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Editorial

'There's a hole in my bucket': 'No-flow', 'low-flow', and resuscitative calculus☆

Wenn der Beltz em Loch hat –	When the jug has a hole -
stop es zu meine liebe Lieses	top it up my dear Liese
Womit soll Ich es zustopfen –	With what shall I stop it -
mit Stroh, meine liebe Liese.	with straw my dear Liese.

Earliest known archetype of the children's song, "There's a Hole in My Bucket" *Bergliederbüchlein* (c 1700)

The resuscitation of cardiac arrest is an exercise in calculus. Fundamentally, ischemic injury accumulates over time until it eventually crosses some irrecoverable threshold. The whole of resuscitation comprises efforts to both attenuate the rate of this accumulation and ultimately cease further accrual by restoring spontaneous (or occasionally extracorporeal) circulation. This scenario is reminiscent of a quintessential mathematical problem, in which one is to account for the simultaneous draining and filling of a bucket and their combined effects on the change in vertical height of water.

Suppose, metaphorically, that the height of water indicates the probability of a given clinical outcome after cardiac arrest (e.g. return of spontaneous circulation [ROSC], survival, neurologic recovery). At the onset of cardiac arrest, a full bucket begins to drain at a given rate (Fig. 1). After some elapsed interval, resuscitation commences and a faucet opens. Superb resuscitation might even temporarily raise the water level, but the rate of drainage eventually eclipses any additional filling and the bucket will ultimately empty unless the drain is occluded (i.e. restoration of circulation). The impact of the rates and intervals of both drainage and filling on the height of water should become apparent. In this fashion, one can model the time-dependent likelihood of clinical outcomes over the course of resuscitation, given sufficient parameters.

The elapsed interval between collapse and onset of CPR is dubbed 'no-flow', whereas the elapsed interval between onset of CPR and restoration of circulation is dubbed 'low-flow'. Historically, their effects on resuscitation outcome were only observed in animal models of cardiac arrest that allowed for experimental manipulation. For example, in porcine models, increasing durations of no-flow, while holding low-flow and other variables constant leads to additional myocardial and neuronal injury.[1] The emergence of registry-based cohorts and granular clinical trial datasets now allows for modeling these interactions in humans. In this issue of *Resuscitation*, Guy, et al. characterize how 'no-flow' affects the likelihood of neurologic recovery at the time of hospital discharge.[2]

The authors conducted a secondary analysis of combined datasets from two Resuscitation Outcomes Consortium (ROC) trials, Prehospital Resuscitation Using an Impedance Valve (PRIMED) and Continuous or Interrupted Chest Compressions during CPR (CCC).[3–5] Both trials enrolled consecutive adult, EMS-treated, non-traumatic cases of out-of-hospital cardiac arrest (OHCA) in North America and were neutral for the primary outcome. ROC trials systematically recorded time-stamped data elements synchronized to the monitor-defibrillator, including all milestones of resuscitation. 'No-flow' was the interval between emergency dispatch notification and onset of professional CPR. To ensure the validity of 'no-flow' estimates, Guy, et al. included only subjects with bystander-witnessed OHCA (presumably, with immediate notification of the emergency dispatch system) and excluded subjects with bystander-initiated CPR or AED use (given the inability to identify the precise onset of CPR prior to EMS arrival. Out of nearly 43,000 subjects in these merged datasets, 7299 eligible subjects (17%) had complete data for both the independent variable and outcome. Poisson regression modeled the relationship between 'no-flow' and modified Rankin scale (mRS) 0–3 at hospital discharge with adjustment for Utstein covariates. The authors also identified the observed 'no-flow' interval beyond which no subject had mRS 0–3 and assessed for interactions with sex and initial cardiac rhythm via stratified analysis of these subgroups. Increasing 'no-flow' interval was associated with lower likelihood of mRS 0–3 (adjusted RR 0.87; 95% CI 0.85–0.90). In other words, for each additional minute of 'no-flow', the adjusted risk of mRS 0–3 decreased by 13% (95% CI 10–15%). Subgroup analysis by sex and initial cardiac rhythm yielded similar results. No subject with 'no-flow' beyond 20 min had eventual mRS 0–3.

The primary strengths of this work are the large population-based cohort from which it is drawn, and the diligent analysis restricted to those subjects with the greatest likelihood of valid time-stamp data. These estimates have a high degree of internal validity. Paradoxically, the primary limitation of these data is also one its strengths. By restricting the sample to just those subjects with valid data, the authors

☆ Editorial regarding "The relationship between no-flow interval and survival with favourable neurological outcome in out-of-hospital cardiac arrest: Implications for outcomes and ECPR eligibility" by Guy et al.

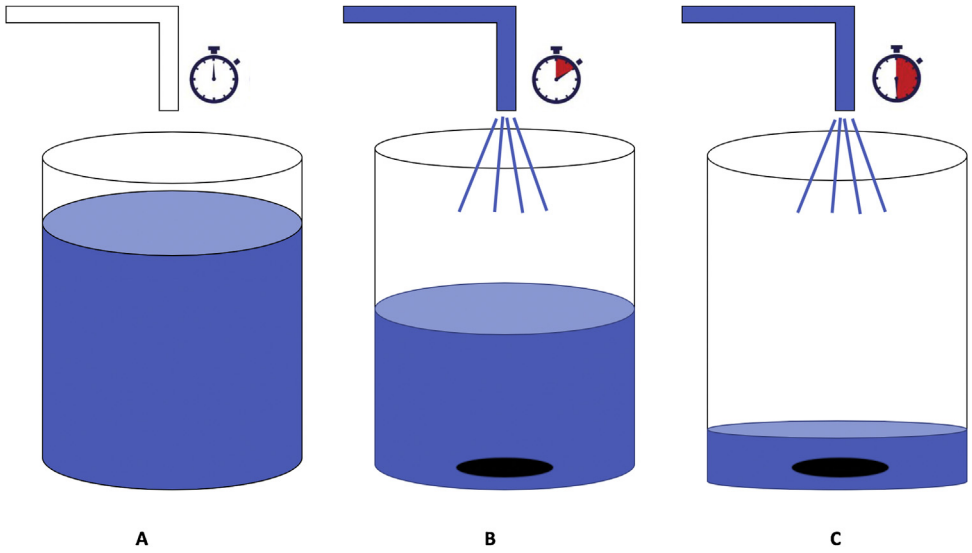

Fig. 1 – A bucket of water illustrating the relationships between the 'no-flow' interval, the 'low-flow' interval, and the time-dependent likelihood of clinical outcomes after cardiac arrest. A: A full bucket at the onset of cardiac arrest. B: After elapsed 'no-flow', in which water drains out of the bottom of the bucket, resuscitation commences and new water fills the bucket. C: After elapsed 'low-flow', the rate of drainage has outpaced the rate of filling and the bucket approaches empty.

were forced to exclude 83% of subjects in the merged datasets, raising the possibility of selection bias and limited external validity. Additionally, the authors elected not to adjust for subsequent 'low-flow' in the Poisson regression. This approach does highlight the specific impact of 'no-flow' on the likelihood of subsequent neurologic recovery at hospital discharge. The requisite 'low-flow' may depend on the preceding 'no-flow', which could obscure the true relationship between 'no-flow' and clinical outcomes. However, the relative contributions of 'no-flow' and 'low-flow' inherently impact the likelihood of subsequent clinical outcomes and the precise interactions between these two entities have yet to fully characterized. Finally, the included sample spans the 2010 CPR guideline updates, which did introduce a potential confounder in the paradigm shift to prioritize chest compressions and revise resuscitation sequencing from A-B-C (Airway, Breathing Circulation) to C-A-B (Chest compressions, Airway, Breathing).[6]

These data showcase the collective efforts to model the relationships between 'no-flow', 'low-flow', and clinical outcomes. Whereas Guy et al. present the most comprehensive work to date on 'no-flow', similar modeling of 'low-flow' has been conducted in large, North American and Japanese population-based cohorts.[7–11] Consider the comparative effects of 'no-flow' and 'low-flow' on the likelihood of mRS 0–3 at hospital discharge in secondary analyses of ROC trial datasets (Table 1). 'No-flow' appears to impart a greater degree of insult than 'low-flow'. On a practical level, this underscores the critical need for bystander recognition of cardiac arrest, bystander delivery of CPR,

Table 1 – Comparative insults of 'no-flow' and 'low-flow' durations as indicated by the likelihood of subsequent modified Rankin scale (mRS) 0–3 at hospital discharge. The subjects samples were derived from similar large, North American cohorts of out-of-hospital cardiac arrest.

	No-flow (Guy et al. *Resuscitation* 2020)	Low-flow (Reynolds et al. *Circulation* 2016)
n subjects	n = 7299	n = 11,368
Prevalence of mRS 0–3 at hospital discharge	8.4% (95% CI 8.4–9.1%)	8.0% (95% CI 7.5–8.5%)
Association with mRS 0–3 at hospital discharge	RR 0.87 (95% CI 0.85–0.90)	OR 0.93 (95% CI 0.92–0.95)
Approximate % reduction in risk of mRS 0–3 for each additional minute[a]	13% (95% CI 10–15%)	7% (95% CI 5–8%)
Approximate median lethal dose (LD_{50}) for subsequent neurologic recovery[b]	5 min	10 min
Longest observed interval with mRS 0–3	20 min	47 min

[a] OR approximates RR since the risk of mRS 0–3 in both studies is low (~8%).
[b] Elapsed interval at which the likelihood of mRS 0–3 at hospital discharge approaches 50%.

and public access defibrillation, all in order to minimize 'no-flow'. Furthermore, this substantiates the consideration of 'no-flow' and 'low-flow' duration as selection criteria for extracorporeal CPR candidates.[12] Conversely, 'no-flow' and 'low-flow' should not in and of themselves justify termination of resuscitation (TOR). Time-based estimates of the likelihood of clinical outcomes have yet to achieve a sufficient degree of certainty to be used in isolation when considering TOR. Obviously, the likelihood of subsequent survival or neurologic recovery asymptotically approaches zero with sufficiently long 'no-flow' or 'low-flow', but as the denominator of subjects declines over time, the confidence intervals around these point estimates become prohibitively wide.[7–10]

How do the compounding deleterious effects of 'no-flow' and 'low-flow' influence subsequent clinical outcomes? While the mathematical interaction terms have yet to be fully characterized, Adnet et al. offer a glimpse of these relationships in a secondary analysis of a large ($n > 27{,}000$ subjects), population based French OHCA registry. They constructed 3-dimensional plots of unadjusted proportions of 30-day survival (y-axis), 'no-flow' (z-axis), and 'low-flow' (x-axis).[13] The apparent rate of decline in the likelihood of 30-day survival was greater along the 'no-flow' axis compared to the 'low-flow' axis. Instances of 30-day survival were still observed after prolonged 'low-flow', provided that 'no-flow' was brief. The topographical contours of these plots were greatly influenced by subject age, sex, initial cardiac rhythm, and location of cardiac arrest (ostensibly a surrogate for witnessed collapse).

The interactive model of 'no-flow', 'low-flow', and subsequent clinical outcomes remains incomplete with exponential potential for complexity. What are the precise interaction effects of 'no-flow' and 'low-flow' on subsequent clinical outcomes? What relative contributions of 'no-flow' and 'low-flow' are tolerable before crossing some threshold of irreversible injury? Does longer 'no-flow' necessitate longer 'low-flow' before restoration of circulation is possible? Are the influences of 'no-flow' and 'low-flow' on clinical outcomes truly linear? That is, do incremental increases of either impart the same additional degree of injury if they occur earlier or later in resuscitation? How are these interactions modified by Utstein covariates or subject-specific comorbidities? How are these interactions modified by CPR quality during 'low-flow'? The number of additional questions prompted by this work indicates that Guy et al. are pursuing a fruitful line of inquiry.

Conflict of interest

None.

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