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Impact of the route of adrenaline administration in patients suffering from out-of-hospital cardiac arrest on 30-day survival with good neurological outcome (ETIVIO study)

Dissertation

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Zusammenfassung

Nationale und internationale Leitlinien zur kardiopulmonalen Reanimation enthalten spezifische Empfehlungen bezüglich des Applikationswegs für Notfallmedikamente. Trotz regelmäßiger Aktualisierung der Empfehlungen gibt es weiterhin nur geringe Evidenz zur möglichen Überlegenheit einer der verfügbaren Applikationsformen. In der vorliegenden Studie soll daher die Frage nach dem Einfluss von intravenöser (IV), intraossärer (IO) und endotrachealer (ET) Adrenalingabe unter Reanimation bei prähospitalem Herz-Kreislauf-Stillstand auf das klinische Behandlungsergebnis untersucht werden.

Hierzu wurden retrospektiv alle 212.228 Datensätze von prähospitalem Herz-Kreislauf-Stillstand im Zeitraum 1989 bis 2020 aus dem Deutschen Reanimationsregister ausgewertet. Die Einschlusskriterien für die statistische Analyse waren: Herz-Kreislauf-Stillstand, Adrenalingabe und prähospitale Reanimation. Ausgeschlossen wurden Patienten < 18 Jahren, Trauma oder Hämorrhagie als vermutete Ursachen und inkomplette Datensätze. Als klinischer Endpunkt für die verbleibenden 37.106 Datensätze wurde die Krankenhausentlassung ohne relevantes neurologisches Defizit (gemäß Cerebral Performance Category 1 oder 2) gewählt. Die Quantifizierung der statistischen Effekte erfolgte mittels Pair-Matching und durch binäre logistische Regressionsanalyse, jeweils für vier isolierte oder kombinierte Applikationsformen: IV, IO, IO+IV, ET+IV.

Nach Pair-Matching konnten bessere Ergebnisse in der IV-Gruppe (n=2.416) im Vergleich zur IO-Gruppe (n=1.208) [Odds-Ratio (OR): 2,43, 95% Konfidenz-Intervall (KI): 1,54–3,84, p<0,01] nachgewiesen werden. Ebenso zeigte sich IV (n=8.706) gegenüber IO+IV (n=4.353) überlegen (OR: 1,33, 95% KI: 1,12–1,59, p<0,01). Im Gegensatz dazu konnte kein signifikanter Unterschied zwischen IV (n=532) und ET+IV (n=266) demonstriert werden (OR: 1,26, 95% KI: 0,55–2,90, p=0,59). Die logistische Regressionsanalyse erbrachte den Nachweis hiermit übereinstimmender, hoch signifikanter Effekte der Applikationsform auf den klinischen Endpunkt (χ^2=67,744(3), p<0,001) zugunsten der IV- im Vergleich zur IO-Gruppe [Regressionskoeffizient (r.k.)=−0,766, p=0,001] und ohne Unterschied zwischen IV und ET+IV (r.k.=0,117, p=0,770).

Hinsichtlich des restrospektiven Studiendesigns bezüglich des Kausalitätsnachweises limitiert, bekräftigt die vorliegende Registeranalyse den Stellenwert des IV-Zugangs für die Adrenalingabe im Rahmen der prähospitalen Reanimation.

Summary

National and international guidelines for cardiopulmonary resuscitation (CPR) also address recommendations regarding the route of drug administration. In spite of several updates of these recommendations during the past decades, evidence for the potential superiority of one of the available routes remains scarce. The present investigation therefore examines the impact on clinical outcome of intravenous (IV), intraosseous (IO) and endotracheal (ET) adrenaline administration during CPR in out-of-hospital cardiac arrest (OHCA).

This retrospective study was based on all 212,228 data sets on OHCA within the German Resuscitation Registry (GRR) between 1989 and 2020. The inclusion criteria for statistical analysis were: cardiac arrest, adrenaline administration, and out-of-hospital CPR. Exclusion criteria were: patients < 18 years, trauma or hemorrhage as presumed cause for cardiac arrest, and incomplete data sets. As clinical endpoint for the included 37,106 OHCA cases, hospital discharge with good neurological outcome [according to cerebral performance category (CPC) 1 or 2] was set. Statistical effects were assessed via pair matching and via binary logistic regression analysis for four isolated or combined modes of drug administration: IV, IO, IO+IV, ET+IV.

By matched-pair analysis, better outcomes were shown for the IV group (n=2,416) compared to IO (n=1,208) [odds ratio (OR): 2.43, 95% confidence interval (CI): 1.54–3.84, p<0.01)]. IV (n=8,706) also proofed superior to IO+IV (n=4,353) (OR: 1.33, 95% CI: 1.12–1.59, p<0.01). By contrast, no significant difference could be demonstrated between IV (n=532) and ET+IV (n=266) (OR: 1.26, 95% CI: 0.55–2.90, p=0.59). Logistic regression analysis yielded concurrent, highly significant effects by mode of drug application on clinical outcome (χ^2 = 67.744(3), p<0.001), again with superiority of IV vs. IO [regression coefficient (r.c.)=−0.766, p=0.001] and without difference between IV and ET+IV (r.c.=0.117, p=0.770).

Due to the retrospective study design, a proof of causality was not feasible in principle. Nonetheless, the present registry analysis – covering a time frame of 31 years – highlights the significance of IV access for adrenaline administration during out-of-hospital CPR. While the IO application of adrenaline might be less effective, the obsolete endotracheal route could re-gain new relevance as a potential alternative, when IV is not achievable in OHCA.

List of Abbreviations

AED	automated external defibrillator
ALS	advanced life support
BLS	basic life support
CI	confidence interval
CPC	cerebral performance category
CPR	cardiopulmonary resuscitation
ECMO	extracorporeal membrane oxygenation
eCPR	extracorporeal cardiopulmonary resuscitation
EMS	emergency medical services
ERC	European Resuscitation Council
ET	endotracheal
EuReCa	European Registry of Cardiac Arrest
GRR	German Resuscitation Registry
IO	intraosseous
IV	intravenous
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
RACA	ROSC after cardiac arrest
r.c.	regression coefficient
ROSC	return of spontaneous circulation
vaECMO	veno-arterial extracorporeal membrane oxygenation

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1 Introduction

1.1 What do we know about out-of-hospital cardiac arrest?

All untreated severe diseases eventually lead to cardiac arrest. Even with access to a fully staffed and equipped system in a modern prehospital emergency medical service or an emergency department, the diagnosis and treatment of reversible etiologies during cardiac arrest proofs to be highly challenging. A breakdown of circulation immediately sets off systemic ischemia. The time frame to revert this state in order to prevent permanent organ failure – particularly hypoxic-ischemic brain injury – is limited to only a few minutes.

It comes as no surprise that both morbidity and mortality of out-of-hospital cardiac arrest (OHCA) remain strikingly high, given the extreme time constraints and the truncated diagnostic and therapeutic arsenal available to first responders and emergency medical services (EMS) teams.

Across 27 countries in Europe, OHCA has an incidence of 81 cases per 100,000 inhabitants per year [1]. Out-of-hospital cardiopulmonary resuscitation (CPR) is started in around 49 per 100,000 inhabitants per year, with numbers varying across countries to e.g. 77.6 per 100,000 people years in Germany (see Fig. 1). The European Registry of Cardiac Arrest (EuReCa) ONE trial [1] reported for those cases where resuscitation was attempted, a staggering mortality of 90 % after 30 days. The follow-up trial EuReCa TWO, extrapolating from a three-month time span, recorded even graver statistics with a rate of return of spontaneous circulation (ROSC) in 33 % of cases and 30-day survival at only 8 % [2]. Only slightly higher recovery rates have been reported for Germany in 2022 [3] with ROSC in 42.1 % and 30-day survival of 10.7 % (see Fig. 1).

Clearly, every potential lead should be pursued to optimize the treatment outcomes for this most vulnerable patient population. A growing body of evidence concerning interventions, treatment, and diagnostics during basic and advanced life support is reviewed continuously by the European Resuscitation Council (ERC) and condensed into international guidelines, with the current iterations having been published in 2021 [4,5].

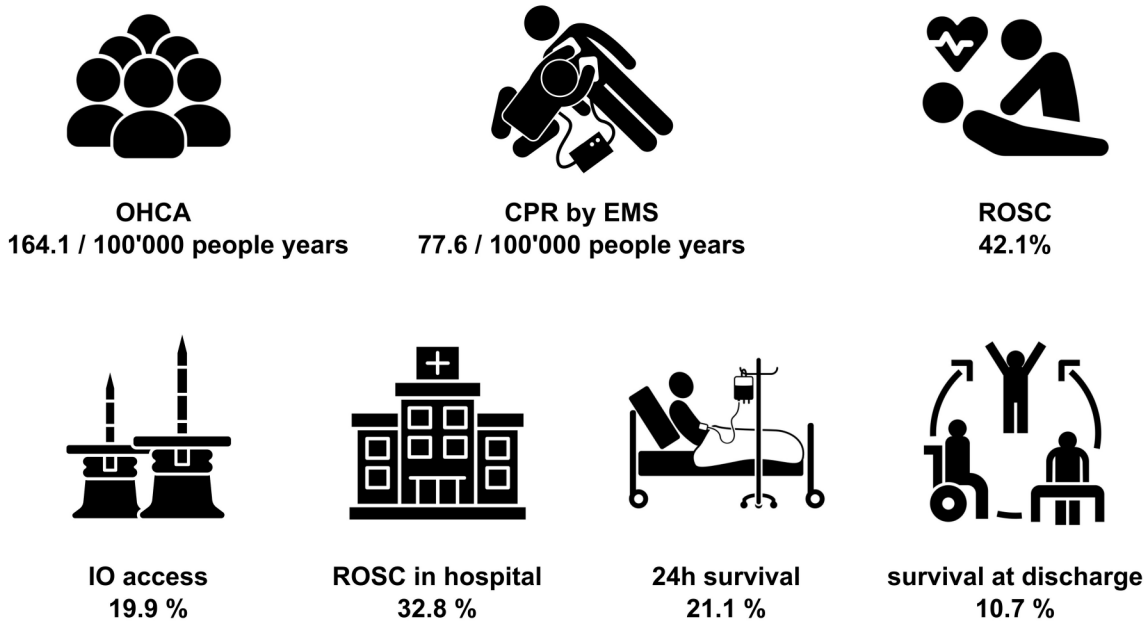

Fig. 1: OHCA in Germany 2022. OHCA related incidence rates and descriptive statistics as reported by the German Resuscitation Council for Germany for the year 2022 [3]. OHCA: out-of-hospital cardiac arrest, 100'000 people years: per 100'000 inhabitants per year, CPR: cardiopulmonary resuscitation, EMS: emergency medical services, ROSC: return of spontaneous circulation, IO: intraosseous, 24h survival: survival at least to 24 hours after hospital admission. With use of illustrations from Noun Project (CC BY 3.0, thenounproject.com).

1.2 Basic life support

Basic life support (BLS) is concerned with the immediate response to out-of-hospital cardiac arrest by bystanders and first responders, typically non-medical personnel without specialized training or equipment. As outlined in Fig. 2, the focus of BLS therefore cannot be the differential diagnosis of underlying causes or the provision of targeted treatment. BLS rather aims at the immediate activation of EMS via phone or cellphone and at the support of minimal perfusion and oxygenation levels to keep permanent organ damage at bay until the arrival of the EMS team.

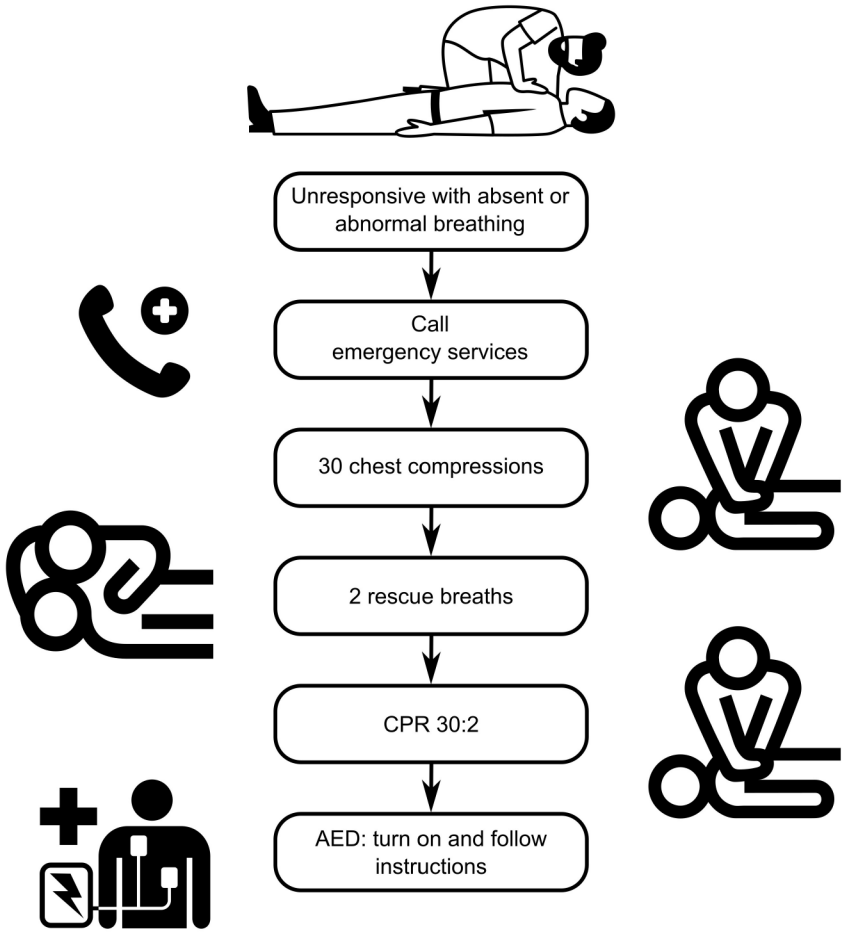

Fig. 2: Basic life support algorithm according to 2021 ERC guidelines. After calling for emergency services, CPR is initiated, prioritizing chest compressions. When responders have been trained accordingly, CPR is continued in a 30:2 rhythm with 30 chest compressions and 2 rescue breaths until an AED or EMS arrive. When available, the AED is turned on and CPR is continued as per AED instructions. CPR: cardiopulmonary resuscitation, AED: automated external defibrillator. Adapted from [4] with use of illustrations from Noun Project (CC BY 3.0, thenounproject.com).

Lacking technical training and equipment, BLS as defined by the European Resuscitation Council [4] prioritizes manual chest compressions to maintain life saving circulation even without treatment of underlying causes. The current guidelines reserve the recommendation for the administration of mouth-to-mouth rescue breaths to specially trained first-responders. If applicable, optional additional rescue breaths are to be provided in a 30:2 alternate rhythm with 30 chest compressions and 2 rescue breaths.

Effective chest compressions without rescue breaths are considered to be a safer bridge to ALS than rescue breaths without chest compressions or rescue breaths with long interruptions of compressions. Insufficient chest compressions prevent effective perfusion pressures to be built and maintained. Indirectly on the other hand, chest compressions lead to a minimal amount of lung ventilation. But without circulation, even fully oxygenated lungs could not provide tissue oxygenation. Hence the emphasis on chest compression over rescue breaths.

One exception from the general absence of technical equipment in BLS are the increasingly available automated external defibrillators (AED). AEDs allow untrained responders to provide electric defibrillation to patients, when the AED is able to detect a cardiac rhythm treatable by defibrillation, namely ventricular fibrillation and pulseless ventricular tachycardia.

AEDs are becoming more and more on hand in public places and buildings due to government and NGO initiatives to provide nationwide coverage. Currently, public AEDs with either 24/7 accessibility or access limited to various opening hours have been installed in a wide range of municipal facilities like town halls, public swimming pools, train stations, fire stations, schools, universities, public places etc., and private businesses like physician practices, banks, gas stations, hotels, supermarkets, factories, corporations etc. Indeed, a 2020 online survey covering 32 countries in Europe [6] reported the availability of online maps in 25 European countries, indicating that the identification and application of the nearest AED will be increasingly feasible for providers of BLS in public spaces.

Nonetheless, even when incorporating the use of AEDs more routinely into first responder provided BLS and even though every minute of perfusion and oxygenation provided during cardiac arrest is invaluable for saving a patient’s life, BLS is not capable of identifying and treating reversible causes of cardiac arrest.

The purpose of BLS within the ERC advised *chain of survival* is to secure a link to advanced life support (ALS).

1.3 Advanced life support

ALS is provided by professional EMS personnel and requires specialized training. The current ERC guidelines for ALS define the core basis of all ALS interventions as “high-quality chest compressions with minimal interruption, airway management and ventilation, venous access, administration of adrenaline and the identification and treatment of reversible causes” [5].

Accordingly, BLS is not simply replaced by ALS techniques. Upon arrival on site, professional EMS teams rather build upon ongoing BLS. If CPR has not been initiated by bystanders, professional teams initially provide the same basic CPR as recommended for BLS.

The sequence of measures to be taken by EMS personnel are prioritized and structured by the ALS algorithm, as illustrated in Fig. 3.

The advanced add-on within the ALS toolbox consists firstly of additional airway management to achieve both oxygenation and decarboxylation. Additionally, ALS includes venous access for both pharmacotherapy and fluid therapy. It includes manual defibrillation, specialized monitoring of vital parameters like waveform capnography, as well as focused diagnostics to detect underlying disease.

Point-of-care ultrasound can be utilized to enhance diagnostic sensitivity and specificity, when sufficiently trained users and appropriate equipment are available on site. The 2021 ALS guidelines recognize the risk for distraction inherent in operating technically and intellectually demanding devices like ultrasound during CPR. Users are strongly advised not to interrupt or delay essential actions like CPR and airway management in favor of optimizing ultrasound imaging.

There are various mnemonics for the most important reversible causes of cardiac arrest. The structure provided by the ERC for systematic evaluation, confirmation or rule-out of causes during ALS is that of grouping differential diagnoses by the initials “H” and “T”.

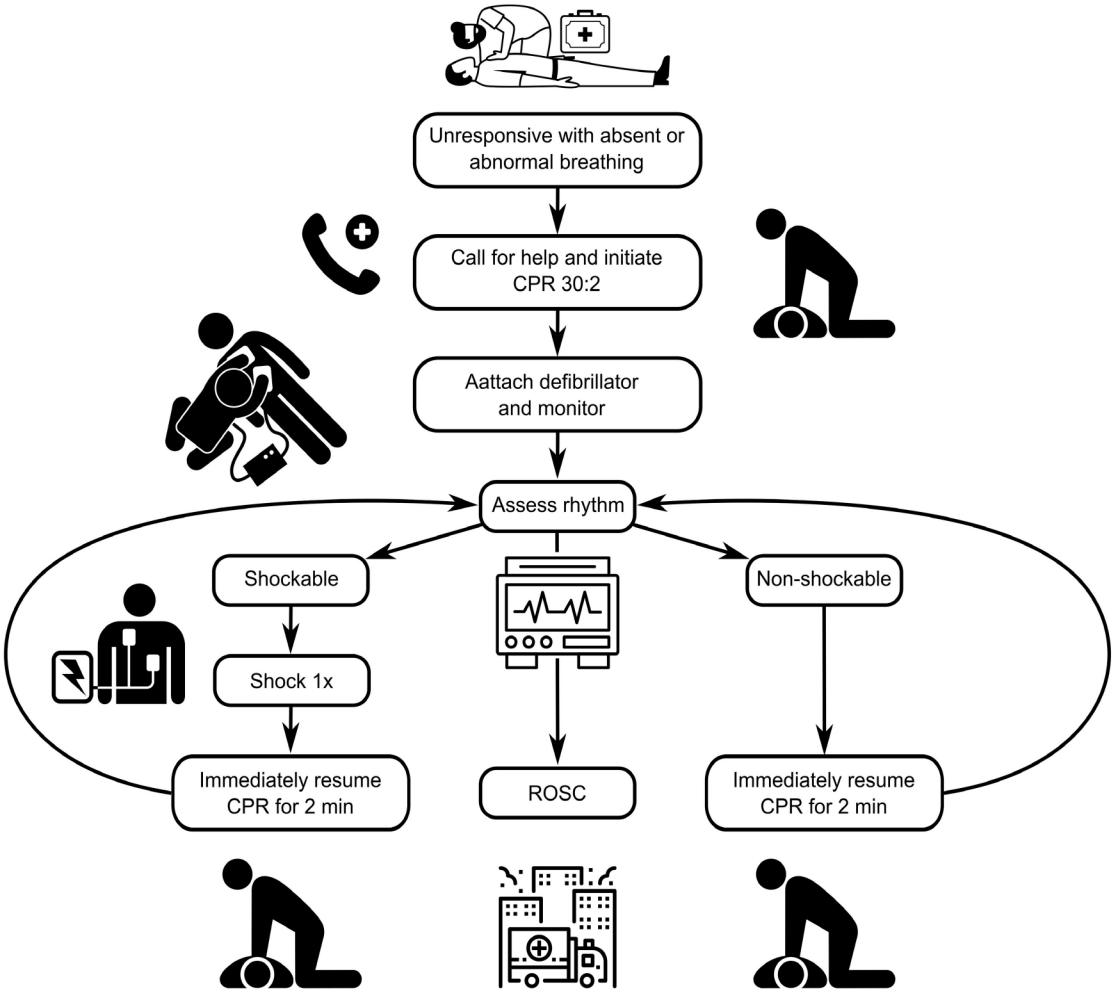

Fig. 3: Advanced life support algorithm according to 2021 ERC guidelines. After calling for backup, initiating CPR and installing a monitor/defibrillator, the algorithm centers around recurring assessments of heart rhythm every two minutes. Until ROSC or termination, CPR is continued with or without defibrillation, depending on shockability. Beyond the measures taken sequentially according to the priorities structured within the ALS algorithm, additional interventions are to be considered and implemented as soon as feasible without interrupting the ongoing ALS resuscitation attempt: application of oxygen, capnography, advanced airway, intravenous or intraosseous access, administration of adrenaline every 3–5 min, administration of amiodarone after third and fifth defibrillation, and treatment of reversible causes. CPR: cardiopulmonary resuscitation, ROSC: return of spontanous circulation. Adapted from [5] with use of illustrations from Noun Project (CC BY 3.0, thenounproject.com).

The four pathologies sharing the initial letter H are: hypoxia, hypovolemia, hypo- or hyperkalemia (and other metabolic disorders), hypo- or hyperthermia. The four T-diagnoses in turn are: thromboembolic events (particularly with respect to coronary or pulmonary arteries), tension pneumothorax, cardiac tamponade, and toxins (as shorthand for general intoxications) [5].

Depending on the determination of potentially reversible, underlying causes of cardiac arrest – with explicit consideration of the four Hs and the four Ts – additional treatments and interventions may be incorporated into ALS on a case-by-case basis.

Notably, these are thrombolytic therapy in case of massive pulmonary embolism and coronary angiography with percutaneous coronary intervention in case of occlusive myocardial infarction. In order to enable prolonged CPR for transport or intervention, mechanical chest compression devices may be incorporated. After individual risk-benefit-assessment, extracorporeal membrane oxygenation (ECMO) can provide effective substitution of lung function as a bridging technique to gain additional time for definite treatment of underlying pathologies. These specialized interventions will be discussed below.

1.4 Special interventions and pharmacotherapy

For prehospital transport under CPR, mechanical chest compression devices may be employed. Safety of ALS providers in moving vehicles and spatial restrictions in most EMS helicopters usually prohibit manual chest compressions during transport, hence requiring a mechanical solution.

For prolonged cardiac arrest in an ALS setting, extracorporeal CPR (eCPR) may be an option, allowing for temporary substitution of both heart and lung function. The venoarterial extracorporeal membrane oxygenation machines (vaECMO) used for eCPR are similar to heart-lung machines. Heart-lung machines are more widely known for their application during cardiac surgery.

By tapping into the circulation with large-bore catheters, blood flow from central veins can be redirected into the vaECMO apparatus. Via internal membranes

permeable by oxygen and carbon dioxide, the blood is oxygenated, decarboxylized and then re-introduced into the central arterial vasculature under sufficient pressures to maintain organ perfusion. With vaECMO, considerable additional time can be gained for the definite treatment of underlying pathologies by interventions like pulmonary thrombectomy, percutaneous coronary intervention, or controlled re-warming from hypothermia, by surgery or by various targeted drug treatments.

Generally, pharmacotherapy indeed represents another hallmark, setting ALS apart from BLS. As such, the ERC guidelines provide recommendations for antiarrhythmic drugs, namely amiodarone and lidocaine for shockable rhythms refractory to defibrillation. Independent of duration of inter-shock intervals and independent of patient status or treatments between shocks, after the third defibrillation of ventricular fibrillation or pulseless ventricular tachycardia, 300 mg of intravenous amiodarone are recommended, followed potentially by another 150 mg after two additional defibrillation attempts [5]. Lidocaine can be used alternatively in a lower dosage of 100 mg after the third and 50 mg after the fifth defibrillation.

Additional recommendations are given for peri-arrest arrhythmias, namely electrical cardioversion, amiodarone or procainamide for tachycardia and atropine, isoprenaline or adrenaline among others for various forms of instable bradycardia. Generally pharmacotherapy of bradycardia can be augmented electrically by external or transvenous pacing.

When pulmonary embolism is identified as underlying cause, or when it is suspected with sufficient certainty, and given a favorable individual risk-benefit-assessment, systemic thrombolytic drugs can be administered. Reverting massive embolism by drug action requires substantial time, necessitating at least one hour of continued ALS after the injection of thrombolytics [5]. As mentioned above, where available, interventional thrombectomy under eCPR might be a viable and potentially more effective alternative to thrombolysis.

Another major aspect of ALS is vasopressive medication. Currently, the guidelines recommend an initial rhythmological assessment to determine whether electric defibrillation is indicated. In the case of defibrillation, adrenaline application is

recommended after the third shock. Otherwise, adrenaline should be given immediately.

In fact, the current ERC ALS guidelines list the early administration of adrenaline in non-shockable rhythms as number four of the overall “five top messages” in their 2021 update [5], as shown in Fig. 4:

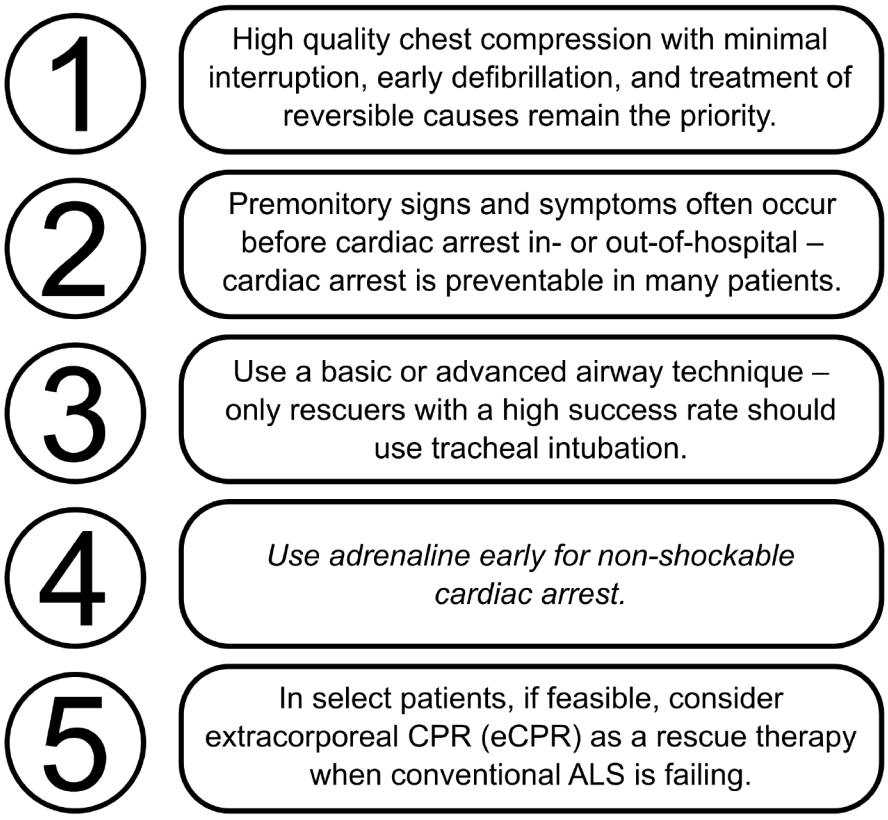

Fig. 4: The five top messages of the 2021 ERC guidelines. eCPR: extracorporeal cardio-pulmonary resuscitation, ALS: advanced life support, ERC: European resuscitation council. Adapted from [5]

Summing up, morbidity of survivors but even mortality remain high in the context of OHCA. While prioritizing chest compressions and, where applicable, defibrillation and the treatment of reversible causes, international guidelines also emphasize the use of vasopressor drugs, namely adrenaline, either as soon as possible or after the third defibrillation attempt.

1.5 Intraosseous venous access

No matter the underlying cause, cardiac arrest implies by definition the lack of sufficient circulation for maintaining perfusion of vital organs. Given the poor peripheral perfusion pressure, even under optimal CPR, it is therefore to be expected, that cardiac arrest patients generally present one of the most challenging context for venous access.

Under the conditions of out-of-hospital cardiac arrest, in an unknown and potentially confined work environment and under acutely heightened time pressure, the difficulty level can only increase. From this follows the predictable and recurring failure in initial IV access attempts in OHCA patients, even by experienced emergency medical staff.

As one alternative to intravenous access, devices to drill or puncture intraosseous access have been developed and introduced into the market almost two decades ago. The subcortical intraosseous space of large tubular bones, otherwise occupied by bone marrow, is arterially well perfused and drains directly into the venous system. Taping into this intraosseous space with a needle thus provides almost immediate access into the central circulation. The intraosseous space can be conceptualized essentially as a non-collapsible vein.

As standard access points for intraosseous access, the tibia, the head of the humerus and – for use in military contexts where simultaneous injuries to all four limbs are more likely – the sternum have been identified. In civilian emergency care, only tibial and humeral insertion points are utilized.

Intact osseous anatomy is necessary at the site of insertion, i.e. no prosthetic bone implant may block the intraosseous space. Likewise, no proximal fracture or laceration may impede blood flow from the intraosseous space to reach central circulation. Both conditions are met in at least one of the four possible access sites (left and right head of humerus, left and right tibia) in the overwhelming majority of civilian OHCA cases.

Since their introduction to the markets, IO devices of various vendors have accordingly found broad acceptance and wide-spread availability. Fig. 5 shows a

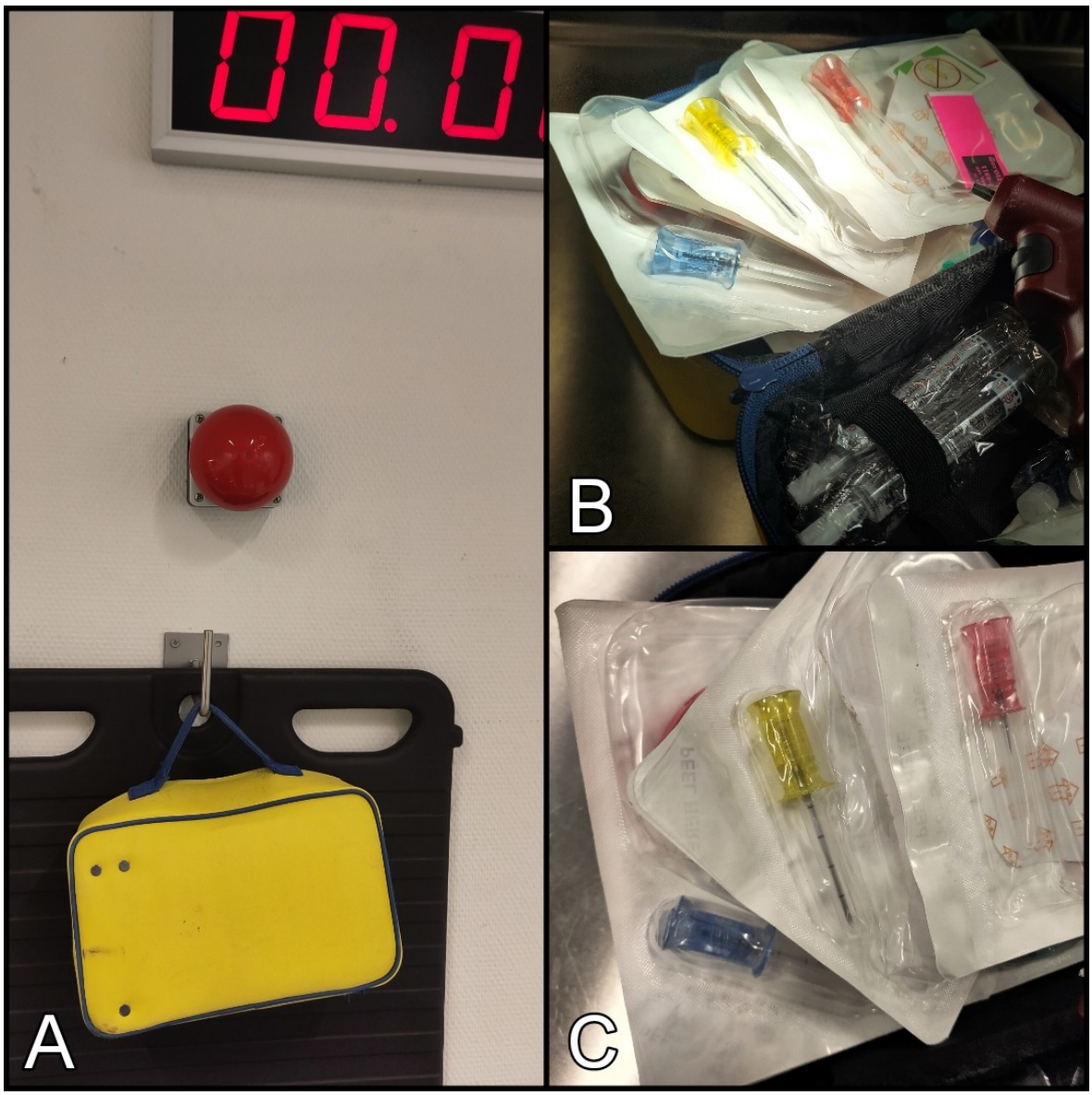

Fig. 5: Intraosseous access device. *Panel A:* Storage of IO device in readily available emergency bag (yellow). *Panel B:* Inside view of emergency bag with battery driven power drill (right), intraosseous needles of varying sizes (above) and sterile solution for flushing (below). *Panel C:* Close-up view of three size options for intraosseous needles: small for children from 3 to 39 kg (pink), medium for adults above 40 kg (blue), large for overweight or muscular adults (yellow). Depicted sample IO device: Arrow EZ-IO System, Teleflex Inc., USA.

real-life example of an exemplary IO device (EZ-IO system by Teleflex Inc.) and how its storage can be achieved readily at hand for emergency use where needed.

As reported by the GRR (see Fig. 1), in 2022 one in five OHCA patients in Germany has been treated using IO access for drug and fluid therapy.

Despite many years of practical experience and a broad every-day application in clinical routine, data validating intraosseous treatment as non-inferior or equivalent to the intravenous route, especially for OHCA, remain scarce.

1.6 What don't we know about pharmacotherapy during CPR?

While adrenaline has been consistently one of the few available pharmacological treatment options during advanced life support in out-of-hospital cardiac arrest, the ERC recommendations concerning the route of drug administration have changed over the past decades. While the intravenous (IV) application has been the gold standard ever since the pharmacological availability of adrenaline, the 2000 guidelines [7] still recommended an endotracheal (ET) administration of adrenaline, whenever intravenous access could not be established in a timely fashion.

The reasoning was the presumed quick absorption of adrenaline into the pulmonary circulation when applied to tracheal and bronchial epithelium. Accessing the bronchial system in turn could be achieved with relative ease through the endotracheal tube in cases, where the airway would be secured before successful placement of a venous catheter. To account for reduced bioavailability after bronchial absorption, a two to three times higher dose was recommended for ET applications, namely 1 mg IV and 2–3 mg ET [7,8].

After intraosseous cannulation devices had been approved for medical use in patients and made available broadly, the 2005 guidelines [8] were updated with respect to the recommendations on alternate drug routes (see Fig. 6). When intravenous catheterization was not feasible, intraosseous access (IO) was now recommended as primary alternative, while endotracheal application of adrenaline still remained optional.

From 2010 on, the ERC guidelines have ceased to recommend ET drug application [9]. Uncertainty about correct ET dosing due to lacking pharmacokinetic studies led to the decision to abandon the heuristic approach of giving "two to three times" the intravenous dose.

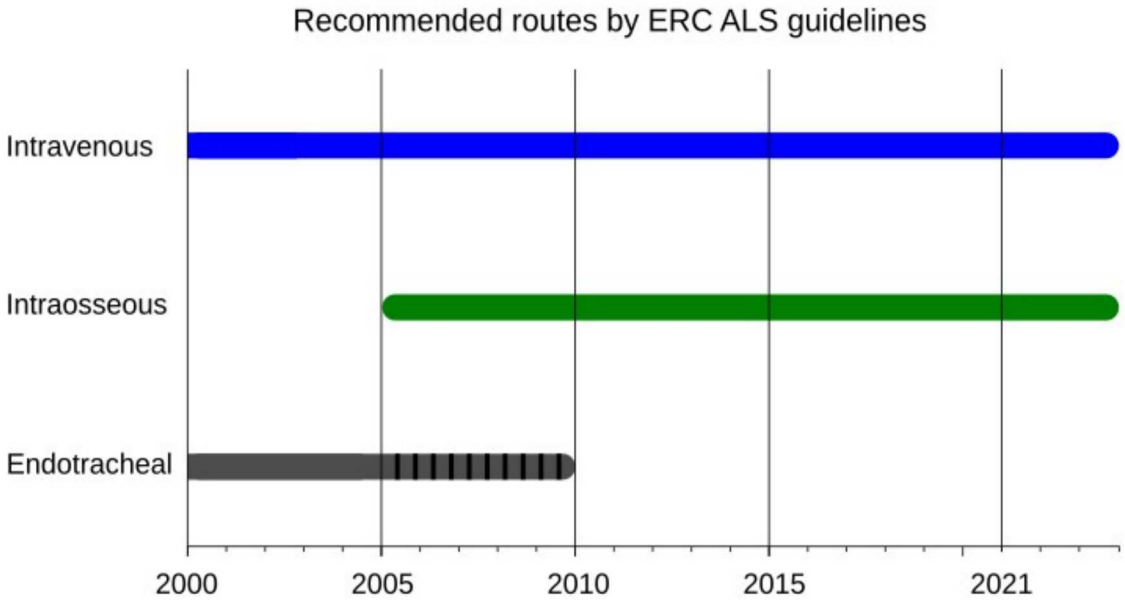

Fig. 6: ERC recommendations for drug administration during ALS from 2000 till 2024. Blue: intravenous access (gold standard throughout). Green: intraosseous access (primary alternative since 2005). Grey: endotracheal application (primary alternative before 2005, secondary alternative until 2010, not recommended since 2010). ERC: European Resuscitation Council, ALS: advanced life support. Adapted from [10].

Animal studies had raised the concern that inadvertently underdosing adrenaline could have deleterious effects, causing profound hypotension via β-adrenoceptor mediated vasodilation [11]. The endotracheal dose at which the α-adrenergic effects could safely be assumed to outweigh any unintended β-adrenergic impediment to resuscitation was not determined. Instead, the IO access was increasingly considered as a fail-safe route into a non-collapsible vein, that required no modification of existing IV dosage recommendations.

Without new evidence on ET dose-plasma level ratios and overall efficacy of ET adrenaline application in patients undergoing CPR, the ERC did not see cause to further adapt their drug route recommendations in the updates of 2015 [12] and 2021 [5].

Until today, the pharmacokinetics of endotracheal adrenaline in humans remains essentially unknown. Further complicating the matter, both pharmacokinetics and pharmacodynamics are profoundly altered under the extreme hemodynamic,

metabolic and respiratory conditions of cardiac arrest and cardiopulmonary resuscitation.

1.7 Why do we care?

Open questions about an obsolete treatment are not uncommon in the field of evidence based medicine. In fact, the focus of the scientific endeavor arguably should lay primarily on further improvement of current treatment options over abandoned historical approaches.

Yet, the same factors impeding the investigation of resuscitative endotracheal pharmacotherapy also confound the in-depth assessment of the intraosseous route. Ethical as well as logistic limitations prevent an exhaustive, systematic, controlled and randomized study of intraosseous as well as endotracheal medication during OHCA.

IO devices have become broadly available though within the German health care system both in and out-of-hospital and are readily at hand both to physicians and paramedics on German EMS vehicles. National guidelines exist, providing advice on the use of IO access in various emergency settings, also in Germany [13]. IO application has a steep learning curve and can be quickly and safely performed even under pressure in out-of-hospital emergencies [14,15].

IO access has thus been firmly installed as a standard EMS treatment option over the past nearly two decades. Nonetheless, it is still a matter of open debate, whether the conceptualization of the intraosseous space as *non-collapsible vein* is accurate or indeed an oversimplification, missing an essential point of resuscitative physiology. In that case, IV and IO access during OHCA could not in fact be considered as essentially equivalent alternatives with identical dosage requirements, equal efficacy and potentially even safety and speed benefits of the IO access when securing the access in challenging vascular patients. The reason could be that e.g. for fluid therapy during shock or for emergency antagonist therapy during drug over-dose, autonomous circulation and ensuing continuous intraosseous perfusion pressures still exist.

But *in extremo*, in the physiological environment when resuscitative adrenaline therapy comes into play, perfusion pressures plummet to a minimum, maintained only by ongoing chest compressions. Further breakdown results from any delay or interruption. The entire vascular system in turn will likely centralize circulation as much as physically possible in favor of brain, heart and lung perfusion, thereby further decreasing intraosseous blood flow. Under those constraints, intraosseous adrenaline infusion might fail to meet one essential requirement: arrival at the site of action within its very short half-time.

Indeed, a growing body of evidence from Europe [16,17] as well as North America [18–24] hints towards a potential inferiority of intraosseous pharmacotherapy in OHCA – not in terms of speediness or feasibility of access securement, but with respect to the hallmark of medical therapy: the clinical outcome. With respect to OHCA survival, a meaningful measure for clinical outcome is not merely initial return of spontaneous circulation (ROSC) or short-term survival, but survival to hospital discharge or at least 30 days with a good neurological outcome.

If these theoretical considerations bear clinical weight, it should be possible to detect such access type dependent effects of OHCA pharmacotherapy on clinical outcome also within the large database of the German Resuscitation Registry (GRR).

On this conceptual background, this study sets out to retrospectively analyze the body of GRR data from 1989 to 2020. A specific focus is given to potential effects of drug routes on patient outcome as determined by 30-day survival without or with only mild neurological deficit. Shedding light on the unexamined yet already existing evidence will inform the recent debate on optimal trade-offs between time, safety and efficacy of drug routes for adrenaline during resuscitation in OHCA.

Furthermore, an evaluation of the available registry data on endotracheal adrenaline administration, though obsolete and not recommended by international guidelines since 2010, could spark novel interest in further explorations of this formerly accessible backup option.

1.8 The German Resuscitation Registry

The German Resuscitation Registry (GRR) is maintained, organized and financed by the German Society of Anaesthesiology and Intensive Care Medicine [3]. Additional funding comes from membership fees of participating EMS and hospitals. It is the largest comparable database in the German language area with currently 160 EMS providers and 150 hospitals participating across Germany, Austria and Switzerland. Participation is motivated by individualized performance reviews as a basis for continued improvement of quality of care.

For Germany alone, 114 EMS providers reporting to the GRR database represent 32 million of the 83 million inhabitants [3]. In spite of its voluntary participation, the GRR has grown into a representative resource for reanimation science.

Originally formed in 2007, the GRR has been purposefully adhering to the Utstein style, the international reference framework for reporting on out-of-hospital cardiac arrest [25]. This enables international comparability of studies based on GRR data.

After the initial formation, decades worth of decentralized data, previously maintained by various EMS have been manually added into the GRR database, allowing for longitudinal analysis and reaching back as far as 1989.

In its current form, the GRR contains several datasets. For the study of OHCA, two are of particular interest: the prehospital dataset on initial care and the intrahospital dataset on continued care and long-term outcomes [26].

More recently, an additional dataset was added, dealing with the incidence, factors, care and outcomes of intrahospital cardiac arrest. This particular dataset is outside the scope of this analysis.

The prehospital dataset contains 118 variables on descriptive statistics pertaining to OHCA. These include risk factors and assumed underlying causes, as well as interventions and treatments provided by EMS teams. Data on clinical outcomes like ROSC and survival at hospital admission are also reported.

The dataset on the hospital side of care collects data on the initial treatment upon hospital admission as well as follow-up data on 156 variables. This is to document

the progression of treatments, clinical condition over hours and days and eventually long-term outcomes, including neurological outcomes.

Data entries are added in a decentralized fashion by local EMS or hospital representatives. Additional software based checks of data integrity and clinical plausibility enhance the validity of entries [26].

1.9 Study objective and hypothesis

Both the ongoing data-driven evaluation of state-of-the art treatment alternatives, as well as the critical re-appraisal of largely abandoned routes are of immediate interest to emergency care providers who eagerly fight for every incremental ounce of improvement when treating a clinical condition as dire as out-of-hospital cardiac arrest.

Structured in line with the PICO (patients, intervention, comparison, outcome) format [27], the hypothesis can be phrased as follows, explicitly stating the patient population, intervention, comparison and outcome:

> In adult, non-trauma OHCA patients undergoing advanced life support, intravenous compared to intraosseous or endotracheal adrenaline administration leads to substantially different 30-day survival with good neurological outcome.

1.10 Ethics approval

Prior to data acquisition, the scientific paradigm was submitted to the local research ethics committee at Heinrich Heine University. Due to the retrospective design and due to full anonymization of all patient related data, a waiver for consent requirements was granted. Approval was given and the study protocol was registered with protocol number 2020-1018.

Separately, approval was obtained from the scientific advisory council of the GRR, where the study was registered under 2020-02.

2 Published original journal article

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ORIGINAL RESEARCH Open Access

Impact of the route of adrenaline administration in patients suffering from out-of-hospital cardiac arrest on 30-day survival with good neurological outcome (ETIVIO study)

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Abstract

Background Over the past decades, international guidelines for cardiopulmonary resuscitation (CPR) have changed the recommendation for alternative routes for drug administration. Until now, evidence for the substantial superiority of one route with respect to treatment outcome after CPR has been lacking. The present study compares the effects of intravenous (IV), intraosseous (IO) and endotracheal (ET) adrenaline application during CPR in out-of-hospital cardiac arrest (OHCA) on clinical outcomes within the database of the German Resuscitation Registry (GRR).

Methods This registry analysis was based on the GRR cohort of 212,228 OHCA patients between 1989 and 2020. Inclusion criteria were: OHCA, application of adrenaline, and out-of-hospital CPR. Excluded from the study were patients younger than 18 years, those who had trauma or bleeding as suspected causes of cardiac arrest, and incomplete data sets. The clinical endpoint was hospital discharge with good neurological outcome [cerebral performance category (CPC) 1/2]. Four routes of adrenaline administration were compared: IV, IO, IO + IV, ET + IV. Group comparisons were done using matched-pair analysis and binary logistic regression.

Results In matched-pair group comparisons of the primary clinical outcome hospital discharge with CPC 1/2, the IV group (n = 2416) showed better results compared to IO (n = 1208), [odds ratio (OR): 2.43, 95% confidence interval (CI): 1.54–3.84, p < 0.01] and when comparing IV (n = 8706) to IO + IV (n = 4353), [OR: 1.33, 95% CI: 1.12–1.59, p < 0.01]. In contrast, no significant difference was found between IV (n = 532) and ET + IV (n = 266), [OR: 1.26, 95% CI: 0.55–2.90, p = 0.59]. Concurrently, binary logistic regression yielded a highly significant effect of vascular access type ($\chi^2 = 67.744(3)$, p < 0.001) on hospital discharge with CPC1/2, with negative effects for IO (regression coefficient (r.c.) = − 0.766, p = 0.001) and IO + IV (r.c. = − 0.201, p = 0,028) and no significant effect for ET + IV (r.c. = 0.117, p = 0.770) compared to IV.

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Conclusions The GRR data, collected over a period of 31 years, seem to emphasize the relevance of an IV access during out-of-hospital CPR, in the event that adrenaline had to be administered. IO administration of adrenaline might be less effective. ET application, though removed in 2010 from international guidelines, could gain importance as an alternative route again.

Keywords Out-of-hospital cardiac arrest, Adrenaline, Route of drug administration, Intravenous access, Intraosseous access, Endotracheal access

Introduction

Sudden out-of-hospital cardiac arrest (OHCA) is the third leading cause of death in Europe [1]. According to the results of the European Registry of Cardiac Arrest (EuReCa) ONE trial, 30-day survival is at 10% [1]. The three-month EuReCa TWO trial showed for data of 25,171 patients an OHCA incidence of 56 per 100,000 inhabitants, with a return of spontaneous circulation (ROSC) rate of 33% and a hospital discharge rate of 8% [2].

According to the international guidelines for advanced life support (ALS) by the European Resuscitation Council (ERC), the administration of adrenaline (epinephrine) is part of recommended standard actions during cardiopulmonary resuscitation (CPR) for both shockable rhythms (ventricular fibrillation and pulseless ventricular tachycardia) and non-shockable rhythms (asystole and pulseless electrical activity) in the out-of-hospital setting [3].

However, it remains unclear through which route of administration adrenaline seems to be most beneficial for overall survival and clinical outcome after OHCA. The gold standard for adrenaline application is the intravenous (IV) access [3], while the intraosseous (IO) access provides an alternative route. For Germany, a national guideline is available for IO infusion within emergency settings [4]. Therefore, in order to ensure quick drug and fluid resuscitation despite insufficient venous conditions, nearly all out-of-hospital rescue vehicles have been equipped with IO access devices. In 2010, endotracheal administration (ET) was removed from international recommendations.

IO devices have thus been established as effective tools in various emergency settings. However, due to the obvious ethical and practical limitations that come with researching CPR, evidence remains scarce as to the effects of various routes of drug administration during CPR within the particularly demanding setting of OHCA.

Therefore, this study analyzes the available registry data from the German Resuscitation Registry (GRR) to determine whether application routes are associated with effects on clinical outcomes, namely ROSC and survival with good neurological outcome. The results will allow for international comparisons with other physician-based emergency medical systems (EMS). Additionally, the analysis of a currently not recommended route – endotracheal administration – will be provided.

Materials and methods

German resuscitation Registry

This study was designed as a registry analysis of all OHCA compiled in the GRR between 1989 and 2020. The GRR is a prospective registry, maintained by the German Society of Anesthesiology and Intensive Care Medicine. It covers 30 million inhabitants in Germany [5] and 1.2 million inhabitants in Austria (unpublished for 2020) with comparable physician-based out-of-hospital emergency health care systems [6]. All participating EMS dispatch both paramedic-staffed ambulances and physician-staffed vehicles to suspected OHCA cases. The design of the GRR follows the Utstein style [7]. Registry participation is voluntary. Data entries are carried out by EMS physicians or other EMS staff and have to be cleared by the responsible chief medical officer. In order to maintain overall database consistency and to minimize selection bias, only data from ambulance services meeting the following criteria were added to the present analysis: yearly OHCA prevalence of at least 30 per 100,000 inhabitants, mean ROSC rate under 80%, ROSC after cardiac arrest (RACA) score availability above 60%, follow-up data documenting post-admission outcomes for at least 30% of cases. The RACA score [8] provides one method to assess the likelihood for ROSC after cardiac arrest. Cases from ambulance services not meeting the quality criteria were excluded from further analysis, especially when long-term outcome could not be assessed due to lacking follow-up data.

Inclusion criteria

The analysis was based on 212,228 anonymous data sets of adult patients with OHCA. Further inclusion criteria were CPR – independent of the initiation by bystanders or EMS personnel – and the administration of adrenaline by EMS (Fig. 1).

Exclusion criteria

The exclusion criteria were age < 18 years, trauma or bleeding as suspected causes of cardiac arrest and incomplete data sets (Fig. 1).

Primary and secondary endpoints

Primary endpoint: discharge with good neurological outcome, defined as cerebral performance category (CPC) 1

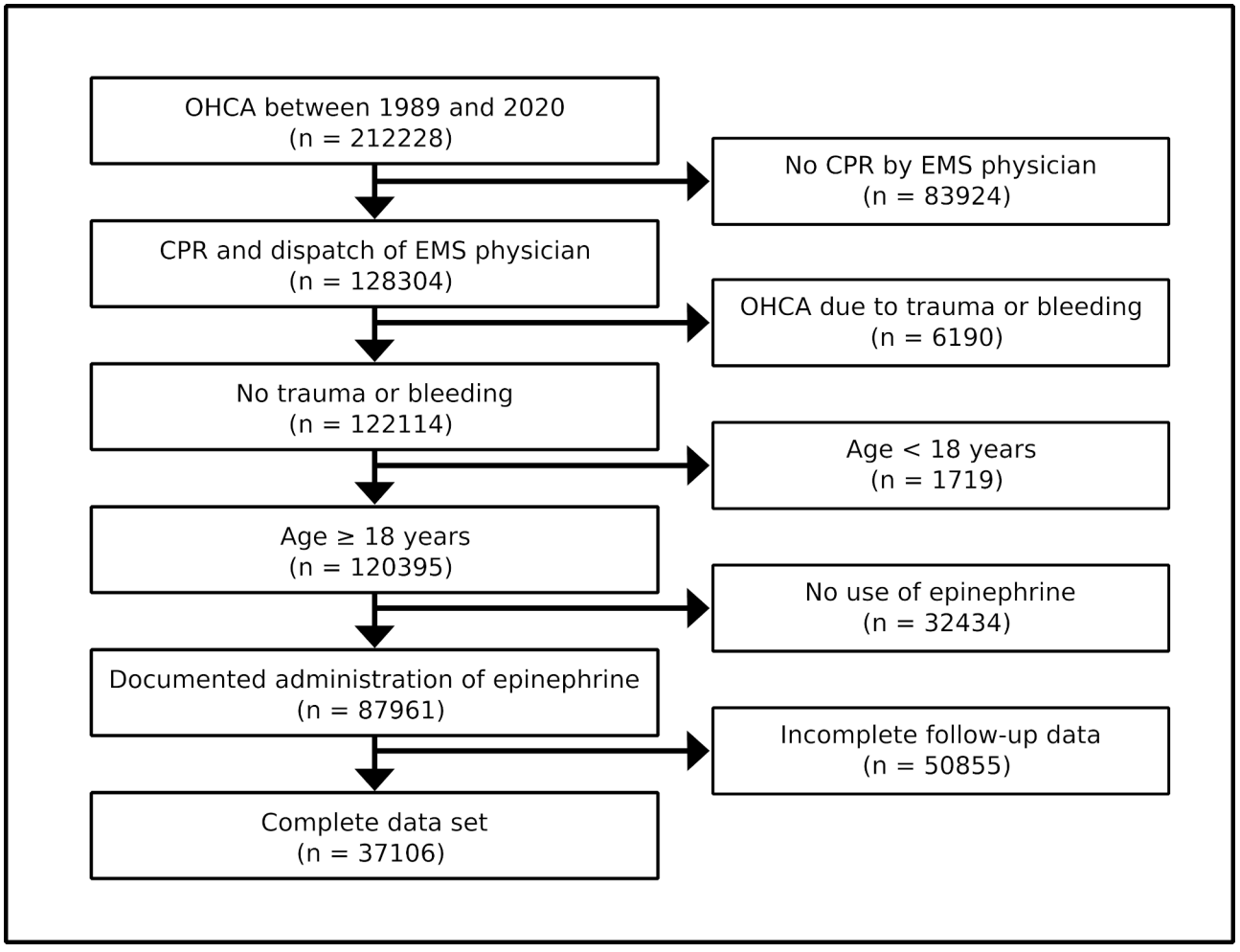

Fig. 1 Inclusion and exclusion criteria. OHCA: out-of-hospital cardiac arrest, CPR: cardiopulmonary resuscitation, EMS: emergency medical service

Table 1 Outcome Parameters

Primary Endpoint:

• Discharge with good neurological outcome (CPC 1 or 2)

Secondary Endpoints:

• ROSC during out-of-hospital care
• Survival (ROSC) at hospital admission or admission under ongoing CPR
• 24 h survival
• Survival at hospital discharge or 30d-survival

Additional Parameters:

• age (years)
• gender (m/f/n)
• etiology of cardiac arrest (non-traumatic vs. traumatic)
• witness of cardiac arrest (no witness, lay-person, EMS personnel)
• initial heart rhythm (v-fib,v-tach, asystole, PEA)
• bystander-CPR (yes/no)
• EMS response time (minutes) in groups
• duration of resuscitation (EMS on-site arrival until hospital admission in minutes)
• out-of-hospital administration of medication (e.g. adrenaline, amiodarone) with dose, frequency and route (IV, IO, ET, IO + IV, ET + IV, IO + ET + IV)

or 2 (Table 1). Secondary endpoints: ROSC during out-of-hospital care, survival at hospital admission or admission under ongoing CPR, 24 h survival, and survival at hospital discharge or 30 day survival.

Additional parameters

The following data were also acquired and used for inclusion, exclusion and risk-adjusted pair-matching: age (years), sex (male, female), etiology of cardiac arrest (non-traumatic, traumatic), pre-emergency status (no/minor/major/severe/unknown prior disease), initial heart rhythm (ventricular fibrillation, ventricular tachycardia, asystole, pulseless electrical activity), bystander-CPR (yes, no), EMS response time (minutes), duration of resuscitation (EMS on-site arrival until hospital admission in minutes), out-of-hospital administration of medication (e.g. adrenaline, amiodarone) with dose, frequency and route (IV, IO, ET, IO + IV, ET + IV, IO + ET + IV), deltaROSC: the difference between observed ROSC and ROSC after cardiac arrest (RACA) score [8].

Group definitions

Patients were pooled in four groups regarding the route of adrenaline administration: IV access, IO access, IO followed by IV access (IO+IV), and ET followed by IV access (ET+IV). Outcomes were analyzed for three group contrasts after risk-adjustment through pair-matching: IV vs. IO, IV vs. IO+IV, and IV vs. ET+IV.

Data processing and statistical analysis

Anonymous registry entries were processed in Microsoft Excel 365 MSO 16.0 64-Bit (Microsoft, Redmond, WA) and analyzed with IBM SPSS Statistics 26 (IBM, Armonk, NY), using Student's two-sided t-test for parametric data and the χ^2-test for non-parametric variables. Statistical significance was assumed for *p*-values below or equal 0.05.

In order to minimize confounding and selection bias, group comparisons were performed by matched-pair analysis including the following variables, known to affect clinical outcome after OHCA [8]: time from emergency call to arrival of EMS, percentage of shockable rhythms (ventricular fibrillation or ventricular tachycardia), asystole, cardiogenic cause, hypoxia, OHCA witnessed by bystander, OHCA witnessed by EMS, bystander CPR, age above 80 years, age between 18 and 65 years, OHCA in public or at doctor's office, OHCA at home, OHCA at nursing home, sex, initial electrocardiogram.

Confounder corrected group analysis was achieved by matched-pair group comparisons via the custom-built software PairMatcher [9, 10]. Due to its larger size, the IV group was matched 2:1 with all other groups, i.e. two IV patients were matched with respect to all control variables with one patient each of the IO, IO+IV, and ET+IV group respectively. As internal validation for adequate pair-matching, the ROSC after cardiac arrest (RACA) score [8], derived from multivariate logistic regression to predict likelihood of ROSC after OHCA, was calculated for each group contrast, confirming the clinical comparability of the matched groups prior to further analysis.

A secondary regression analysis was performed to assess the amount of variance explained by vascular access type. Hospital discharge with good neurological outcome was set as clinical outcome parameter. A binary logistic regression model with vascular access type as independent variable was calculated through SPSS, taking all above-mentioned parameters of the pair-matching approach into account, and additionally correcting for age, adrenaline dosage, intervention with coronary catheter and treatment with mild therapeutic hypothermia during hospital stay.

Results

Descriptive statistics

During the study period between 1989 and 2020, the analysis of the GRR database revealed 212,228 cases of OHCA. After application of the aforementioned inclusion and exclusion criteria, 37,106 complete data sets were subjected to further analysis (Fig. 1). Of those OHCA patients, 29,688 had received an IV access, 1,303 an IO access, 4,827 both IO and IV accesses and 276 patients had received both ET and IV therapy (Table 2). 20 patients had received adrenaline exclusively via ET, 5 via ET and IO, and 23 via a combination of ET, IO and IV accesses. For 964 cases, no route of drug administration was documented.

Remarkably, all groups with sufficient data (IV, IO, IO+IV, ET+IV) showed RACA scores of comparable magnitudes, centering around a mean ± SD of 41.7% ±1.9, suggesting roughly equal pre-CPR conditions on average. The actual ROSC rates in contrast were more than twice as variable with a mean ± SD of 41.1% ±4.7.

Group effects of route of adrenaline administration on clinical outcomes were calculated after separate pair-wise matching of every IO, IO+IV and ET+IV case with two IV cases each with comparable pre-CPR OHCA conditions.

Internal validation

Table 2 shows that the average RACA score of each IV-subgroup closely matched the respective comparison group with no divergence exceeding 0.6%. This confirmed the intended matching procedure. Differences between the various IV subgroups were an expected effect of the pair-matching procedure, reflecting pre-CPR differences between the matched IO, IO+IV and ET+IV groups.

Statistical analysis of primary and secondary endpoints

In pair-matched group comparisons of the primary clinical outcome – hospital discharge with CPC of 1 or 2 – the IV group showed significantly better results compared to IO [odds ratio (OR): 2.43, 95% confidence interval (95% CI): 1.54–3.84, $p<0.01$] and compared to IO+IV [OR: 1.33, 95% CI: 1.12–1.59, $p<0.01$] (Fig. 2). In contrast, no significant difference was found between IV and ET+IV [OR: 1.26, 95% CI: 0.55–2.90, $p=0.59$).

As shown in Fig. 2, equivalent effects were found for all secondary endpoints, too: ROSC at any point, admission to hospital with ROSC, survival at 24 h, survival at 30 days or discharge from hospital. In each comparison, OR significantly favored IV over IO and IV over IO+IV, while no statistically significant difference could be demonstrated for IV vs. ET+IV.

The binary logistic regression model of hospital discharge with good neurological outcome, additionally accounting for age, adrenaline dosage, coronary catheter intervention

Table 2 Descriptive statistics and matched-pair analysis with outcome depending on route of administration. IV: all included patients with intravenous access, IO: all included patients with intraosseous access, IO + IV: all patients with both IO and IV access, ET + IV: all patients with both endotracheal and IV access, ET: all patients with only ET access, ET + IO: all patients with both ET and IO access, ET + IO + IV: all patients with all three access routes, n.sp.: not specified, $IV_{[IO]}$: IV-subgroup to match IO, $IV_{[IO+IV]}$: IV-subgroup to match IO + IV, $IV_{[ET+IV]}$: IV-subgroup to match ET + IV, n: number of patients included, ROSC: return of spontaneous circulation with 95% confidence interval, VF/VT: ventricular fibrillation or ventricular tachycardia, Cardiogenic: cardiogenic cause of OHCA, Hypoxia: hypoxia as cause of OHCA, Witn. Byst.: OHCA witnessed by bystander, Witn. EMS: OHCA witnessed by EMS personnel, Byst. CPR: CPR performed by bystander, In public: OHCA in public or at doctor's office, At home: OHCA at private home, Nurs. home: OHCA in a nursing facility, Time to EMS arrival: time from alarm until arrival of first EMS vehicle in minutes:seconds with standard deviation, MTH: percentage of hospitalized patients receiving mild therapeutic hypothermia, Cardiac cath.: percentage of hospitalized patients receiving cardiac catheter intervention, RACA: ROSC after cardiac arrest score, Δ-RACA: ROSC-RACA, hence the difference between actual ROSC and mean predicted ROSC by RACA score, CPR@ED: admission to emergency department under cardiopulmonary resuscitation, ROSC@ED: admission to ED after ROSC, 24 h survival: rate of patients alive 24 h after admission, 30d survival: rate of patients alive or discharged 30 days after admission, CPC 1/2: cerebral performance category 1 or 2

Patient characteristics										**Matched pairs**			**Matched pairs**			**Matched pairs**		
	All cases	IV	IO	IO + IV	ET + IV	ET	ET + IO	ET + IO + IV	n.sp.	$IV_{[IO]}$	IO	Chi^2/t	$IV_{[IO+IV]}$	IO + IV	Chi^2/t	$IV_{[ET+IV]}$	ET + IV	Chi^2/t
Number (n)	37,106	29,688	1303	4827	276	20	5	23	964	2416	1208	–	8706	4353	–	532	266	–
ROSC (%)	45.6	46.8	35.4	42.1	40.2	15.0	20.0	34.8	42.0	44.1	34.9	< 0.001	45.0	41.2	< 0.001	43.2	40.2	0.418
95% CI	(45.1,46.1)	(46.2,47.4)	(32.8,38.1)	(40.7,43.5)	(34.4,46.3)	(3.2,37.9)	(0.5,71.6)	(16.4,57.3)	(38.9,45.2)	(42.1,46.1)	(32.2,37.7)		(44.0,46.1)	(39.7,42.7)		(39.0,47.6)	(34.3,46.4)	
VF/VT (%)	23.9	25.3	15.1	18.5	19.6	10.0	0.0	34.8	20.5	15.1	15.1	1.0	18.8	18.8	1.0	19.9	19.9	1.0
Asystole (%)	54.0	52.7	63.1	58.2	61.6	65.0	40.0	47.8	57.2	64.4	64.4	1.0	59.1	59.1	1.0	61.3	61.3	1.0
Cardiogenic (%)	65.8	67.3	53.3	63.1	53.6	45.0	60.0	52.2	54.1	79.7	79.7	1.0	82.5	82.5	1.0	90.2	90.2	1.0
Hypoxia (%)	12.8	12.2	17.0	15.9	7.3	5.0	0.0	17.4	11.2	15.2	15.2	1.0	13.4	13.4	1.0	5.6	5.6	1.0
Witn. Byst. (%)	44.1	44.8	39.0	42.8	37.7	35.0	20.0	52.2	37.5	38.3	38.3	1.0	43.0	43.0	1.0	38.0	38.0	1.0
Witn. EMS (%)	7.2	7.6	6.0	5.6	3.6	0.0	20.0	4.4	7.0	5.1	5.1	1.0	4.7	4.7	1.0	2.6	2.6	1.0
Byst. CPR (%)	33.3	33.6	33.4	34.3	12.7	15.0	0.0	26.1	26.5	32.4	32.4	1.0	33.8	33.8	1.0	12.0	12.0	1.0
> 80 years (%)	28.2	29.1	23.3	23.9	27.5	20.0	0.0	13.0	29.9	23.5	23.5	1.0	24.7	24.7	1.0	27.4	27.4	1.0
18–65 years (%)	33.6	32.5	40.1	38.8	33.7	35.0	80.0	60.9	32.9	39.2	39.2	1.0	37.3	37.3	1.0	33.1	33.1	1.0
In public (%)	19.5	19.7	18.3	19.0	16.7	15.0	0.0	17.4	19.3	18.0	18.0	1.0	18.5	18.5	1.0	16.5	16.5	1.0
At home (%)	65.2	65.1	66.8	66.5	70.0	70.0	100	56.5	59.8	70.0	70.0	1.0	69.5	69.5	1.0	71.1	71.1	1.0
Nurs. home (%)	9.2	9.1	9.5	9.9	5.8	10.0	0.0	4.4	7.9	7.7	7.7	1.0	8.7	8.7	1.0	4.9	4.9	1.0
Male (%)	65.9	66.7	62.3	62.2	65.9	60.0	60.0	47.8	64.5	63.1	63.1	1.0	64.0	64.0	1.0	66.2	66.2	1.0
Time to EMS arrival ± st.d.	6:21 ± 3:23	06:21 ± 3:24	6:00 ± 3:13	6:21 ± 3:20	6:09 ± 3:04	5:07 ± 2:35	6:30 ± 2:07	5:42 ± 3:08	6:38 ± 3:41	6:27 ± 3:23	5:56 ± 3:08	< 0.001	6:23 ± 3:26	6:21 ± 3:18	0.480	6:08 ± 2:57	6:07 ± 3:04	0.918
MTH (%)	26.6	27.3	19.2	25.0	14.0	25.0	0.0	50.0	24.5	25.0	19.1	0.010	27.9	25.7	0.070	19.3	14.6	0.262
Cardiac cath. (%)	28.5	28.9	21.6	28.4	14.7	25.0	0.0	37.5	25.0	26.1	22.6	0.139	29.0	30.1	0.350	15.5	15.5	0.983
RACA score (%)	43.2	43.5	41.5	42.6	39.1	38.5	52.5	50.5	42.3	40.6	41.0	0.483	41.6	41.9	0.382	39.4	38.8	0.590
Δ-RACA (%)	2.3	3.3	-6.2	-0.6	1.1	-23.5	-32.5	-15.7	-0.3	3.5	-6.1	–	3.4	-0.7	–	3.8	1.4	–
CPR@ED (%)	13.2	12.9	13.9	15.6	11.6	5.0	40.0	8.7	12.7	11.6	13.6	0.092	12.0	15.1	< 0.001	12.6	11.3	0.592
ROSC@ED (%)	36.5	37.9	26.6	31.6	35.1	15.0	20.0	26.1	32.2	35.6	26.3	< 0.001	35.8	30.7	< 0.001	37.0	35.0	0.567
24 h survival (%)	21.5	22.4	16.4	18.1	17.4	5.0	40.0	21.7	18.5	20.0	16.1	0.005	21.3	17.5	< 0.001	20.1	17.7	0.410
30d survival (%)	9.2	9.8	4.8	7.2	6.2	–	–	8.7	7.9	7.6	4.7	0.001	8.9	7.0	< 0.001	7.0	6.4	0.765
CPC 1/2 (%)	5.5	6.0	1.8	4.1	2.9	–	–	8.7	5.3	4.5	1.9	< 0.001	5.3	4.0	0.002	3.8	3.0	0.586

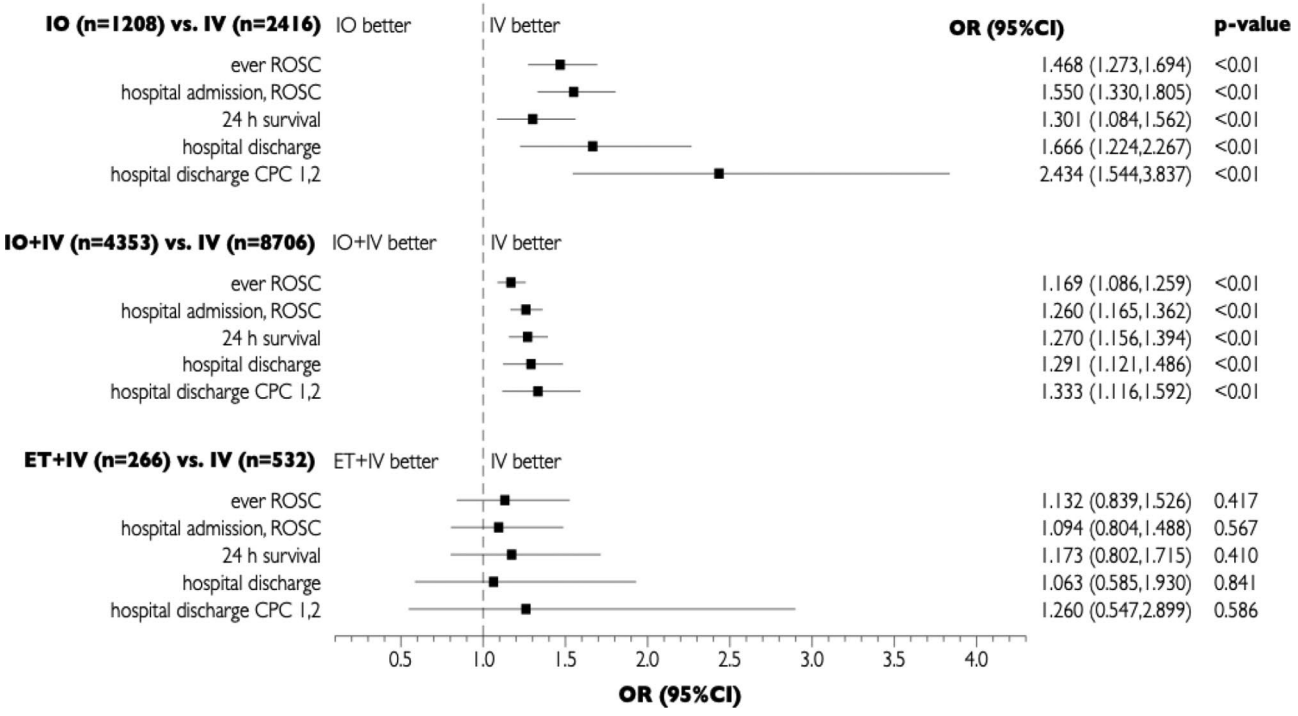

Fig. 2 Matched-pair comparisons of clinical outcomes depending on route of administration. IV: intravenous, IO: intraosseous, IO + IV: intraosseous and intravenous, ET + IV: intraosseous and intravenous, OR: odd's ratio, 95%CI: 95% confidence interval

and provision of mild therapeutic hypothermia, yielded a highly significant effect of vascular access type (χ^2 = 67.744(3), p<0.001) with a sufficient amount of explained variance (Nagelkerke's R^2 = 0.433). Negative effects could be shown for IO (regression coefficient (r.c.)=−0.766, p=0.001) and IO+IV (r.c. = −0.201, p=0,028) with no significant effect of ET+IV (r.c. = 0.117, p=0.770).

Discussion

The GRR covered over 200,000 cases of OHCA within the 31-year time span from 1989 to 2020. Through pair-matched comparisons of clinical outcome parameters after OHCA, depending on route of drug administration, the present study found clinically relevant and statistically significant differences, generally in favor of the IV access. Analysis of secondary endpoints revealed these effects to be robust for both short term outcomes like admission to hospital with ROSC and long-term outcomes like 30-day survival and discharge from hospital with good neurological outcome.

These findings are seemingly in conflict with existing literature emphasizing the safety and speediness of establishing IO accesses [4, 11, 12]. Some animal models even suggested a pharmacological superiority of IO over IV drug application during CPR [13]. A body of literature on cardiac arrest in swine models reported no effect of access route for adrenaline, comparing IV with humeral and tibial IO [14], and comparing IV with tibial IO [15], nor when comparing vasopressin administration via IV or humeral IO routes [16]. A cardiac arrest study in lambs found no effect in adrenaline administration via tibial IO vs. via central venous access [17].

On the other hand, there are pharmacokinetic studies in animal models of cardiac arrest, suggesting lower plasma levels to be achieved when drugs where applied IO vs. IV [18, 19], confirmed by Hoskins et al. [20], who found an additional decrease in plasma levels in tibial IO vs. sternal IO drug delivery. A 2014 review on IO adrenaline during CPR in animal models therefore recommends proximal over distal IO sites [21].

Retrospective studies in humans demonstrated a time advantage of IO vs. IV access [22, 23], while non-inferiority studies failed to find a significant disadvantage of IO access for clinical outcomes [24]. A current systematic review [25], investigating the effects of venous access type on neurological outcome and survival in OHCA, reported no difference between IV and IO access in the pooled analysis of nine observational studies after correcting for time between cardiac arrest and drug administration. Another systematic review [26], comparing IV and IO routes during cardiac arrest, found limited evidence in favor of IV administration in observational studies and no effect in the subgroup analyses of the randomized controlled trials reviewed.

On the other hand, recent reports from North America [27–33], the UK [34], and France [35], all assessed the IO access under CPR conditions very critically with unfavorable clinical outcome parameters (e.g. ROSC, hospital

admission, 30-day survival without neurological deficit). In line with the present GRR data these retrospective studies reported an association of IO treatment during CPR with worse clinical outcomes. Furthermore, a recent systematic meta-analysis [26], also examining the question of application route during CPR, found a probable superiority of IV over IO on the basis of low certainty of evidence. While statistically underpowered for access route analysis, one randomized controlled trial assessing placebo vs. anti-arrhythmic therapy under OHCA [28] found consistently superior clinical outcomes for IV over IO drug administration.

A recent meta-analysis, assessing 23 studies on safety of intravenous peripheral catecholamine administration found a rate of adverse events in under 2% of cases [36].

In summary, while the general safety and rapidness of mere IO placement and the safety of peripheral catecholamine therapy are well documented, the efficacy and effectiveness of IO adrenaline treatment during OHCA remains controversial.

The present findings and literature raising concerns on potential IO inferiority during CPR could have a pharmacokinetic explanation, supported by some of the animal literature referenced above [18–21]. Given the particularly low perfusion pressures present during CPR, transport of adrenaline might prove difficult from the medullary cavity to the place of action within its short half-life of 1 to 2 min, especially for distal IO injection sites like the tibia. Before cardiac and arterial adrenoceptors are reached to elicit the desired arteriolar vasoconstriction as well as inotropic, chronotropic and dromotropic cardiac effects, adrenaline has to exit the medullary cavity, undergo venous return and pass the entire pulmonary circulation. From a pharmacokinetic point of view, an application closer to the target receptors would thus be favorable.

The GRR did not provide information on access site location – specifically, whether an IO access was placed tibially or humerally, or where an IV access was placed. A subgroup analysis of the IO group, challenging the above mentioned hypothesis on proximity to the central circulation was thus not feasible within the present study.

One should not forget that the ET administration of adrenaline via an endotracheal tube used to be recommended in international resuscitation guidelines for many years as an alternative to the IV route, providing independence from venous status (Fig. 3). The 2000 ERC guidelines [37] described the ET delivery of adrenaline with higher dosages (2–3 mg ET vs. 1 mg IV) as an equivalent alternative to IV. In 2005, the ERC recommended IO access as the primary alternative to IV, reserving ET administration as an emergency fallback strategy when neither IV nor IO access could be established [38]. Since its 2010 update, ERC guidelines do not recommend the ET route anymore, due to unknown optimal doses and poor predictability of resulting plasma levels [39].

In the event that future studies would confirm a limited efficacy for IO administered emergency medication,

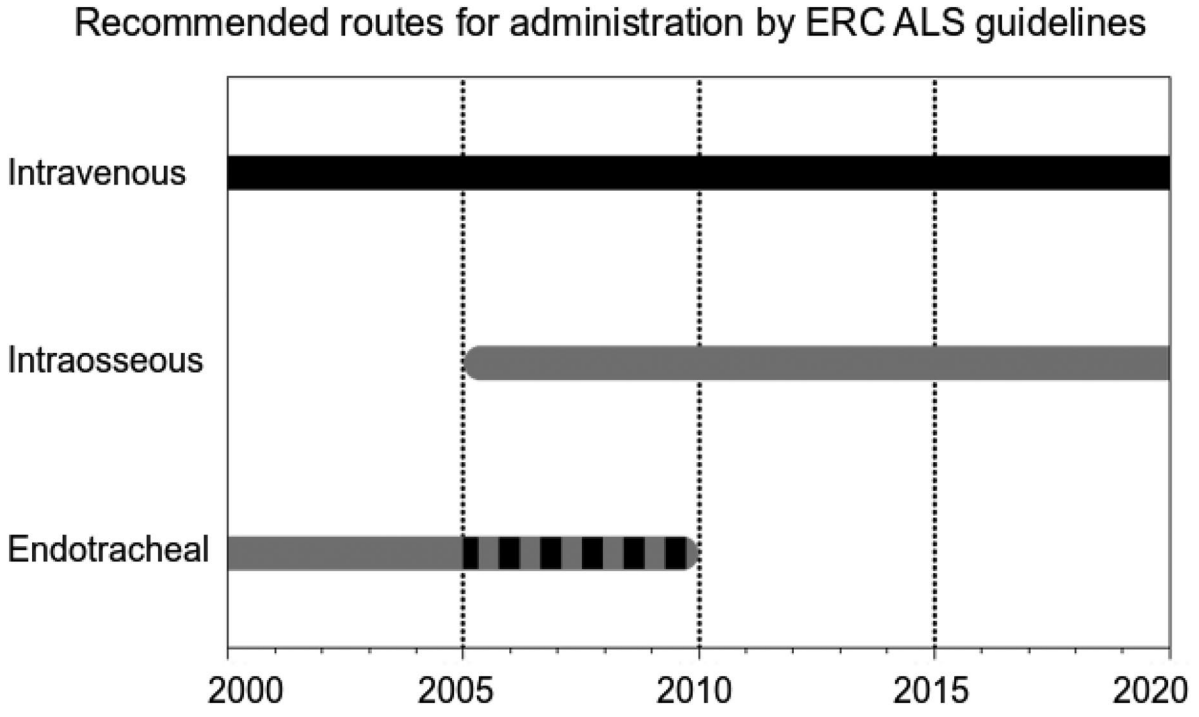

Fig. 3 Routes of drug application as recommended by ERC ALS guidelines from 2000 to 2020. Black: first choice, gray: second choice, striped: fallback strategy, ERC: European Resuscitation Council, ALS: advanced life support

in particular for adrenaline during CPR, the risk-benefit-analysis regarding safety, speediness and efficacy of the different routes would have to be re-assessed.

Surprisingly, the present registry analysis suggested an outcome comparability between IV and ET+IV administration of adrenaline. Hypothetically, the decision to discount the ET option could have been made prematurely. If the main reason against recommending the ET route during OHCA CPR was a lack of data on the required dosage, focused research on ET pharmacokinetics during CPR might prove fruitful. Despite not being recommended since 2010, sporadic use of ET adrenaline was detected in the GRR registry as late as 2019.

While safety, speediness and effectiveness of intraosseous access devices are generally not called into question, there might be good reasons to uphold the intravenous access as the gold standard during the specific conditions of OHCA CPR. Nonetheless, whenever the latter is not readily available, a viable and fast alternative access will be pivotal.

In a scenario of ongoing CPR, when the airway has already been successfully secured while IV access has not been established yet, the endotracheal drug administration could potentially present an acceptable alternate route. Before specific recommendations to this effect can be considered, further research on endotracheal dosage requirements is needed.

Study strength and limitations

As with all registry-based analyses, some limiting factors need to be addressed. First of all, due to the retrospective nature of the study design, control against selection bias through randomization of treatments was not possible. In order to minimize a systematic treatment effect, cases were pair-matched according to the pre-CPR likelihood for ROSC. Internal validation confirmed this approach. Therefore, remaining differences in outcomes cannot be merely explained by postulating a systematic selection bias.

Other potential confounders were implicitly accounted for by referring to the largest available CPR registry in the German-speaking area, hoping to eliminate random effects by collecting a sufficiently large sample. Nonetheless, even this registry did not contain sufficient data to include an exclusively endotracheal treatment group in the analysis, and a substantial number of cases could not be included into the analysis due to incomplete follow-up data. Data on direct comparisons between access routes remain scarce and at times contradictory.

Conclusions

The GRR data, collected over a 31-year period, provide evidence for using the IV access as primary route during out-of-hospital CPR. IO administration of adrenaline might be less effective. An ET application, while removed in 2010 from international guidelines, could gain in importance as an alternative route again.

List of abbreviations

ALS	advanced life support
CI	confidence interval
CPC	cerebral performance category
CPR	cardiopulmonary resuscitation
EMS	emergency medical system
ERC	European Resuscitation Council
ET	endotracheal
EuReCa	European Registry of Cardiac Arrest
GRR	German Resuscitation Registry
IO	intraosseous
IV	intravenous
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
RACA	ROSC after cardiac arrest
ROSC	return of spontaneous circulation

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Author Contribution
TM: conceptualization, methodology, formal analysis, data curation, original draft, review & editing, visualization; MF: conceptualization, methodology, formal analysis, resources, review & editing; MM: review & editing; IH: review & editing; RW: review & editing; SR: review & editing; JTG: review & editing; MB: conceptualization, review & editing, supervision, funding acquisition.
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Data Availability
The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved and registered by Heinrich Heine University's institutional research ethics committee in Düsseldorf, Germany, under protocol number "2020 – 1018". The study was additionally approved by the scientific advisory council of the GRR (registration number "2020-02").

Consent for publication
Not applicable.

Competing Interest
The authors declare no conflicts of interest. JTG and MF are members of the Steering Committee of the German Resuscitation Registry.

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Publisher's Note

3 Discussion

3.1 Confirmation of hypothesis

In adult, non-trauma, non-hemorrhagic OHCA patients undergoing advanced life support, intravenous compared to intraosseous adrenaline administration was associated with substantially improved 30-day survival with good neurological outcome. No clinically relevant or statistically significant difference between intravenous and combined intravenous and endotracheal adrenaline administration was found.

Though collectively representing over 200,000 OHCA cases between 1989 and 2020, the German Resuscitation Registry did not contain enough cases of isolated endotracheal adrenaline therapy to allow for a separate IV vs. ET analysis with sufficient statistical power.

With respect to the existence of relevant differences between treatment outcomes, the hypothesis was thus confirmed. In fact, both matched-pair analysis and logistic regression modeling revealed beneficial 30-day survival with good neurological outcome for IV vs. IO and for IV vs. IO+IV comparisons, but no difference between IV and ET+IV.

Not only could the hypothesized difference in treatment effects be confirmed, the difference could be qualified in a multi-modal statistical approach as IV-superiority over IO and indifference between IV and ET+IV. Furthermore, the same findings were found in the matched-pair analyses of all secondary endpoints, i.e. the more short-term treatment effects within minutes to 24 hours after out-of-hospital resuscitation.

3.2 Conflicting evidence in the literature

These results might come as a surprise, given the broad utilization of intraosseous cannulation during OHCA in the field and given the long standing endorsement by international guidelines.

After all, the main concerns when introducing novel techniques and devices into emergent care have been thoroughly and repeatedly addressed: both safety and speediness of securing vascular access through IO devices, given appropriate training and equipment, has been tested and proven on a single-study basis as well as on a review level [13,28,29].

Even with respect to the aspects of pharmacokinetics, IO data have been generated. Of course, controlled prospective investigations on deviations from standard care rightfully underlie heavy ethical restrictions. But animal studies, e.g. in a pig model of in-hospital CPR with simultaneous IV and IO access [30], have gone beyond confirming equivalent efficacy when reporting even higher adrenaline plasma levels after intraosseous vs. intravenous administration.

Multiple groups have tackled similar questions in varying animal models of cardiac arrest. As early as 1990, the adrenaline plasma levels were obtained after intraosseous or central venous administration during CPR in a hypoxic cardiac arrest model in 13 lambs, weighing ca. 9 kg [31]. Because no differences in peak plasma concentrations were found between IO and central venous application, the authors expressly concluded: “Standard doses of epinephrine should be used for intraosseous injection.” [31].

It has to be stressed however that even though optimal chest compressions under lab conditions can be assumed and even though small animals, weighing roughly as much as a one year old human infant, were used, peak adrenaline plasma levels showed profound delays under CPR. While peak levels were recorded 15 s after central venous application, time to peak took a whole minute after IO injection. In adult humans, especially when choosing tibial cannulation, the vascular distances and transit times between IO injection site and adrenoceptor locations most likely will be considerably longer than in 9 kg lambs. The observed dosage response curves therefore should not have been simply assumed to also apply in a human CPR setting.

In a series of lab studies with ca. 70 kg pig models of cardiac arrest due to ventricular fibrillation, the problem of transferability to humans can be supposed to be at least superior to a 9 kg lamb model. When comparing ROSC rates after inducing ventricular fibrillation in 32 pigs and performing CPR and defibrillation

under lab conditions, no difference was found between tibial intraosseous, humeral intraosseous or intravenous application [32]. Of note, all forms of adrenaline therapy markedly improved ROSC rates compared to control treatment with saline. The authors thus concluded that “the anatomical distance of the route of IO infusion from the heart did not affect measures of short-term resuscitative outcome” [32].

Similar findings were reported in a study with 21 pigs undergoing ventricular fibrillation and mechanical chest compressions, assessing ROSC rates and plasma levels after tibial IO vs. IV vasopressin therapy [33]. Again, clinical effects were identical between both access routes while intravenous application yielded higher plasma levels.

A follow-up study on 27 pigs in a similar paradigm, comparing humeral IO vs. IV vasopressin treatment after ventricular fibrillation found no pharmacokinetic or clinical difference between access routes [34]. The authors conclude full pharmacokinetic equivalence of intravenous and humeral intraosseous vasopressin treatment during CPR.

The mounting evidence on interchangeability of intravenous, humeral and even tibial intraosseous pharmacotherapy during resuscitation is challenged by a central flaw though. The most prevalent site for intraosseous cannulation in humans is the proximal tibia. None of the cited big animal models was able to account for the vascular dimensions in adult humans and the delays in circulation this distance causes.

Of course, this very aspect is particularly challenging to ethically approach in a human patient population. OHCA patients don’t present with readily available, randomizable access option. And prospective study designs carefully accounting for all the biases, that retrospective paradigms cannot rule out, are facing a myriad of ethical and logistic obstacles.

One study in almost 200 adult OHCA patients did attempt to prospectively randomize access type during advanced life support in a paramedics staffed EMS. The authors randomly assigned patients to tibial intraosseous, humeral intraosseous and peripheral intravenous access and primarily explored the

respective rates of successful placement upon first attempt [14]. Indeed, tibial IO access had the highest success rates on the first try. Notably, the overall times until secure placement could be achieved did not differ among groups. Also significantly less fluid volume was administered in both IO groups while a markedly increased rate of accidental dislocations was observed after humeral IO placement. Transferal of these findings to physician staffed EMS systems will likely be limited. Importantly though, no clinical outcome parameters were assessed.

While other studies did attempt to study the clinically relevant patient outcomes between IO and IV treatment in OHCA, none did so in a prospective protocol. A non-inferiority analysis of ROSC rates without data on long-term outcome in 1300 OHCA patients found no significant difference between IO and IV [15].

In records of 3000 OHCA cases from a paramedics staffed EMS, the time to drug application in IO cases was faster, leading the authors to strongly recommend the “prehospital use of IO vascular access for time-dependent medical conditions” [35]. Such blanket endorsement for primary IO access in *all* out-of-hospital emergencies goes far beyond the OHCA setting under investigation. This recommendation did not take into consideration parameters of clinically relevant patient outcome, simply assuming positive results based on faster access times.

In an attempt to condense the existing literature comparing IV with IO approaches in OHCA, a recent meta-analysis from 2021 combined over 111,000 OHCA cases from nine independently published retrospective studies [36]. Here, no significant difference in long-term neurological outcome between IV and IO could be detected after correcting for the time until pharmacotherapy. The validity of this finding has to be seen in light of pronounced heterogeneity among the different data sets and whilst acknowledging the insufficient power to correct for potential biases due to varying resuscitation times [36].

Summing up the body of literature in apparent contradiction with the current findings, the existing evidence is hardly conclusive. Many practical studies have focused on mere speediness of IO access placement rather than clinical patient outcomes. OHCA relevant out-of-hospital designs often are undertaken in paramedics staffed EMS environments with limited transferability to physician staffed counterparts.

Furthermore, even when clinically relevant outcomes are rightfully put into the focus of investigators, existing studies in humans are confined to bias-vulnerable and underpowered retrospective paradigms even when accumulating unprecedented data set size through meta-analysis.

But where animal models even in large animals are employed to overcome these limitations, significant differences both to human physiology and to human pathophysiology harshly limit the direct mapping of experimental findings onto the practical patient care. Neither OHCA etiologies nor pathophysiological responses during CPR nor the external influences affecting out-of-hospital advanced life support can sufficiently be replicated in a laboratory environment.

Animal studies therefore can aid in proof-of-concept paradigms or assist in critical appraisal of existing hypotheses. A replacement of evidence and insights from the systematic experience with human patients is not possible.

3.3 Supporting evidence in the literature

As detailed above, a host of recent publications retrospectively compared various measures of clinical outcome after IO vs. IV access in out-of-hospital cardiac arrest [16–24]. Limited by relatively small sample sizes and vulnerability to both systematic and random error due to retrospective study design, all studies found associations of varying degree with negative clinical outcomes for IO access in OHCA.

A systematic review, trying to incorporate the collective evidence of six studies and two randomized controlled trials, also contrasted IV and IO routes of vascular access during resuscitation in OHCA [37]. The authors summarized the overall assessment as slightly negative impact of IO access, limited by very low certainty of evidence. A sub-analysis by access route within the two included randomized controlled trials yielded no significant result.

While many studies have focused on the safety of IO pharmacotherapy during resuscitation, a systematic review and meta-analysis of 23 studies established the general safety of peripheral venous catecholamine administration [38]. On the

basis of 16,000 adult cases and nearly 400 children, parallel risk ratios for adult and pediatric adverse events after peripheral vasopressor therapy were reported as 2 % in adults and 3 % in children, respectively.

In spite of the growing number of observational publications calling IO efficacy into question, subgroup analysis with similar implications from a rare prospective, randomized and controlled OHCA trial were phrased in most careful terms [19]. In this trial, anti-arrhythmic drugs for refractory ventricular fibrillation or tachycardia were randomized in OHCA patients. Ex post, subgroups were defined by type of vascular access and analyzed with respect to survival and neurological status at hospital discharge. The authors, in fact observing worse clinical outcomes in IO cases, vehemently stressed the low statistical power. The paradigm indeed had not been designed for a comparison between access types. The inevitable conclusion from the presented data that the same drugs at the same dose might not have the same clinical effects when given either intravenously or intraosseously was qualified as “provocative implication” [19].

It can be noted that the volume of evidence calling into question the efficacy of intraosseous adrenaline application in OHCA might have grown over the past few years. In the absence of well-powered, dedicated prospective studies to illuminate this question, the literature is hardly consistent, complete and conclusive though.

Conflicting evidence does exist and the overarching emphasis concerning the intraosseous route for life support lays on safety and speediness of the application, not the efficacy of the treatment. While controversy exists on academic grounds, guidelines did clearly decide the matter in 2010 and have not provided another alternative for IV access since.

For the time being, the most fruitful prospect for substantial contributions to this debate might be provided by the kind of physiological and pharmacokinetic data, only obtainable from animal models of cardiac arrest in controlled laboratory environments.

3.4 Concurrent data from animal models

While relatively inapproachable in humans, pharmacokinetic patterns of adrenaline, when applied through various access routes during CPR has been extensively studied in animal models. As early as 1992, a Philadelphia based group determined in a study of 18 pigs undergoing CPR after induced ventricular fibrillation, that much higher doses of adrenaline where necessary when applied via a tibial intraosseous needle to noticeably affect systemic blood pressure [39].

A more recent study on 21 pigs, also in a ventricular fibrillation model of cardiac arrest, determined both faster onset and overall higher plasma levels of adrenaline when applied through intravenous vs. tibial intraosseous access during CPR [40]. Both studies are in line with less effective intraosseous pharmacotherapy during CPR, especially when given without dose adjustment.

This reasoning is further substantiated by findings from a cardioplegic cardiac arrest model in 13 pigs of around 30 kg [41]. Here, the authors generated visual prove of site-specific dose requirements for intraosseous medication during CPR by injecting die through tibial IO, sternal IO or central venous access respectively and measuring peak arterial concentrations. Much lower concentrations at later peak time were observed after tibial IO injection. While peak times at the arterial sampling site were identical between sternal IO and central venous injection, sternal IO application yielded only 86% of the dose that central injection achieved to deliver [41].

These effects might be even more pronounced in humans with significantly longer vascular distances between tibial IO injection and the heart at potentially worse perfusion pressures than achievable in 30 kg pigs under optimized lab CPR conditions. Certainly, the results of this paradigm would also support the present findings from GRR analysis, that tibial IO injection of adrenaline without adjusted dosage is associated with worse ROSC rates and worse long-term outcomes.

A structured review on all available data from animal models on pharmacokinetic characteristics of intraosseous adrenaline treatment during CPR came to a similar conclusion [42]. Plasma levels from intravenous injection were consistently found to be higher and to be arriving faster compared to IO injection. The choice of IO

site was also determined to be essential with sternal and humeral IO yielding better plasma levels than tibial IO.

Based on strong effects found across animal models, the authors went as far as explicitly recommending the preferential use of humeral or sternal over tibial insertion sites for IO placement in humans “whenever possible when administering advanced cardiac life support drugs to rapidly achieve maximal therapeutic plasma concentrations” [42].

A current animal study from the United States tried to assess both pharmacokinetics and short-term clinical outcomes of endotracheal adrenaline administration in a pediatric model of hemorrhagic cardiac arrest [43]. In 25 pigs, weighing 20–30 kg and corresponding in body mass to children aged 5–9 years, the investigators induced cardiac arrest through exsanguination followed by electrocution. In four randomized groups, resuscitation was attempted through mechanical CPR alone, CPR plus defibrillation, CPR with intravenous adrenaline or CPR with endotracheal adrenaline with tenfold increased dose.

In line with existing clinical data and of little surprise, both adrenaline groups showed markedly higher ROSC rates. Notably though, all obtained pharmacokinetic parameters obtained for adrenaline plasma concentration were the same for intravenous and endotracheal treatments, including absolute peak plasma levels and time to peak plasma level.

The main group difference between ET and IV was observed in a considerably faster time to ROSC in the ET group, which the authors attribute to a possible benefit of drug deposition in close spatial proximity to cardiac vasculature [43].

Of course, a pediatric animal model of hemorrhagic cardiac arrest can hardly serve as template to inform the medical treatment of adults in non-hemorrhagic OHCA as was the case in the present study’s population. As a proof of principle, these data from 2022 do encourage the scientific endeavor to re-visit the question of the potential existence of viable ET adrenaline dosing for adults.

At least in 30 kg pigs in the above lab setting, it was indeed possible to show that a tenfold increase in dosage applied endotracheally lead to a near perfect reproduction of adrenaline plasma level dynamics. Surprisingly, in spite of identical

plasma results, ET administration markedly reduced time to ROSC, hinting to a potential benefit in clinical outcome.

These data show that safe and effective ET adrenaline treatment in OHCA might merely be a practical question of determining the appropriate dosing, rather than a principle matter of impossibility.

3.5 Limitations

The findings of the present study have to be appraised in light of the limitations inherent to the scientific paradigm that has been employed. By design, a retrospective registry analysis can never serve to demonstrate causal effects. All observed links between vascular access type and short- and long-term outcomes, even though statistically proven beyond random statistical probability, have to be appreciated cautiously as associations rather than as definite effects of the respective form of access.

Though statistically significant, the postulated underlying connections have to be confirmed prospectively in a randomized approach. Without randomization prior to group allocation, various forms of biases could confound the conclusions. By seeking out the largest available data set on long-term clinical outcome after OHCA, the likelihood of data contamination due to random variation has been assumed to be kept minimally. The biggest cohort of OHCA cases analyzed for clinical effects of venous vs. intraosseous access during CPR among the publications retrieved during the literature review for this dissertation tacitly accepted substantial data variance by including records from nine different studies [36].

Even this broad and current meta-study approach achieved in 2021 to accumulate only half of the database size of the GRR dataset underlying the present study. In terms of mere case numbers, further improvement could not reasonably be achieved.

Unfortunately, even in spite of the large overall sample size, no sufficient number of patients receiving only endotracheal adrenaline were available for meaningful

statistical analysis. All findings pertaining to the endotracheal route in this study are based on OHCA cases where at some point during CPR, IV access was also successfully established.

Another aspect of lacking randomization that is more difficult to account for is systematic selection bias, because large numbers only shield against random errors. In order not to fall victim to various known, likely or unknown factors that might have contributed to the choice of access type by EMS personnel on site, an elaborate multi-dimensional pair-matching technique was used. This approach ensured granular comparability between access type groups according to a host of known predictors of likelihood for ROSC after OHCA [44].

Next to internally validating the effective shielding of the pair-matching approach against inadvertent allocation bias, a parallel regression analysis was performed, yielding concurrent results. It was thus concluded that to the highest technically achievable degree, observed differences in outcomes can most likely be attributed to differences in drug route for pharmacotherapy in OHCA.

The possibility of persistent bias due to non-randomization or as effect of the unfortunate number of incomplete data sets can nonetheless never fully be ruled out in a retrospective analysis.

With respect to the adjacent question of access site-specific efficacy of intraosseous pharmacotherapy, a subgroup analysis comparing tibial, humeral and sternal IO conditions was not possible. Sternal IO cannulation most likely did not occur at all within the civilian scope of the GRR. But essentially, no information on the likely occurring tibial or humeral site for IO cases was available within the registry.

3.6 Potential applications for clinical practice

The immediate consequence of the present findings should be to revisit the assumption of perfectly equivalent efficacy of IV and IO pharmacotherapy during ALS, should such notion have been formed over the past years.

While backup strategies for failed initial attempts at venous access are always of essence, a more careful assessment of vascular status might be indicated. At least the IV access should be acknowledged as the actual goal with certain superiority in terms of maximum flow for fluid therapy and only potentially matched, likely superior pharmacokinetic properties compared to IO administration.

Deviation from that goal when its achievement would pose unacceptable time demands should be considered the secondary backup, available as rescue option, not as primary route.

Opening up the endotracheal path again as such secondary route would certainly be premature at this point, based only on retrospective data and theorizing upon evidence from animal models.

Before such practice changing recommendation could be given with evidence-based justification, some imminent questions have to be addressed first.

3.7 Prospects for future research

As evidenced by its surprising ongoing sporadic employment, endotracheal adrenaline application might be waiting for a reboot on a new foundation of evidence. Within the scope of the German Resuscitation Registry endotracheal adrenaline could be detected as late as 2019 – precisely 14 years after having been phased out and almost a decade after explicitly not being recommended anymore by national and international guidelines.

Before such a development could unfold, several scientific questions on pharmacotherapy in OHCA will have to be robustly answered.

Firstly, pharmacokinetics of tibial intraosseous adrenaline during low perfusion states such as the conditions of CPR have to be understood. If plasma peak times really fail to meet the strict half-life requirements of adrenaline – as has been hypothesized and as is one possible explanation for the findings in this study – tibial IO would have to be downgraded from a readily available alternative to IV access to a rather desperate measure of last resort.

The immediate follow-up question is that of other placement sites for IO cannulae. Prominently, the humeral placement should be thoroughly examined with the same pharmacokinetic rationale, but additionally with respect to safety and speed. Most broad IO endorsements focus on the ease at which tibial placement can be achieved. Humeral placement being considerably more challenging and hence time demanding, some of the perceived IO benefits might not hold up for humeral IO in practice.

Currently not applied in the civilian context, sternal IO access could also prove worthy of closer consideration. The advantage of accessibility – even in extended trauma to all four extremities – might remain a rationale mainly relevant in a military context. And the risk for significant mediastinal injury or pneumothorax – both non-issues for tibial IO placement – could quickly be outweighed, if hypothetically pharmacokinetics and clinical outcomes should prove to be beneficial due to shorter circulation distance in sternal vs. tibial and/or humeral cannulation.

All those questions would highly benefit from dedicated, prospective and controlled study paradigms. Some further light could be shed from further retrospective subgroup-analyses. This would require large scale data on IO site specific OHCA outcomes though, which as of now are not systematically available in existing big registries.

As discussed, the practical implementation of the required clinical studies will face tremendous and complex difficulties.

The same holds true for the other promising prospect of potentially improving patient outcome in OHCA: endotracheal pharmacotherapy. As discussed above, there are good conceptual reasons – and some evidence from dedicated animal models – to revisit this obsolete treatment option.

Certainly, careful studies of the pharmacokinetics in humans would be of highest priority. Without proof for safe and effective dosing, no responsible recommendations for practical applications can be made. The lingering deleterious potential for unbalanced β-adrenergic stimulation from accidental underdosing should not be treated lightly.

Moreover, no data on possible long-term effects of high-dose endotracheal catecholamine application is available. The prolonged response of lung tissue to the amounts of adrenaline required to facilitate ROSC is not known. Necrotic damage is not difficult to imagine as one pathophysiologically plausible path to harm.

Primum non nocere is a not the noble ideal of high-minded scholars, but the firm duty of every clinician. It cannot be achieved without full appraisal of the scope of potential risks as well as intended benefits associated with clinical interventions.

Once again, this underscores the need for clinical studies with steady focus on clinical outcomes.

4 Conclusions

IO devices have been part of the standard repertoire of emergency medical services in the German speaking area for many years. They are widely available and routinely being used, especially during advanced life-support after out-of-hospital cardiac arrest.

Nonetheless, the present registry analysis – covering a time frame of 31 years – highlights the significance of IV access for adrenaline administration during resuscitation of out-of-hospital cardiac arrest. Whenever possible, IV access should be attempted. The IO application of adrenaline might be less effective, which might lead to worse patient outcome.

Due to the retrospective study design, a proof of causality was not feasible in principle.

For the foreseeable future, IO access will remain an important alternate route for drug and fluid treatment in urgent care. Especially whenever time is as critical as during cardio-pulmonary resuscitation and when IV access cannot be obtained, IO access should serve as immediate backup strategy.

Even though abandoned in 2010, the obsolete endotracheal route could re-gain new relevance as a potential secondary backup option. Before practice-changing clinical recommendations can be made, further pharmacokinetic studies of endotracheal therapy are needed though. As of now, no evidence-based dose recommendation can be made for the endotracheal route with good confidence.

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