·述评·

Will models of naturally occurring disease in animals reduce the bench-to-bedside gap in biomedical research?

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The bench-to-bedside gap in many areas of biomedicine continues to be of great concern. Promising basic research findings often fail to succeed in clinical trials [1-5]. One reason may be the difficulties of implementing clinical research that is powered enough to detect a treatment effect, especially in complex disease processes such as severe sepsis where patient heterogeneity is tremendous [6]. Another is that animal disease models developed to mimic a certain characteristic of the target disease often lack key features of their real life human entity[7]. Sophisticated animal models closely resembling the relevant human pathophysiologic aspects are necessary to test a specific therapeutic target prior to clinical testing[8-11]. Vivid interplay between basic and clinical scientist is essential to achieve this[12].

With that in mind we have developed a rodent model of emergency cardiopulmonary bypass (ECPB)[13-14]. A large proportion of victims of sudden cardiac arrest (CA) do not achieve return of spontaneous circulation (ROSC) when using conventional advanced life support (ALS) alone. Around 80% of adult out-of-hospital cardiac arrest (OHCA) patients and 55% of in-hospital cardiac arrest (IHCA) patients in whom cardiopulmonary resuscitation (CPR) was initiated do not achieve ROSC [15-17]. In pediatric patients with IHCA around 35% to 60% achieve ROSC [18]. Furthermore, duration of CPR is negatively correlated with survival to hospital discharge [19]. ECPB offers the opportunity to rescue those patients that are refractory to conventional CPR, and has been employed in that indication in both pediatric and adult patients [20]. However, next to serving as blood flow generator and a gas exchange element, ECPB offers tremendous control over the reperfusion process and gives way to a multitude of opportunities for therapeutic interventions, such as the inclusion of antioxidant or white blood cell filters. Given the complexity of cellular and subcellular responses to ischemia and reperfusion, multi-component therapeutics are a logical solution to a multiple pathway disease like reperfusion injury. Nevertheless, the optimal constituents of such a reperfusion cocktail to take full advantage of this unique opportunity need to be further elucidated [11]. Testing the collective group of pharmacological components is therefore an important step towards optimizing clinical ECPB, and a whole animal model is necessary to test the effect of such a strategy in the context of manifold interactions between severity of injury, multi organ dysfunction and therapeutics. But even when using complex whole animal models such as a rodent ECPB model, limitations will exist in how these predict treatment effects in human subjects. As much as CA and ECPB animal studies are designed to mimic reality, research subjects are anesthetized, healthy, adolescent and single gender animals [21-22]. This leads to problems with the external validity and generalizability of the models[10], since attributes of the OHCA human population include older age, a female : male ratio of 1 : 2, numerous co-morbidities (e.g. coronary artery disease, hypertension, diabetes mellitus), and highly variable CA to CPR (no flow) to ROSC (low flow) intervals [23]. Inhalant and other anesthetics that are a frequent part of experimental animal studies but are rarely part of human peri-arrest management, are capable of inducing marked, dose-dependent preconditioning and can lead to protection even hours after discontinuation of anesthesia when the vast majority of the anesthetic is washed out[24]. However, not using carefully administered anesthesia to reduce animal suffering will cause numerous and significant neuroendocrine effects that can affect severity of injury and outcomes, violates animal welfare principles and is regarded as unacceptable in the scientific community.

Some of these limitations could be avoided by learning from animals that experience CA for natural causes. Thousands of pet dogs experience CA every year for causes that may be similar to the conditions found in people. The

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Reassessment campaign on Veterinary Resuscitation （RECOVER）recently provided the first consensus based CPR guidelines on how to treat these animals best after conducting an evidence evaluation process similar to the one used by the International Liaison Committee on Resuscitation （ILCOR）[25-26]. RECOVER in collaboration with their colleagues from human medicine will start to systematically collect data from naturally occurring CA cases and the resuscitation efforts by using electronic registries and databases. This will enable the researchers to test novel therapeutics during these spontaneously occurring resuscitation efforts with the potential to resemble far more closely the real human condition than any bench top model, reducing some of the confounding elements typical to experimental models and limiting the use of laboratory animals. And most importantly, these spontaneously occurring disease models could hold great promise in reducing the bench-to-bedside gap by more reliably predicting whether a promising therapeutic intervention based on pre-clinical work translates into a measurable clinical benefit in human subjects.

生物医学研究中应用自发性疾病动物模型能否使基础研究更加贴近临床实践？（译文）

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在诸多生物医学研究领域，实验室与临床之间的差异受到极大的关注。一些“看上去很美”的基础研究结果在应用于临床研究时却完全不是那么回事儿[1-5]。其中原因之一是多种复杂疾病，如脓毒症，其临床表现千变万化，病程衍变多样，即使经过精心设计的临床研究也很难准确验证某项新治疗的疗效[6]。另外一个原因是，大多数动物疾病模型着重模仿目标疾病的某一个特性，却常常缺少人类发病时作为一个完整生命体所体现出来的关键疾病特征[7]。因此，在一项新的治疗手段开始实施临床研究前，需要精心设计一些与人类相关疾病病理生理过程贴近的动物模型，以验证其疗效[8-11]。毋容置疑，基础和临床研究科研人员之间的充分互动是实现这一目标的前提[12]。

秉承使基础研究更加贴近临床的理念，我们设计出了一种急诊心肺体外循环（ECPB）的啮齿类动物模型[13-14]。现有数据表明，仍有大量心搏骤停（CA）患者在接受传统高级生命支持后没有出现自主循环恢复（ROSC），约有 80%院外心搏骤停（OHCA）和 55%住院心搏骤停（IHCA）的成年患者在接受心肺复苏（CPR）后没有实现 ROSC[15-17]；在儿科 IHCA 患者中仅 35%～60%可以实现 ROSC[18]；而且，CPR 的持续时间与出院生存率呈负相关[19]。无论对于儿科患者还是成年患者，ECPB 均可为那些使用传统 CPR 不能实现 ROSC 的患者提供一种生存的机会[20]。在应用 ECPB 时，除了可以为患者提供血流循环驱动力和气体交换外，人们通过调控灌注过程中的各种参数，使多种干预措施成为可能。同时，通过精心选择灌注时所使用的药物种类，可进一步优化 ECPB 的临床应用。机体对于缺血和再灌注损伤有复杂的细胞和亚细胞水平反应，对于类似再灌注损伤这样多途径参与的疾病过程而言，实施“鸡尾酒”式的组合治疗是合理选择。例如，在体外循环过程中，应用抗氧化剂和/或血液白细胞滤过组合治疗可以有效减少再灌注损伤。然而，还需要更多的基础研究来验证在“鸡尾酒”灌注疗法中如何优化配方以充分利用这项独特的治疗技术[11]。研究者评估 ECPB 治疗中各个参与因素（如损伤的严重程度）、器官功能障碍和治疗手段等之间的相互作用时，应将动物整体作为研究对象。但即使应用如啮齿类 ECPB 模型这样十分复杂的整体动物模型，仍存在很多制约因素干扰了对 ECPB 真实临床疗效的评估。同 CA 模型一样，ECPB 的研究模型仅仅是对真实疾病过程的某一个方面的模拟。研究对象是在麻醉状态下，健康、未成年的雄性动物[21-22]。而在 OHCA 人群中，男女比例约为 1∶2，患者中不但包括老年人，而且也常患有多种基础疾病（如冠心病、高血压、糖尿病等），且发生 CA 后从 CPR（无灌注）到 ROSC（低灌注）的间隔也不尽相同[23]，因此，现有动物模型不可避免地存在有效性和代表性的问题[10]。在实验动物模型中，常使用吸入性麻醉药物或其他麻醉药物，而人类 CA 治疗过程中很少使用此种干预措施。吸入性麻醉药

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物可以产生显著的剂量依赖性预处理作用，甚至停止用药后很长时间，大部分麻醉药已经被代谢的情况下，这种保护作用仍然存在[24]。不恰当应用麻醉药物会产生复杂、显著的神经－内分泌效应，可能会增加模型动物的痛苦，影响动物的损伤程度以及预后。同时这种行为会被视为违反保护动物福利的原则，并不被科学界所接受。

然而，通过研究一些可自然发生 CA 的动物，可以避免上述动物实验模型中的诸多缺陷。每年都有大量的宠物狗发生与人类相似的 CA。新近动物医学的心肺复苏再评价运动（RECOVER）通过采取与国际急救与复苏联合会（ILCOR）相似的证据评估体系，提出首个关于动物 CPR 规范的专家共识，用以指导为发生 CA 的动物提供最好的治疗[25-26]。在 RECOVER 团队中，临床医学专家们通过电子登记和数据库系统广泛收集了在动物界中自然发生 CA 的案例。与实验模型中的动物相比，这些自发性 CA 的动物与人类真实的临床情况十分相似，建立 CA 动物的数据库将有助于研究者检验临床治疗新策略，避免实验动物模型中典型的混淆因素，并减少实验动物的使用数量。

最重要的是，这些自发性疾病模型为减少基础与临床之间的差异提供了希望。借助这些模型，人们可以准确预测在临床前阶段看起来十分有前景的某项治疗是否可以使人类患者临床受益。

参考文献

[1] Opal SM, Patrozou E. Translational research in the development of novel sepsis therapeutics: logical deductive reasoning or mission impossible?. Crit Care Med, 2009, 37: S10-15.

[2] Hackam DG, Redelmeier DA. Translation of research evidence from animals to humans. JAMA, 2006, 296: 1731-1732.

[3] Böttiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. N Engl J Med, 2008, 359: 2651-2662.

[4] Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. N Engl J Med, 2008, 359: 21-30.

[5] Aufderheide TP, Nichol G, Rea TD, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. N Engl J Med, 2011, 365: 798-806.

[6] Marshall JC, Deitch E, Moldawer LL, et al. Preclinical models of shock and sepsis: what can they tell us?. Shock, 2005, 24 Suppl 1: 1-6.

[7] Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. J Immunol, 2004, 172: 2731-2738.

[8] Aigner B, Renner S, Kessler B, et al. Transgenic pigs as models for translational biomedical research. J Mol Med (Berl), 2010, 88: 653-664.

[9] Hollenberg SM. Mouse models of resuscitated shock. Shock, 2005, 24 Suppl 1: 58-63.

[10] van der Worp HB, Howells DW, Sena ES, et al. Can animal models of disease reliably inform human studies?. PLoS Med, 2010, 7: e1000245.

[11] Becker LB, Weisfeldt ML, Weil MH, et al. The PULSE initiative: scientific priorities and strategic planning for resuscitation research and life saving therapies. Circulation, 2002, 105: 2562-2570.

[12] Mankoff SP, Brander C, Ferrone S, et al. Lost in translation: obstacles to translational medicine. J Transl Med, 2004, 2: 14.

[13] Boller M, Jung SK, Odegaard S, et al. A combination of metabolic strategies plus cardiopulmonary bypass improves short-term resuscitation from prolonged lethal cardiac arrest. Resuscitation, 2011, 82 Suppl 2: S27-34.

[14] Han F, Boller M, Guo W, et al. A rodent model of emergency cardiopulmonary bypass resuscitation with different temperatures after asphyxial cardiac arrest. Resuscitation, 2010, 81: 93-99.

[15] Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14 720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation, 2003, 58: 297-308.

[16] Stiell IG, Wells GA, Field B, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med, 2004, 351: 647-656.

[17] Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. JAMA, 2005, 293: 305-310.

[18] Topjian AA, Nadkarni VM, Berg RA. Cardiopulmonary resuscitation in children. Curr Opin Crit Care, 2009, 15: 203-208.

[19] Meaney PA, Nadkarni VM, Kern KB, et al. Rhythms and outcomes of adult in-hospital cardiac arrest. Crit Care Med, 2010, 38: 101-108.

[20] Gaieski DF, Boller M, Becker LB. Emergency cardiopulmonary bypass: a promising rescue strategy for refractory cardiac arrest. Crit Care Clin, 2012, 28: 211-229.

[21] Wenzel V, Padosch SA, Voelckel WG, et al. Survey of effects of anesthesia protocols on hemodynamic variables in porcine cardiopulmonary resuscitation laboratory models before induction of cardiac arrest. Comp Med, 2000, 50: 644-648.

[22] Papadimitriou D, Xanthos T, Dontas I, et al. The use of mice and rats as animal models for cardiopulmonary resuscitation research. Lab Anim, 2008, 42: 265-276.

[23] Engdahl J, Holmberg M, Karlson BW, et al. The epidemiology of out-of-hospital 'sudden' cardiac arrest. Resuscitation, 2002, 52: 235-245.

[24] Wang L, Traystman RJ, Murphy SJ. Inhalational anesthetics as preconditioning agents in ischemic brain. Curr Opin Pharmacol, 2008, 8: 104-110.

[25] Boller M, Fletcher DJ. RECOVER evidence and knowledge gap analysis on veterinary CPR, part 1: evidence analysis and consensus process: collaborative path toward small animal CPR guidelines. J Vet Emerg Crit Care (San Antonio), 2012, 22 Suppl 1: S4-12.

[26] Fletcher DJ, Boller M, Brainard BM, et al. RECOVER evidence and knowledge gap analysis on veterinary CPR, part 7: clinical guidelines. J Vet Emerg Crit Care (San Antonio), 2012, 22 Suppl 1: S102-131.

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