the large range of values, the goal parameters were transferred into categories low, medium

(if applicable), and high. Noncategorical, numerical target values of perfusion parameters are shown in Table 2 in the appendix. The units of flow were aligned to each other by a standardized cardiac index and body weight. When a range of values instead of a distinct value was given, the mean value was calculated. A CA-to-ECPR implantation time of ≤ 60 minutes was considered short and >60 minutes was considered long, according to the best practice 2018 report by Hutin et al. (17). Fjølner et al. and Ellouze et al. reported a relatively short but not distinctly given no-flow time (5, 18). Nevertheless, the low-flow period was extraordinary long in both studies, so that we decided to disregard the no-flow time to calculate the CA-to-VA-ECMO implant time. Flow ranges were defined as low (<1.5 L/min/m², <2.88 L/min), medium (1.5 – 2.2 L/min/m², 2.88 – 4.22 L/min), and high (>2.2 L/min/m²,

>4.22 L/min, 60 mL/kg/min). The mean arterial pressure (MAP) was defined as low (<65 mmHg), medium (65 mmHg to <70 mmHg), and high (70 mmHg). Kagawa et al. reported all three options of flow units (19). We allocated the studies to the respective categories depending on the described target values.

Statistical Analyses

We performed the statistical analyses using the statistical software R. We conducted random- and mixed-effects meta-analyses applying the metafor package where the probability of survival and probability of a CPC score of 1–2 were used as endpoints and are reported together with 95% confidence intervals (CI) (20). The level of heterogeneity was analyzed by the I^2

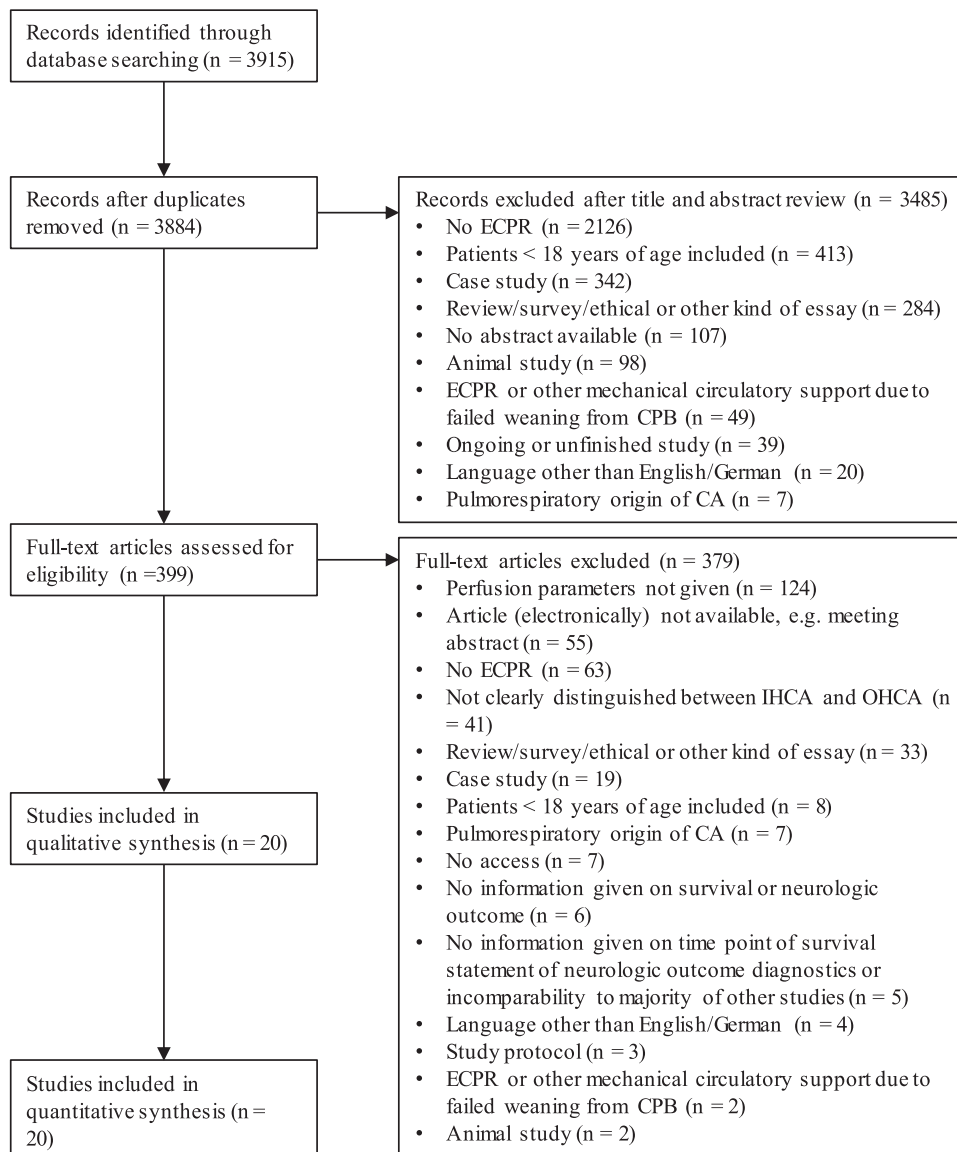


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. CA, cardiac arrest; CPB, cardiopulmonary bypass; ECPR, extracorporeal cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.

statistic and Cochran's Q test. All statistical analyses with a p -value $< .05$ were considered significant.

RESULTS

We performed a broad literature search according to our previously published protocol (13) followed by a meta-analysis of the entire ECPR literature to identify the impact of the perfusion strategy and parameters on survival and neurological outcomes, separately for IHCA and OHCA. The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart (Figure 1) shows the research process. Most of the articles were excluded due to the presentation of non-ECPR cases and the absence/lack of perfusion parameters.

Studies and Patients

We included 20 single-armed cohort studies (Table 1) in the final analysis. Some studies presented OHCA and IHCA patient cohorts, which led to a number of 12 IHCA and 17 OHCA data sets. Overall, $n = 1,282$

(100%) patients who were treated with ECPR were included, with an equal distribution of $n = 615$ (48%) cases for IHCA and $n = 667$ (52%) cases for OHCA. ECPR was implemented in an out of the hospital setting only in one study by Lamhaut et al. (21). Most of the included studies were performed in Asian and European countries, with six studies in Japan, four studies each in France and Germany, three studies in Korea, and one study each in Denmark, Taiwan, and Australia (Table 1).

Perfusion Parameters

Perfusion parameters included MAP, flow, arterial pulse pressure, systolic pressure, arterial partial pressure of oxygen, and central venous mixed oxygen saturation. Flow on VA-ECMO and MAP were most commonly provided among perfusion goal parameters. The unit of flow was presented either as flow per minute (L/min) or as flow per minute per body surface area (L/min/m²), or per body weight (mL/min/kg). Arterial pulse pressure, systolic blood pressure, partial pressure of oxygen or carbon dioxide, and central venous mixed oxygen saturation were rarely defined as goal parameters and thus were not included in

Table 1. Studies, perfusion parameters, and outcome.

Author	T CA to ECPR	Flow	MAP	Number survived	Number CPC 1–2	Number of patients	Country
Location of CA: IHCA							
Komeyama, S (2019)			Low		17	51	Japan (39)
Ellouze, O (2018)	Short	High	Low	10	9	43	France (5)
Kim, YS (2017)	Long	High	Low	8	8	16	Korea (40)
Gil, E (2017)	Short	Medium	Medium	62	52	200	Japan (41)
Ryu, JA (2017)		Medium	Medium		16	35	Korea (42)
Spangenberg, T (2016)		High	Low	6		13	Germany (43)
Jung, C (2016)		High			14	83	Germany (44)
Brunet, J (2015)		High		4		19	France (45)
Stub, D (2015)		Medium	High	9	9	15	Australia (46)
Chou, TH (2014)	Short	High		15		43	Taiwan (47)
Haneya, A (2012)		Medium	Low	25		59	Germany (48)
Kagawa, E (2010)	Short	High		11	10	38	Japan (19)
Location of CA: OHCA							
Komeyama, S (2019)			Low		3	16	Japan (39)
Otani, T (2018)		Low		32	20	102	Japan (49)
Goto, T (2018)	Short		Medium	28	10	144	Japan (6)
Chouihed, T (2018)	Long	High	High	9	8	46	France (50)
Ellouze, O (2018)	Long	High	Low	6	6	22	France (5)
Yukawa, T (2017)	Short	Medium	Medium	17	11	79	Japan (51)
Fjolner, J (2017)	Long	High		7	7	21	Denmark (18)
Ryu, JA (2017)		Medium	Medium		3	7	Korea (42)
Spangenberg, T (2016)	Long	High	Low	5		22	Germany (43)
Jung, C (2016)		High			3	34	Germany (44)
Brunet, J (2015)		High		2		10	France (45)
Stub, D (2015)		Medium	High	5	5	9	Australia (46)
Kim, SJ (2014)		Low			8	55	Korea (3)
Lamhaut, L (2013)	Long	Medium	Low		1	7	France (21)
Leick, J (2013)		Medium	Low	11	8	28	Germany (52)
Haneya, A (2012)		Medium	Low	4		26	Germany (48)
Kagawa, E (2010)	Short	High		5	4	39	Japan (19)

Empty spaces indicate that the information was not given. Survival and CPC 1–2 are presented as the number of patients at hospital discharge. CA, cardiac arrest; CPC, cerebral performance category; ECPR, extracorporeal cardiopulmonary resuscitation; IH, in-hospital; MAP, mean arterial pressure; OH, out-of-hospital; and T, time.

the meta-analysis. Some publications gave information on temperature management by describing exact target values or the time frame of temperature management or stating that a targeted temperature was applied. Explicit target values for all goal parameters, which were included in the final analysis, are presented in Table 1.

Location of CA

The random-effects analysis showed that the location of CA has a significant ($p = .006$) effect on survival at hospital discharge (Figure 2), with a survival probability of 11% in patients with IHCA compared to OHCA. The probability of a neurological outcome of CPC 1–2 at hospital discharge was shown to be significantly ($p = .005$) higher (+12%) in patients who had IHCA compared to those who had OHCA (Figure 3). We analyzed the effect of time from CA to ECPR

with absolute values reported in the publications and transferred value ranges. Absolute values did not show a significant effect of time from CA to ECPR in a linear model. Analysis of categorized time values led to a significant effect of time from CA to ECPR with a superior neurological outcome in the subgroup “long” (Table 1).

Reperfusion Parameters

The sole effect of flow and MAP on survival and neurological outcome was not significant in a mixed-effects model. In a second mixed-effects model, the impact of combining flow and MAP as high and high, medium and high, or medium and medium was compared with a noncombination of respective categories for survival (Figure 4) and neurological outcomes (Figure 5). The combination of medium and high resulted in a significantly ($p =$

Survival: Random-effects Analysis

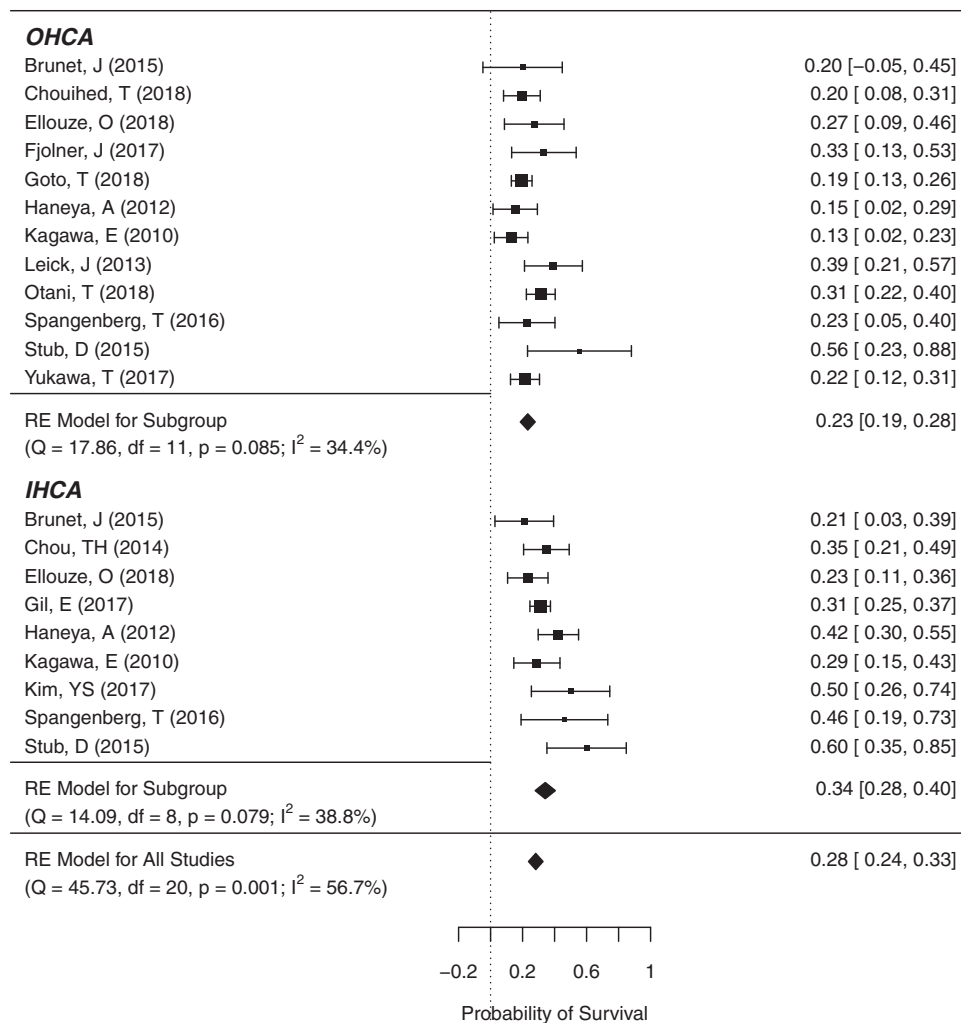
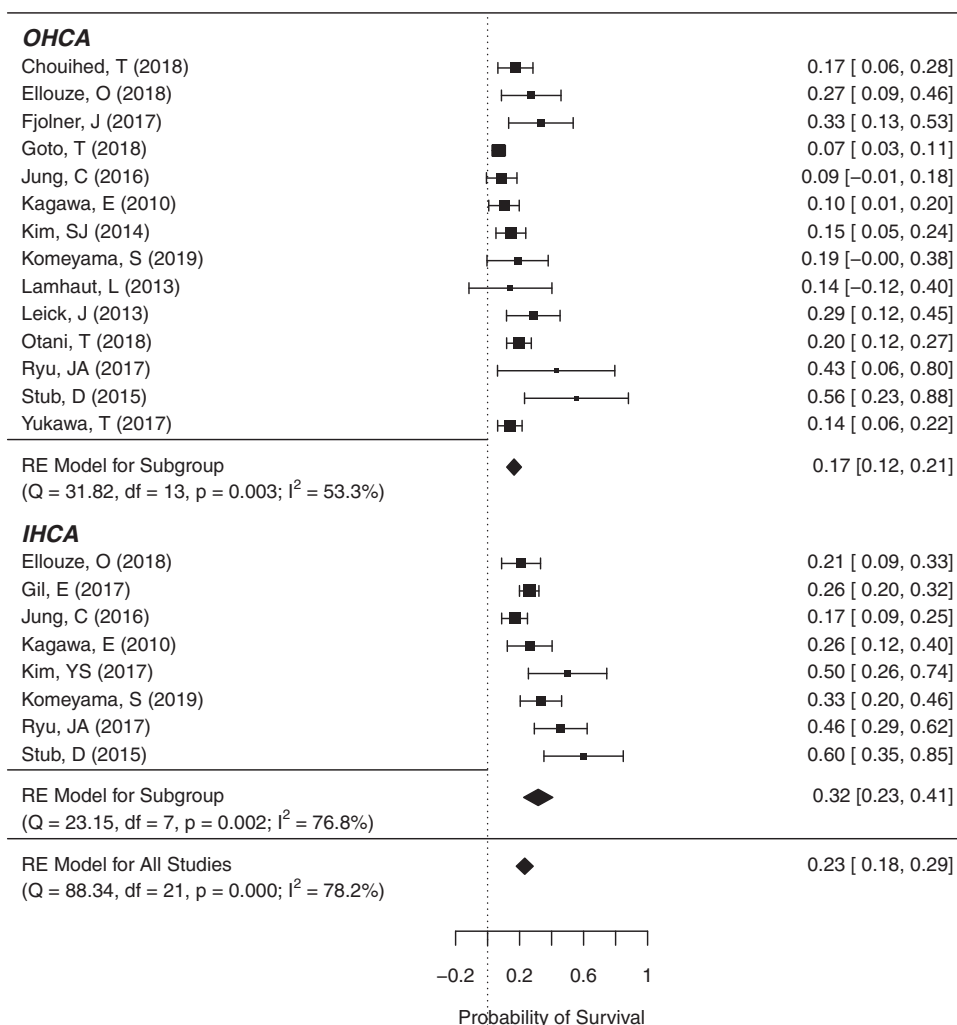


Figure 2. Effect of location of cardiac arrest on survival. The figure shows the probability of survival at hospital discharge dependent on the location of cardiac arrest in a random-effects model, separated into subgroups of OHCA and IHCA, and the overall probability of survival at hospital discharge; 95% confidence intervals are shown. IHCA, in-hospital cardiac arrest; I^2 , residual heterogeneity; OHCA, out-of-hospital cardiac arrest; RE, random-effects model.

Neurological Outcome of CPC 1–2: Random-effects Analysis

Figure 3. Effect of location of cardiac arrest on neurological outcome. The figure shows the probability of a neurological outcome of CPC 1–2 at hospital discharge dependent on the location of cardiac arrest in a random-effects model, separated into subgroups of OHCA and IHCA, and the overall probability of a neurological outcome of CPC 1–2 at hospital discharge; 95% confidence intervals are shown. CPC, cerebral performance category; IHCA, in-hospital cardiac arrest; I^2 , residual heterogeneity; OHCA, out-of-hospital cardiac arrest; and RE, random effects.



.023) improved probability of survival of 52% (95% CI: 29%, 74%) for OHCA and 60% (95% CI: 35%, 85%) for IHCA. Survival analysis of the whole population, including all studies, showed a probability of survival of 62% when flow and pressure were adjusted to medium and high. The same combination also showed a best and significantly superior neurological outcome rate of CPC 1–2 at hospital discharge of 62% in the whole population ($p = .0284$), with a probability of 53% (95% CI: 78%, 27%) for OHCA and 62% (95% CI: 38%, 86%) for IHCA. For the other combinations, no significant effect on outcome parameters was shown.

We did not find major heterogeneity ($I^2 = 33.8\%$) of flow and MAP combination effects between OHCA and IHCA for the endpoint of survival ($p = .192$). For the endpoint neurological outcome, the heterogeneity of the combination of flow and MAP was slightly above 50%.

DISCUSSION

This meta-analysis addresses the impact of perfusion parameters during ECPR on survival and neurological outcomes. The outcomes of patients who had OHCA and IHCA after ECPR have been compared with the outcomes of those in observational clinical trials other than those included in this report, with which our results are consistent (22). However, one meta-analysis assessed the different results of OHCA and IHCA and did not show a difference in the outcomes of the two groups (19). Nevertheless, the statistically proven effect of the location of CA in this report is reasonable. In OHCA, bystander CPR is usually performed rather than CPR by medical experts or conventional CPR (4).

Furthermore, the time from CA to initiation of ECPR is likely to be longer due to the distance of the location. Additionally, only one study reported out-of-hospital

Survival: Mixed-effects Analysis
Moderators: Location of CA, Flow and MAP

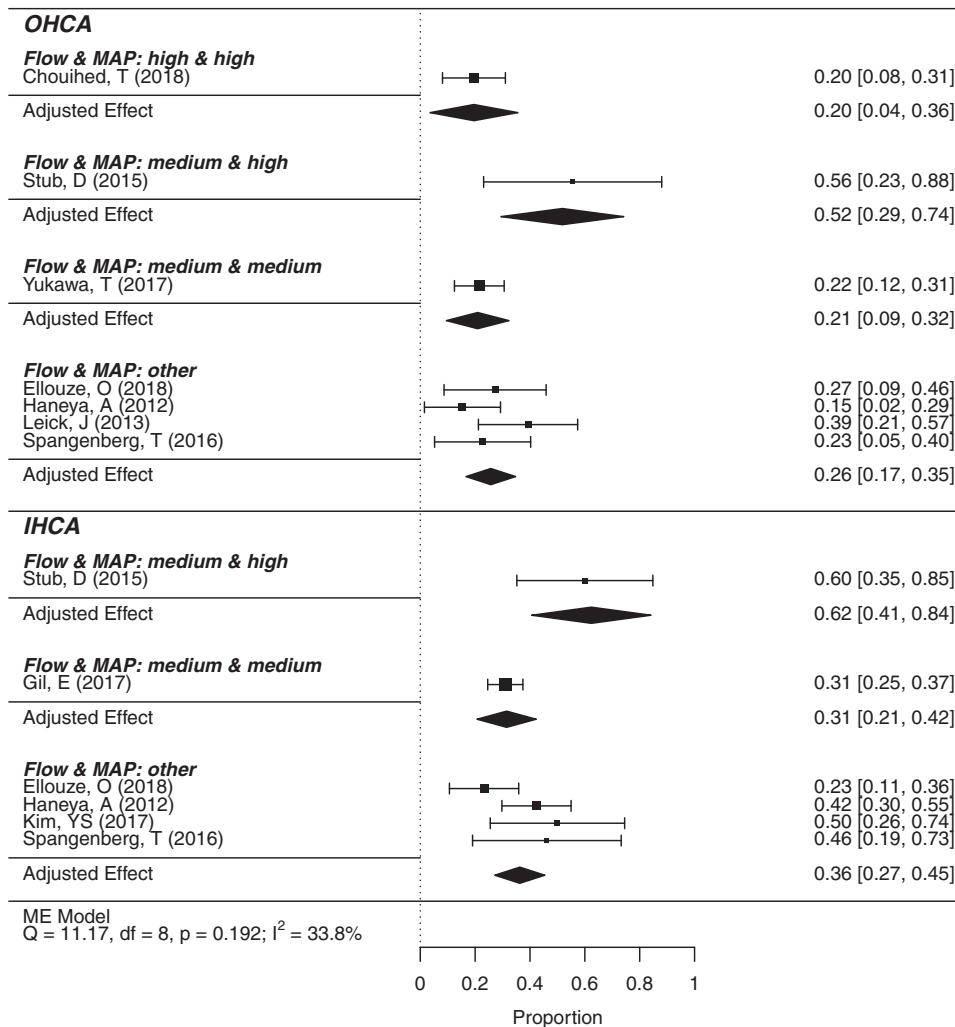


Figure 4. Combined effect of flow and mean arterial pressure on survival. The figure shows the probability of survival at hospital discharge dependent on a combined effect of flow and mean arterial pressure in a random-effects model separated into sub-groups of OHCA and IHCA and the overall probability of survival at hospital discharge. CPC, cerebral performance category; IHCA, in-hospital cardiac arrest; I^2 , residual heterogeneity; MAP, mean arterial pressure; ME, mixed-effects model; OHCA, out-of-hospital cardiac arrest.

ECPR for OHCA (21). Patients with OHCA are usually transferred to the hospital before ECPR begins, probably leading to an even longer low-flow time. Surprisingly, this analysis showed that a long CA-to-ECPR time leads to a better neurological outcome. However, this is in sharp contrast to a meta-analysis from D'Arrigo et al., who described that a short low-flow time is an independent predictor for survival in ECPR (23). Therefore, the beneficial effect of a long CA-to-ECPR time is questionable. The appearance or absence of return of spontaneous circulation has a major impact on the outcome and might lead to a biased effect of CA-to-ECPR time (24).

A nonproven sole effect of high MAP on survival and neurological outcomes is comparable to that of a randomized controlled trial (RCT) on blood pressure management during CPB (25), a preclinical ECPR study (26), and an RCT in patients with septic shock (27). Nevertheless, as known from cardiovascular surgery and the corresponding

setting and regimen of up-to-date heart-lung machine operation, low MAP (28) or low blood flow (29) is not able to supply the body sufficiently, therefore, leading to global malperfusion and relative ischemia. Consequently, we conclude that both parameters of the reperfusion regimen potentially have also a combined impact on the outcome of patients treated with ECPR.

The reperfusion paradox (30), a phenomenon known from myocardial ischemia, is characterized by the onset of various pathophysiological processes activated by reperfusion of the ischemic tissue. A potential reason for the improved neurological outcome and survival of medium flow rather than high flow combined with high pressure could be that subnormal blood flow in the early reperfusion process might reduce reperfusion injury. This hypothesis is supported by RCTs that showed a decreased infarct size, reduced troponin T and creatine kinase levels, and improved long-term recovery after ischemic

Neurological Outcome of CPC 1–2: Mixed-effects Analysis Moderators: Location of CA, Flow and MAP

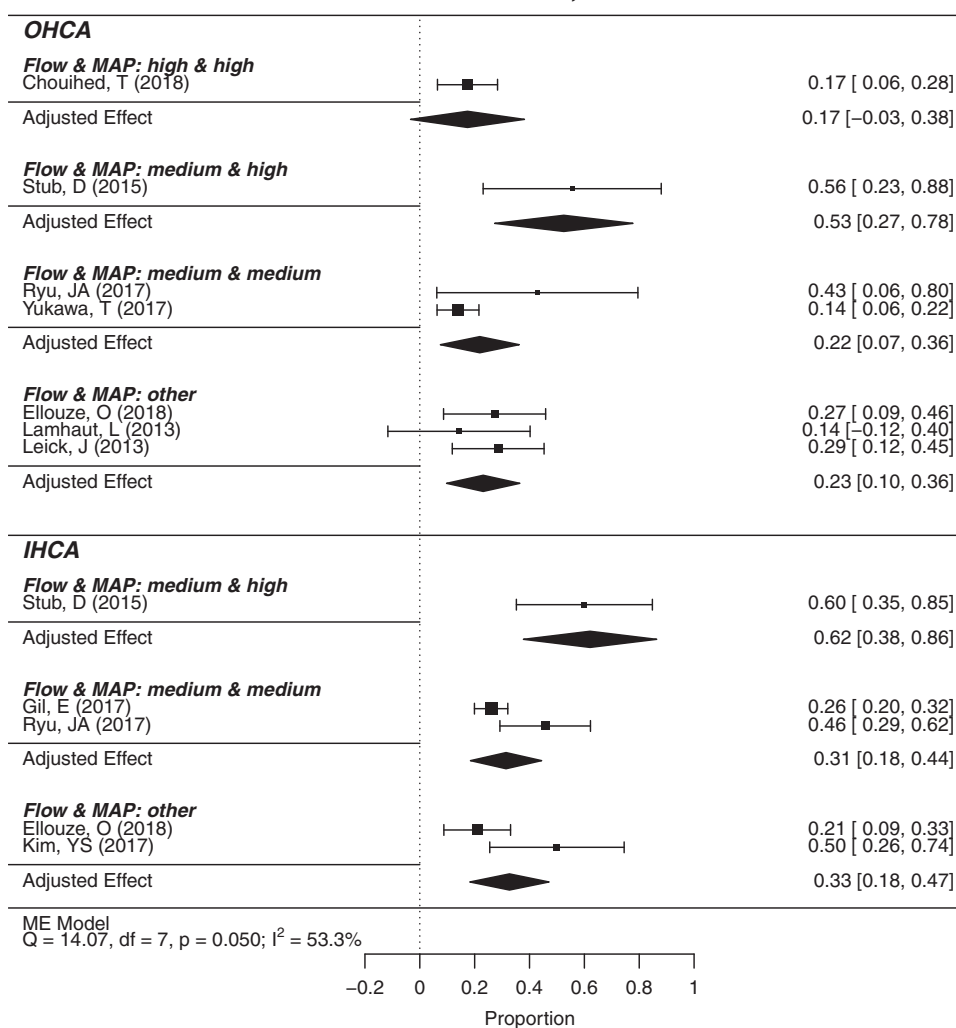


Figure 5. Combined effect of flow and mean arterial pressure on neurological outcome. The figure shows the combined effect of flow and mean arterial pressure on the prevalence of neurological outcome of cerebral performance category 1–2 at hospital discharge in a mixed-effects model, separated into subgroups of OHCA and IHCA, and the overall prevalence of a neurological outcome of CPC 1–2 at hospital discharge. The adjusted effect per sub-subgroup has been calculated. The sub-subgroup “other” shows residual categories; 95% confidence intervals are shown. CPC, cerebral performance category; IHCA, in-hospital cardiac arrest; I², residual heterogeneity; ME, mixed-effects model; and OHCA, out-of-hospital cardiac arrest.

postconditioning of the infarcted myocardium by periodically inflating and deflating a balloon during angioplasty after coronary artery stenting, causing reduced blood flow during the initial reperfusion (31–33). Furthermore, the implementation of high flow rates in patients with CA often requires high-volume replacement with human transfusion products such as human albumin or red blood cells and plasma concentrates (34, 35). High transfusion volumes are likely to be associated with adverse events and increased morbidity and mortality, as shown in a systematic literature review by Delaney et al. (36). Finally, only two studies were included in the combined analysis of high flow and high pressure, limiting interpretation on this parameter.

Inadequate Reporting

The partially insufficient keywording or study labeling lead to the necessity to use broadly defined search items,

which resulted in an extensive exclusion of search results (Figure 1). Consequently, we identified predominantly non-ECPR studies among the excluded articles. Nevertheless, many studies also incorrectly included non-ECPR patients in analyzing a so-called ECPR group, e.g., those who had a cardiogenic shock. Another major restriction of study inclusion was the lack or absence of perfusion parameters. Only a few of the publications described perfusion parameters. Even when the flow was reported, units (mL/kg/min or L/min/m²) were often given without reference to body surface area or body weight, making it difficult to compare studies from Asian populations with those of European populations. The respective units used in the publications are shown in Table 2. Several studies have already demonstrated that perfusion parameters during ECPR have a considerable influence on neurological outcomes and survival of patients and are therefore of great importance during ECPR (7–11).

Table 2. Distinct values of perfusion parameters. APP: Arterial pulse pressure. CA: Cardiac arrest. CvmSO₂: central venous mixed oxygen saturation. CPC: Cerebral performance category. ECPR: Extracorporeal cardiopulmonary resuscitation. MAP: Mean arterial pressure. N: Number of patients at hospital discharge. SP: Systolic pressure. Pa: Partial pressure. T: Time.

Author	Location of CA	Location of ECPR	CA to ECPR time in min	Flow	Unit of Flow	MAP in mmHg	APP in mmHg	SP in mmHg	PaO ₂ in mmHg	PaCO ₂ in mmHg	cvmSO ₂ in %	N Survival	N CPC1-2	Sample size	Country of the study
Komeyama, S (2019)	IHCA	IH				>60							17	51	Japan
Komeyama, S (2019)	OHCA	IH				>60							3	16	Japan
Otani, T (2018)	OHCA	IH		2.5-3	L/min							32	20	102	Japan
Goto, T (2018)	OHCA	IH	57					90				28	10	144	Japan
Chouhied, T (2018)	OHCA	IH	86	4.3	L/min	65-75						9	8	46	France
Ellouze, O (2018)	OHCA	IH	90	2.5 - 3.5	L/min/m ²	≥ 60				35-45		6	6	22	France
Ellouze, O (2018)	IHCA	IH	60	2.5 - 3.5	L/min/m ²	≥ 60						10	9	43	France
Kim, YS (2017)	IHCA	IH	67	2.0 - 2.8	L/min/m ²	50-70	>10 mmHg					8	8	16	Korea
Yukawa, T (2017)	OHCA	IH	45	3-4	L/min	65						17	11	79	Japan
Gil, E (2017)	OHCA	IH	35	2.2	L/min/m ²	>65					70	62	52	200	Japan
Fjolner, J (2017)	OHCA	IH	121	50 - 70	mL/kg/min	>65						7	7	21	Denmark
Ryu, JA (2017)	OHCA	IH		2.2	L/min/m ²	>65					70		3	7	Korea
Ryu, JA (2017)	IHCA	IH		2.2	L/min/m ²	>65					70		16	35	Korea
Spangenberg, T (2016)	OHCA	IH	72	≤5	L/min	≥ 50						5		22	Germany
Spangenberg, T (2016)	IHCA	IH		≤5	L/min	≥ 50						6		13	Germany
Jung, C (2016)	OHCA	IH		4.5	L/min	≥ 50								34	Germany
Jung, C (2016)	IHCA	IH		4.5	L/min	≥ 50							14	83	Germany
Brunet, J (2015)	IHCA	IH		2.5	L/min/m ²							4		19	France
Brunet, J (2015)	OHCA	IH		2.5	L/min/m ²							2		10	France
Stub, D (2015)	OHCA	IH		3	L/min	70						5	5	9	Australia
Stub, D (2015)	IHCA	IH		3	L/min	70						9	9	15	Australia
Chou, TH (2014)	IHCA	IH	60	60	mL/kg/min							15	8	55	Taiwan
Kim, SJ (2014)	OHCA	IH		2.5 - 3.0	L/min										Korea
Lamhaut, L (2013)	OHCA	OH	79	2.5 - 4	L/min	>60						11	1	7	France
Leick, J (2013)	OHCA	IH		3-4	L/min	60			>100			8	8	28	Germany
Haneva, A (2012)	OHCA	IH		≤4	L/min	50-60						4		26	Germany
Haneva, A (2012)	IHCA	IH		≤4	L/min	50-60						25		59	Germany
Kagawa, E (2010)	IHCA	IH	25	>60	mL/kg/min							11	10	38	Japan
				≥2.0	L/min										
				>2.5	L/min/m ²										
Kagawa, E (2010)	OHCA	IH	59	>60	mL/kg/min							5	4	39	Japan
				≥2.0	L/min										
				>2.5	L/min/m ²										

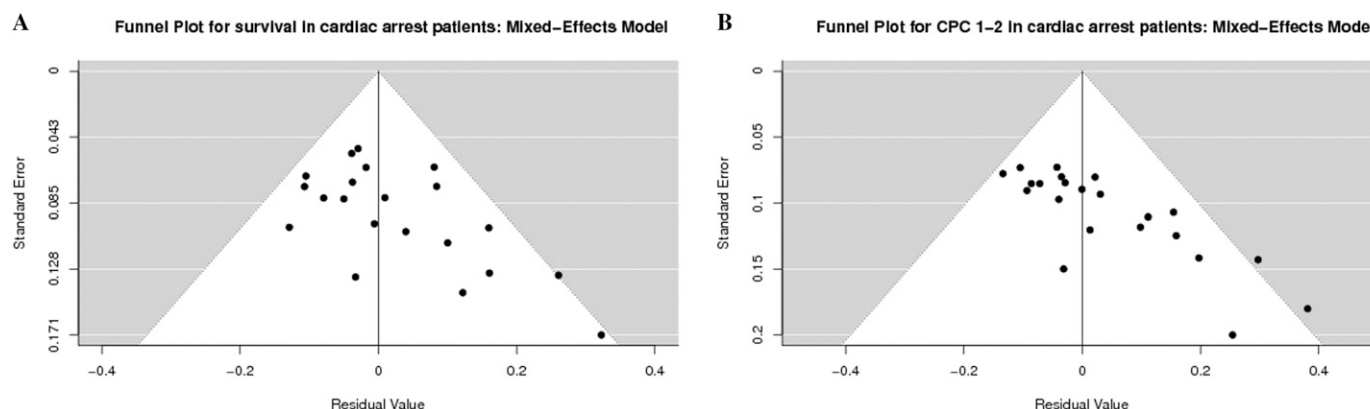


Figure 6. Funnel plots. These funnel plots were constructed for (A) survival and neurological outcome. (B) dependent on the location of cardiac arrest.

Furthermore, the location of CA was often not differentiated as IHCA or OHCA, which led to a significant loss of information. We also identified a repetitive publication bias by funnel plot analysis for survival (Figure 6A) and neurological outcomes (Figure 6B), which indicated a lack of small studies with negative results. Another important aspect is left ventricular unloading during VA-ECMO therapy. Left ventricular unloading may impact the outcome, too (37). Therefore, it should always be clarified if left ventricular unloading was performed. If so, the number of patients receiving left ventricular unloading and the respective type of unloading strategy should be specified.

Limitations

This meta-analysis is limited by unavoidable factors based on the current setting of ECPR publications. Blood flow and MAP were reported as goal parameters with target values but not as calculated means throughout all studies included in the meta-analysis. Additionally, the interpretation of the effect of flow and MAP was complicated and restricted by the necessity to transfer values into categories. Furthermore, perfusion parameters and outcomes in OHCA and IHCA were reported insufficiently in most of the studies, so that only a small number of studies were included in the final quantitative analysis.

CONCLUSIONS

The location of CA has a significant impact on survival and neurological outcomes after ECPR. RCTs should be performed to investigate whether an out-of-hospital ECPR leads to improved outcomes for patients with OHCA. A sole significant impact of flow or MAP during reperfusion on both outcome parameters was not noted. A combination of medium flow and high MAP seems to improve survival significantly, and neurological

outcome at hospital discharge in patients with OHCA and IHCA treated with ECPR. This meta-analysis is affected by poor reporting. It was shown that the reperfusion regimen after CA is of major importance, but reporting has to be significantly improved, as stated by the Modified Utstein Reporting Definitions (38). Consequently, there is the need to conduct RCTs for controlled reperfusion of patients who have CA, including perfusion target parameters during ECPR.

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