Review

Carotid artery and cerebral blood flow during experimental cardiopulmonary resuscitation: A systematic review of the literature

Luca Lucchetta [a,g,h], Timothy N. Kwan [a], Junko Kosaka [b], Aiko Tanaka [c], Glenn M. Eastwood [a], Matthew Chan [a], Johan Martensson [a,d], Clive N. May [e], Rinaldo Bellomo [a,e,f,*]

[a] Department of Intensive Care, Austin Hospital, Melbourne, Victoria, Australia

[b] Department of Anesthesiology, Okayama Univerisyt, Okayama, Japan

[c] Department of Anesthesiology, Osaka University, Osaka, Japan

[d] Department of Physiology and Pharmacology, Section of Anaesthesia and Intensive Care, Karolinska Institutet, Stockholm, Sweden

[e] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Melbourne, Australia

[f] School of Medicine, University of Melbourne, Parkville, Melbourne Australia

[g] Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

[h] Vita-Salute San Raffaele University of Milan, Milan, Italy

Abstract

Background: The carotid artery blood flow (CABF) or cerebral blood flow (CBF) achieved with current techniques of cardiac compression in humans are unknown. Animal experiments may provide useful information on such flows and on possible techniques to optimize them.

Objectives: To obtain an estimate of carotid and cerebral blood flows during cardiac compression with different techniques.

Methods: We performed a systematic review of all studies in the English literature that measured the CABF and/or CBF during cardiac compression in experimental models of cardiac arrest, expressed as a percentage of baseline (pre-arrest) values. We compared the effect of vasopressor use, thoracic compression technique, pre-arrest infusion and animal model on maximum blood flows using standard statistical methodologies.

Results: Overall, 133 studies were reviewed. Of these, 45 studies provided information only on CABF; 77 only on CBF, and 11 studies on both flows. The overall weighted mean ($\pm$SD) CABF was $35.2 \pm 27.7\%$ of baseline. Porcine studies showed lower CABF when vasopressors were used ($p = 0.0002$). Studies of CBF reported a weighted mean value of $66.5 \pm 48.5\%$ of baseline. Adjunctive vasopressor therapy significantly increased CBF ($p = 0.007$), as did fluid administration ($P = 0.049$). In studies reporting both CABF and CBF, the median CABF/CBF ratio was 0.67 (range 0.21–1.96).

Conclusions: During experimental cardiac compression, compared to baseline, CABF appears to decrease much more than CBF. However results should be regarded with caution. They are affected by ancillary interventions and measurement methods, variability is marked and, in experiments measuring CABF and CBF simultaneously, their ratios range well outside physiologically plausible values.

Keywords: Cardiac arrest, Cardiac massa, ge, Cardiopulmonary resuscitation, Carotid artery flow, Cerebral blood flow

* Corresponding author at: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.
E-mail address: rinaldo.bellomo@austin.org.au (R. Bellomo).

Introduction

Cardiac arrest is a critical condition associated with a high morbidity and mortality.[1,2] Cardiopulmonary resuscitation (CPR) aims to provide adequate perfusion to vital organs during cardiac arrest, especially heart and brain. The brain, however, may not receive adequate perfusion despite technically optimal CPR. This notion is supported by the observation that, despite CPR, most resuscitated patients following cardiac arrest have neurological injury and many die because of such injury.[3-9]

Such poor neurological outcome is logically explained by inadequate cerebral blood flow (CBF), decreased brain oxygen levels and reduced glucose delivery during CPR, even in the presence of seemingly adequate arterial pressures.[8-13] Unfortunately, CBF cannot be measured in humans during CPR, making it difficult to assess how different approaches to CPR (closed chest thoracic compression with or without machine assistance, open chest thoracic compression) might optimize CBF. Moreover, the relationship between CABF and CBF is highly variable and unclear.[14,15] Thus, estimation of CABF during CPR in humans is unlikely to provide robust information on CBF. Given the near impossibility of measuring CABF or CBF during CPR in man, animal models have been used to estimate how different approaches to CPR may affect CBF or CABF and to estimate what percentage of pre-arrest values might be achieved during CPR. Such experimental data might provide important information on the likely adequacy of standard CPR in man, on what technical aspects of CPR may achieve best cerebral perfusion, and on whether CABF has a robust and reliable association with CBF.

Accordingly, we systematically evaluated all experimental studies of CPR that reported CABF and/or CBF. We aimed to test whether such animal experiments yielded consistent CBF and CABF values across different experiments and species, whether such values were influenced by closed vs. open CPR and whether the relationship between CABF and CBF was consistent and robust across different experiments and species. Specifically, we hypothesized that CABF and CBF during CPR would decrease by a similar amount to <50% of baseline, that open-chest CPR would yield higher CABF and CBF values than closed-chest CPR, and that ancillary interventions (vasopressor therapy, use of machine compression and fluid administration) would be associated with greater CABF and CBF.

Methods

We interrogated the electronic reference libraries of MEDLINE (1950–Oct 2018), EMBASE (1947–Oct 2018) and CINAHL (1987–Oct 2018). At first, we performed the search using the Boolean operator 'OR' with the following medical subject heading terms and text words: 'heart arrest', 'cardiac arrest'. Second, we searched studies using the link 'OR' with the following additional words: 'cardiac massage', 'heart massage', 'cardiopulmonary resuscitation', 'cardio-pulmonary resuscitation', 'chest compression', 'chest massage'. Third, we used the link 'OR' with the following additional words: 'carotid artery flow', 'carotid blood flow', 'cerebral blood flow', 'brain blood flow', 'regional blood flow', 'organ blood flow', 'cerebrovascular circulation'. These three
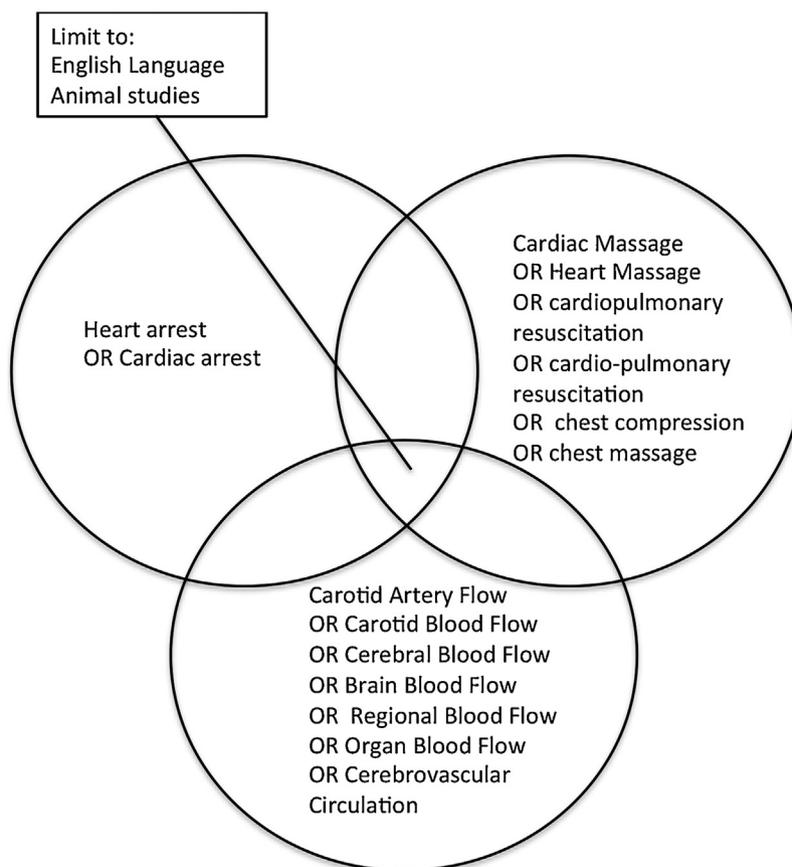

Fig. 1 – Electronic search strategy. This diagrammatic representation illustrates in details the string search and the limits utilized.

search results were then combined using the Boolean operator 'AND' (Fig. 1). Additionally, we obtained other possible studies that might report these flows during thoracic compression and that had not been identified by our search strategies, but from the reference lists of each study.

The search was conducted in November 2018 and was limited to experimental models and the English language. Firstly, we obtained a group of citations from which duplicates were removed manually and by means of Covidence, a core component of Cochrane's review production toolkit. After exclusion of non-relevant citations, abstracts were inspected in order to define eligible manuscripts for a detailed evaluation. Only studies reporting original data of CABF and/or CBF in animals during thoracic compression after an induced cardiac arrest were included.

Study inclusion criteria

Population
We included experimental studies of any type of cardiac arrest model and animal species.

Intervention — cardiopulmonary resuscitation
This study aimed to evaluate the effect of cardiopulmonary resuscitation after an induced cardiac arrest. Cardiopulmonary resuscitation was performed by means of different techniques, technologies, therapeutic strategies and drugs.

Outcome — carotid artery blood flow and cerebral blood flow during CPR
We extracted the highest CABF or/and CBF reported during CPR in each study. In most studies, the data for CABF and CBF were reported

as ml/min or ml/min/100 g, respectively. However, some studies used other measurement units; thus, from all studies we also extracted flows as highest percentage of baseline values before cardiac arrest. Flow data were considered valid if extractable from either tables or figures contained in the paper.

Data collection and management
We collected data on vasopressor use, open or closed-chest thoracic compression with or without assist devices, animal species, number of animals, flow measurement technique, pre-cardiac arrest interventions, as well as bibliographic information.

Due to a wide variety of experimental protocols for the use of vasopressors (epinephrine, norepinephrine, vasopressin, phenylephrine, angiotensin II and endothelin I) during CPR we divided the data into two groups. These groups were studies 'with vasopressor use' and those 'without vasopressor use'. In addition, the porcine category was also subdivided into 'piglets' and 'new-born piglets' as there is a difference in the size. Among pre-arrest interventions, for each study we checked for fluid infusion, adrenaline, hypotensive drugs (propranolol and prazosin) and the possible effect of other drugs (heparin and indomethacin).

Statistical analysis
A meta-analysis approach could not be applied because of the degree of study heterogeneity. All statistical analysis was descriptive with comparisons according to CPR technique and measurement technique using non-parametric statistics. For each study, the best CABF/CBF values achieved during resuscitation as a proportion of baseline CABF/CBF were recorded. Where these were not reported, mean absolute values for baseline CABF/CBF and best CABF/CBF achieved during CPR were recorded and used to estimate this
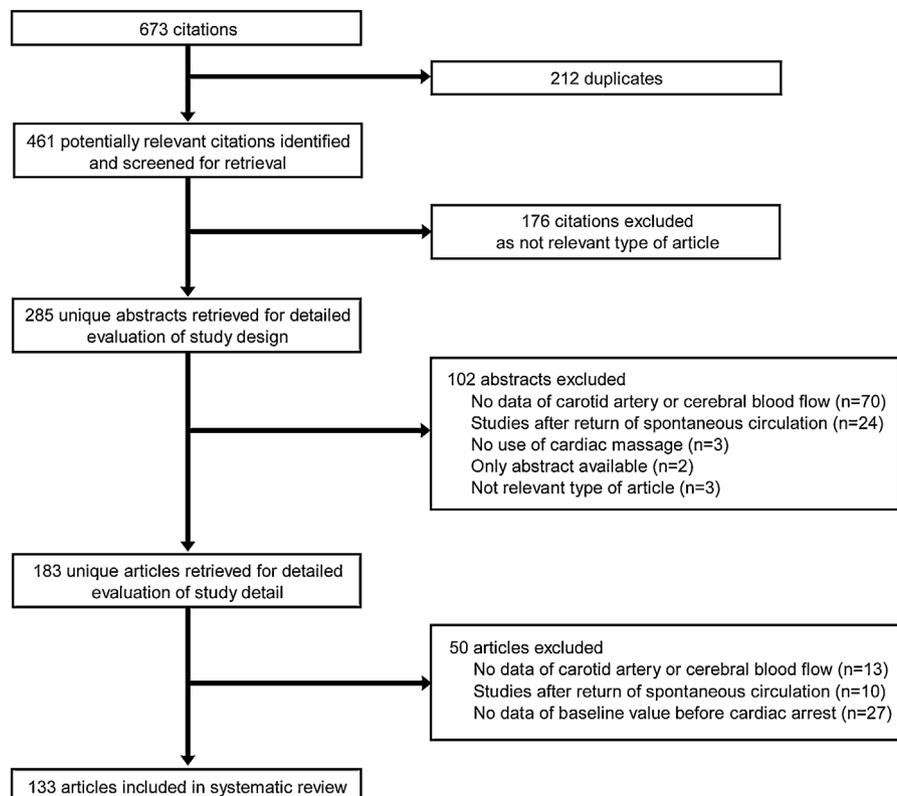

Fig. 2 – Study selection. Flow chart describing the search strategy adopted to obtain the final articles of interest.

proportion. With studies reporting median values, these were converted into parametric estimates with the assumption that the CABF and CBF data are normally distributed. Such values were either recorded from study tables or estimated from study graphs to the nearest millilitre per minute. Pooled data were then aggregated to calculate weighted arithmetic mean, standard deviation, and standard error, using study sample size as the weighting variable (Figs. 3 and 4 in Appendix).

In sensitivity analyses, we compared pooled results using Welch's *t*-test for different study characteristics: use of vasopressors; method of thoracic compression for resuscitation; instrument used for flow measurement; use of a fluid infusion pre-arrest; publication date (earliest 50% of studies vs. latest 50% of studies); and choice of study animal. Data were pooled and analyzed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) & STATA version 13.0 (StataCorp, College Station, TX). A two-tailed p-value < 0.05 was considered statistically significant.

Results

Electronic search

We identified 425 potentially relevant citations between January 1947 and October 2018. Of these, 285 studies were chosen for detailed evaluation because they were considered as having a relevant type of citation. A total of 102 unique abstracts were excluded as these focused on the period after ROSC, not reporting carotid artery or cerebral blood flow data, not focusing on CPR, due to lack of availability of the full text study and not relevant type of article. A total of 183 studies were thus screened for inclusion. A final assessment aimed at obtaining baseline data values before cardiac arrest, identified 133 eligible publications (Fig. 2).

Animal numbers and species, study details, and thoracic compression techniques for the selected studies are reported in Tables 1 and 2 . Overall, 45 studies provided information only on

Table 1 – Carotid artery blood flow during cardiac compression in animals with cardiac arrest.

	Best carotid artery blood flow achieved during resuscitation as a proportion of baseline carotid artery blood flow (%)				
	Number of experimental cohorts	Weighted mean	Weighted SD of the mean	Weighted SE of the mean	p-value
All subjects	75	35.2%	27.7%	3.2%	–
Use of vasopressors					
With vasopressors	23	33.5%	34.4%	7.2%	0.770
Without vasopressors	52	35.9%	24.8%	3.4%	*
Method of resuscitation					
Closed chest massage – manual	17	29.5%	23.4%	5.7%	*
Closed chest massage – manual + assistive device	5	45.8%	35.4%	15.8%	0.423
Closed chest massage – machine	41	33.9%	25.2%	3.9%	0.541
Open chest massage – manual	11	44.0%	35.2%	10.6%	0.267
Open chest massage – manual + assistive device	1	40.3%	–	–	–
Method of measurement					
Ultrasound flowmeter	42	39.8%	27.8%	4.3%	*
Electromagnetic flowmeter	22	34.2%	28.7%	6.1%	0.465
Bubble flowmeter	8	18.0%	11.3%	4.0%	0.001
Other	3	30.8%	28.4%	16.4%	0.701
Pre-arrest fluid infusion					
With infusion	19	30.3%	13.2%	3.0%	*
Without infusion	33	33.8%	26.8%	4.7%	0.941
Unknown	23	42.6%	37.4%	7.8%	0.162
Publication date					
1986 or earlier	30	30.4%	27.8%	5.1%	*
After 1986	45	39.2%	27.0%	4.0%	0.188
Animals					
Dog	30	30.0%	27.4%	5.0%	–
No use of vasopressor	7	47.5%	44.2%	16.7%	0.056
No use of vasopressor	23	25.3%	17.7%	3.7%	*
Pig	27	46.8%	31.0%	6.9%	.
Use of vasopressor	13	19.2%	6.2%	1.7%	0.0002
No use of vasopressor	25	48.0%	26.3%	5.2%	*
Piglet	3	30.6%	20.8%	12.0%	–
Newborn piglet	1	110%	–	–	–
Baboon	1	36.3%	–	–	–
Newborn lamb	2	19.2%	6.8%	4.8%	–

– = not applicable; * = other subgroups compared with this group.

Table 2 – Cerebral blood flow during cardiac compression in animals with cardiac arrest.

	Best cerebral blood flow achieved during resuscitation as a proportion of baseline cerebral blood flow (%)				
	Number of experimental cohorts	Weighted mean	Weighted SD of the mean	Weighted SE of the mean	p-value
All subjects	95	66.5%	48.5%	5.0%	–
Use of vasopressors					
With vasopressors	65	74.4%	51.4%	6.4%	0.007
Without vasopressors	30	49.0%	35.7%	6.5%	*
Method of resuscitation					
Closed chest massage – manual	20	59.2%	49.0%	11.0%	*
Closed chest massage – manual + assist device	6	66.9%	37.1%	15.2%	0.709
Closed chest massage – machine	52	69.5%	52.4%	7.3%	0.449
Closed chest massage – unclear	3	49.1%	11.4%	6.6%	0.480
Open chest massage – manual	12	64.1%	38.9%	11.2%	0.765
Open chest massage – machine	2	96.5%	4.5%	3.2%	0.007
Method of measurement					
Microspheres	59	73.2%	57.8%	7.5%	*
Laser Doppler flowmeter	19	59.4%	17.7%	4.1%	0.115
Other/unknown	17	49.5%	36.7%	8.9%	0.053
Pre-arrest interventions					
No fluid infusion & no drugs	15	48.1%	38.5%	9.9%	*
Fluid infusion	20	77.2%	38.8%	9.4%	0.049
Drug with no haemodynamic effects	6	39.3%	15.3%	6.3%	0.067
Adrenaline	2	97.0%	18.2%	12.9%	0.163
Hypotensive drug	2	63.0%	2.7%	1.9%	0.180
Unknown	53	71.5%	56.1%	7.7%	0.078
Publication date					
1995 or earlier	45	61.0%	54.5%	8.1%	*
After 1995	50	70.2%	43.4%	6.1%	0.372
Animals					
Dog	26	70.2%	65.8%	12.9%	–
Use of vasopressor	15	86.7%	76.7%	19.8%	0.178
No use of vasopressor	11	51.0%	43.0%	13.0%	*
Pig	47	70.2%	47.1%	6.9%	–
Use of vasopressor	36	72.7%	48.6%	8.1%	0.090
No use of vasopressor	17	51.2%	33.0%	8.8%	*
Piglet	15	67.1%	29.6%	8.2%	–
Use of vasopressor	11	74.7%	28.6%	8.6%	0.074
No use of vasopressor	4	45.5%	11.9%	5.9%	*
Rat	2	38.3%	23.8%	16.8%	–
Cat	1	67.0%	–	–	–
Rabbit	1	28.0%	–	–	–

– = not applicable; * = other subgroups compared with this group.

CABF; 77 only on CBF, and 11 studies on both flows. The total number of publications exploring the use of vasopressor during CPR was 70; the effect of open thoracic compression was investigated in 23 studies, and mechanical chest compression was examined in 80 studies. Pigs, dogs and piglets were employed in the majority of the experiments. Rats, rabbits, cats, lambs and baboons contributed only 4%.

Carotid artery blood flow

Overall, the weighted mean point estimate for best CABF during CPR, as a proportion of baseline CABF, was 35.2% (Table 1). However, variability was marked, with a weighted 95% confidence interval (CI) between 28.9% and 41.5%. Moreover, bubble flowmeter measurements reported a significantly different CABF compared with ultrasound flowmeter technology (Table 1). In pigs, a higher CABF

was seen without vasopressors, while in dogs, vasopressors were associated with a non-significant increase in CABF (Table 1). CABF using open thoracic compression and different compression devices were not significantly different (Table 1).

Cerebral blood flow

The highest mean CBF achieved during CPR was 66.5% of baseline values. As seen with CABF, the level of CBF was highly variable with a weighted 95% CI between 55.5% and 77.5%. Overall, vasopressor therapy was associated with higher CBF values as a percentage of baseline (74.4% with vasopressors vs. 49.0% with no vasopressors), but this only occurred in pigs not dogs (Table 2). Fluid infusion before cardiac arrest was also associated with increased CBF values (Table 2). Machine assisted open chest thoracic compression

improved CBF, but no other permutations of open or closed chest with different compression techniques affected CBF (Table 2).

Carotid artery blood flow vs. cerebral blood flow

Across the 11 studies (and 12 comparisons), including a simultaneous measurement of the best CABF and best CBF during CPR as a proportion of baseline, the CABF/CBF ratio was found to be between 0 and 1 in eight studies and greater than 1 in three studies (Table 3), with a median value of 0.67 and a range from 0.21 to 1.96.

Discussion

Key findings

We conducted a systematic review of the experimental literature on CPR and identified experimental studies reporting data on carotid artery blood flow (CABF) and/or cerebral blood flow (CBF) as a percentage of baseline values during CPR. Such studies showed that, during cardiac compression, CABF appears to decrease by two thirds of baseline while CBF appears to decrease by one third. However, results were affected by ancillary interventions and measurement methods, variability was marked and, in experiments measuring CABF and CBF simultaneously, ratios achieved conflicting and physiologically implausible values.

Comparison with previous studies

To our knowledge this is the first systematic review of the literature of carotid artery blood flow and cerebral blood flow measurements during CPR in experimental studies. In humans, where the carotid circulation is believed to provide most of the CBF,[16] very low levels of CBF were measured by C14-iodoantipyrine during CPR in 6 patients who were unsuccessfully resuscitated.[17] Another recent prospective cohort study estimated CABF in humans during CPR, using ultrasound Doppler technology.[18] They demonstrate a peak systolic velocity in the common carotid artery during CPR similar to healthy subjects. However, increased velocity may reflect vasoconstriction

and cannot be used to accurately estimate blood flow. Moreover, in humans, close to 80% of cerebral perfusion comes from the anterior circulation implying that CABF should, on average, deliver a similar percentage of CBF and could never logically exceed CBF.[16] However, in animal experiments where CABF and CBF were simultaneously measured, mean CABF was almost half of mean global CBF and the ratios of CABF to CBF varied from 0.21 to 1.96. Such values appear physiologically impossible and raise concerns about the accuracy of CABF and CBF measurement techniques in the experimental setting.

Implications of study findings

Our findings imply that there may be dissociation in the effect of cardiac compression on CABF compared to CBF. Moreover, they imply that open thoracic compression without mechanical assistance may not deliver higher CABF or CBF compared to closed chest thoracic compression. They also imply that the effects of ancillary interventions, such as vasopressors, are variable according to the animal model used. Finally, the fact that ratios of CABF to CBF obtained from simultaneous measurements range outside of physiologically logical or possible estimates implies that the reliability of both CABF and CBF measurements during experimental cardiac arrest is low.

Strengths and limitations

This study has several strengths. To our knowledge, it is the first to systematically review the best CABF and CBF recorded during experimental CPR. We analysed the physiological impact of CPR on CABF and CBF in different animal species, using multiple methods of CPR. Our wide search criteria, considering three separate sources and hand searching references decreased the risk of inclusion bias and made it unlikely that relevant studies would have been missed.

Our study has some limitations. Our final analysis was affected by the limited reproducibility and robustness in CBF and CABF data. We extended our search to a 69 year period, and it was possible that the oldest studies influenced our results with more unreliable methods of measurement. However, we took into

Table 3 – Studies reporting both Carotid Artery Blood Flow (CABF) and Cerebral Blood Flow (CBF) during cardiac compression in animals with cardiac arrest Gap between cardiac arrest and start of cardiac compressions.

	CABF/CBF	CABF %	CBF %	Time gap[*]	Chest massage
Gedeborg et al. 2000	0.21	13.8	65	10 min	Open
Suzuki et al. 1985	1.61	66.6	41.3	Unknown	Open
Arai et al. 1984	1.96	131	67	Unknown	Open
Arai et al. 1984	1.74	33	19	Unknown	Closed
Sunde et al. 1998	0.40	24.8	62.7	0 min	Closed
Ristagno et al. 2007	0.52	19	36.7	0 min	Closed
Ristagno et al. 2009	0.27	16	60	2 min	Closed
Langhelle et al. 2002	0.63	38.5	61	0 min	Closed
Luce et al. 1983	0.70	23.1	32.8	2 min	Closed
Debaty et al. 2015	1.75	61.5	35.2	1.5 min	Closed
Lewis et al. 1994	0.55	17	31	0 min	Closed
Steinberg et al. 2018	0.72	43	60	Unknown	Closed
Median value with range in brackets	0.67 (0.21–1.96)	28.9 (16–66.6)	50.7 (19–65)	n/a	n/a

Details of references are presented in the appendix.
[*] Gap between cardiac arrest and start of cardiac compressions.

consideration this bias by dividing studies according publication date and we did not demonstrate any major effect. We did not account for the specific anatomical region where the blood flow was measured during CPR. Considering CABF, we could not accurately distinguish whether the data was from the common or internal carotid artery. Similarly for CBF, the available data did not allow us to distinguish total brain from supra-tentorial brain, left or right hemisphere or different cortical regions (occipital, parietal and frontal). However, such deficiencies further highlight the limited quality of experimental data.

Conclusions

Animal experimentation shows that, during cardiac compression, CABF appears to decrease to one third of baseline while CBF appears to decrease to two thirds of baseline. However, results are variably affected by ancillary interventions and measurement methods, overall variability is marked and, in experiments measuring CABF and CBF simultaneously, ratios achieve physiologically impossible values. Our findings suggest that current estimates of CABF and CBF during experimental cardiac arrest are of limited accuracy. They imply the need to add multimodal forms of cerebral perfusion and/or oxygenation assessment (e.g. Laser Doppler flowmetry, invasive tissue oximetry, near infrared spectroscopy, magnetic resonance arterial spin labelling) to future experimental work in this field.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.016.

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