

Cardiopulmonary Resuscitation Skills Retention and Self-Confidence of Preclinical Medical Students

Lorraine Avisar MD^{1*}, Arthur Shiyovich MD^{1*}, Limor Aharonson-Daniel PhD^{1,2} and Lior Nesher MD^{1,3}

¹Department of Emergency Medicine, Recanati School for Community Health Professions, ²PREPARED Center for Emergency Response Research, and ³Division of Internal Medicine, Soroka University Medical Center, all affiliated with Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

ABSTRACT: **Background:** Sudden cardiac death is the most common lethal manifestation of heart disease and often the first and only indicator. Prompt initiation of cardiopulmonary resuscitation (CPR) undoubtedly saves lives. Nevertheless, studies report a low level of competency of medical students in CPR, mainly due to deterioration of skills following training. **Objectives:** To evaluate the retention of CPR skills and confidence in delivering CPR by preclinical medical students. **Methods:** A questionnaire and the Objective Structured Clinical Examination (OSCE) were used to assess confidence and CPR skills among preclinical, second and third-year medical students who had passed a first-aid course during their first year but had not retrained since. **Results:** The study group comprised 64 students: 35 were 1 year after training and 29 were 2 years after training. The groups were demographically similar. Preparedness, recollection and confidence in delivering CPR were significantly lower in the 2 years after training group compared to those 1 year after training ($P < 0.05$). The mean OSCE score was 19.8 ± 5.2 (of 27) lower in those 2 years post-training than those 1 year post-training (17.8 ± 6.35 vs. 21.4 ± 3.4 respectively, $P = 0.009$). Only 70% passed the OSCE, considerably less in students 2 years post-training than in those 1 year post-training (52% vs. 86%, $P < 0.01$). Lowest retention was found in checking safety, pulse check, airway opening, rescue breathing and ventilation technique skills. A 1 year interval was chosen by 81% of the participants as the optimal interval for retraining (91% vs. 71% in the 2 years post-training group vs. the 1 year post-training group respectively, $P = 0.08$). **Conclusions:** Confidence and CPR skills of preclinical medical students deteriorate significantly within 1 year post-training, reaching an unacceptable level 2 years post-training. We recommend refresher training at least every year.

IMAJ 2013; 15: 622–627

KEY WORDS: cardiopulmonary resuscitation (CPR), medical students, retention, skills, self-confidence

Sudden cardiac death is often the first manifestation of heart disease and is often lethal [1,2]. In Israel, the rate of successful resuscitation to hospital discharge was reported to be 11%

[3]. It is known that survival rates in cardiac arrest events fall between 7% and 10% for each minute following collapse without cardiopulmonary resuscitation being performed [4]. In Israel it has been reported that the mean response time of the mobile intensive care units is 10.3 minutes; compounding that, only in 14% of the cases does a bystander perform basic cardiac life support before the arrival of the mobile unit [3]. It is therefore not surprising that any improvements in advanced life support therapies are less successful in promoting patient survival than successfully engaging a lay rescuer to perform high quality CPR [5]. Hence CPR is a very important clinical skill for medical students as potential first responders in various clinical settings and in the community. It should therefore be taught during early training, as early as the preclinical years [6-8].

Appreciating its importance, many medical schools worldwide schedule CPR courses during the early years of training, employing various programs and methods including high fidelity patient-simulating mannequins, multimedia computer-based guidance, and virtual reality [6-10]. Nevertheless, studies report relatively low competency of medical students in CPR [11,12]. This can be attributed to the deterioration of skills due to the time lapse after training [7,13,14]. At the Faculty of Health Sciences of Ben-Gurion University of the Negev, all medical students undergo CPR training during a basic first-aid course in their first year; retraining is required only at the beginning of the fourth year as part of a more advanced course. The aims of the current study were to evaluate the retention of CPR skills and to assess students' self-confidence in their ability to deliver efficient CPR, 1 and 2 years after their first year.

SUBJECTS AND METHODS

In this cross-sectional study we included preclinical, second and third-year medical students (1 year post-training and 2 years post-training) from the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel, throughout 2009–2010. Inclusion criteria were as follows: all students who attended the basic first-aid course during the first year (i.e., 1 and 2 years prior to the study) and passed the written and

*The first two authors contributed equally to this study

CPR = cardiopulmonary resuscitation

practical exam at the end. Exclusion criteria were previous or current experience in emergency medicine (e.g., paramedics) or enrollment in other external CPR training or any type of formal retraining since the first year course. Students who did not fully complete the study requirement (a questionnaire and a practical exam) were also excluded.

The CPR training program at Ben-Gurion University, completed by all study participants 1 or 2 years before the study, included a 2 hour frontal lecture followed by 6 hours of simulated practice on mannequins. The training was based on the 2005 American Heart Association guidelines [5]. Notably, the course completed by all study participants (both second and third-year students) during their first year was identical, with no changes in curriculum, duration, or final exam.

The study received approval from the university's Faculty of Health Human Research Ethics Committee. After the nature and the purpose of the study were explained, the participants provided written consent.

ASSESSMENTS

In order to assess preparedness, recollection and self-confidence in delivering CPR according to the guidelines, a questionnaire was used. To assess CPR skills students took a practical exam.

- **The questionnaire** contained three parts; a) demographics (age and gender), previous resuscitation training or CPR experience; b) six questions with six categories on a Likert-type scale (1 = low, 6 = high) asking the student to evaluate his/her preparedness and recollection in delivering CPR; c) students were asked about the correct rate of chest compressions and breaths per minute in a single adult CPR, to rate their willingness to receive a refresher CPR training (1–6), and their perceived optimal interval of such training (1 to 4 years).
- **The practical exam** included the Objective Structured Clinical Examination, using mannequin simulators. A skill checklist was developed to grade students across the criteria required for performance of resuscitation and included 27 items [Table 1]. Each skill on the checklist was marked in two categories: not done or done and was scored 0 or 1 respectively. Every subject was evaluated according to the latter list by an experienced CPR instructor. Subsequently the instructors were asked to rate the order, the effectiveness of compressions, the effectiveness of CPR, and a general evaluation using five categories on a Likert-type scale (0 = low, 4 = high). The evaluation of the OSCE was equivalent to the evaluation used in the first-year OSCE, using the same passing score for both tests.

Table 1. OSCE criteria scores according to the post-training duration

Criterion/skill	All students (n=64) (%)	One year post-training (n=35) (%)	Two years post-training (n=29) %	P value
Total score (mean ± SD)	19.8 ± 5.2	21.4 ± 3.4	17.8 ± 6.35	0.009
Passed the OSCE	70	86	52	0.01
1. Ensures safety	69	66	72	0.565
2. Attempts to speak with the patient	84	91	76	0.088
3. Taps the mannequin to check consciousness	64	69	59	0.409
4. Calls for help	63	60	66	0.650
5. Opens the mouth and checks for secretions	64	63	66	0.825
6. Puts palm on the mannequin's forehead	69	71	66	0.612
7. Places palm on chin/jaw	49	49	45	0.765
8. Head tilt	70	80	57	0.062
9. Bends to listen and feel breathing	77	86	66	0.058
10. Keeps two hands at head tilt	38	47	24	0.044
11. Checks breathing for 5–10 seconds	66	83	45	0.001
12. Pinches nostrils shut for mouth-to-mouth breathing	70	74	66	0.445
13. Covers the mannequin's mouth, sealing it	77	86	66	0.058
14. Succeeds in delivering air	69	77	59	0.112
15. Gives two breaths	83	94	69	0.008
16. Mannequin's chest rises	70	80	59	0.062
17. Places fingers on the carotid artery	86	86	86	0.955
18. Checks pulse for 5–10 seconds	67	83	45	0.003
19. Places hands at the center of the chest, between the nipples	83	83	83	0.992
20. Performs compressions with only the heel of the hand	81	83	79	0.717
21. Keeps hands on the chest (does not bounce)	86	91	79	0.165
22. Keeps elbows straight	83	83	83	0.992
23. Delivers 30 compressions	94	100	86	0.023
24. Delivers 30 uninterrupted compressions	92	94	90	0.492
25. Ceases delivering 2 breaths	73	83	62	0.061
26. Time of 2 breaths ≤ 6 seconds	73	86	59	0.015
27. Performs CPR continuously for at least 2 minutes	78	86	69	0.107
Integrated skills (mean ± SD)				
Initial phase (0–16)	10.8 ± 3.58	11.77 ± 2.75	9.58 ± 4.12	0.019
Pulse check (0–2)	1.5 ± 0.69	1.69 ± 0.63	1.34 ± 0.72	0.048
Ventilation technique (0–4)	2.9 ± 1.53	3.17 ± 1.38	2.48 ± 1.63	0.073
Chest compressions technique (0–4)	3.33 ± 1	3.4 ± 0.88	3.24 ± 1.15	0.535

DATA ANALYSIS AND DEFINITIONS

Data were entered into Microsoft Excel worksheets and analyzed using SPSS V.19 software. Data are presented as mean and standard deviation for continuous variables and as frequencies and a percent of categories for other variables. Internal consistency of the questionnaire and the OSCE was

OSCE = Objective Structured Clinical Examination

evaluated using Cronbach's α coefficient and resulted in $\alpha = 0.91$ and $\alpha = 0.85$ respectively. Additional variables were composite variables, or grouping of items from the questionnaire or the OSCE skill checklist as follows:

- Preparedness for delivering CPR – mean score of three questions on preparedness for delivering CPR
- Recollection of CPR protocol – mean score of three questions on recollection of the sequence of CPR and techniques of various CPR stages
- Self-confidence for delivering CPR – mean score of the above six questions
- Performance in the initial phase (items 1–16) – pulse assessment (items 17 & 18), chest compressions technique (items 19–22), ventilation technique (items 12,13,14,16).

Comparisons between groups were performed with Student's *t*-test for continuous variables and with the χ^2 test for categorical variables. All tests of hypotheses were considered significant when two-sided probability values were $P < 0.05$.

RESULTS

Of the 134 medical students (67 students in each year), 88 gave their consent to participate in the study. Twenty-four were excluded for the following reasons: 9 did not adhere to the study requirements (did not attend the OSCE) and 15 had previous or ongoing experience in emergency medicine. Accordingly, 64 students (35 in second year and 29 in third year) qualified for the study. The age of the students was 24.8 ± 2.25 years (range 21–31), and 53% in both years were female.

SELF-REPORTED PREPAREDNESS, RECOLLECTION AND CONFIDENCE

The self-reported preparedness, recollection and confidence of the students in delivering CPR were low-intermediate (lower for preparedness than for recollection), whereas all three parameters were significantly lower in third as compared to second-year students [Figure 1].

OSCE-ASSESSED RETENTION OF CPR SKILLS

The mean score in the OSCE was 19.8 ± 5.2 (highest possible score 27), which was significantly lower in the 2 years post-training compared with the 1 year post-training students (17.8 ± 6.35 vs. 21.4 ± 3.4 , respectively, $P = 0.009$). Furthermore, only 70% of all students passed the OSCE, with a significantly lower rate among the 2 year post-training group than the 1 year group (52% vs. 86%, $P < 0.01$). The results of the evaluated OSCE skills according to the post-training year are displayed in Table 1. The performance was consistently better in the 1 year group compared to the 2 year group. The 1 year group received significantly higher grades in the integrated scores accounting for the initial phase and the pulse check, a tendency towards a higher grade in the ventilation technique score, and similar

Figure 1. Self-assessed preparedness, recollection and overall confidence for delivering CPR according to post-training duration

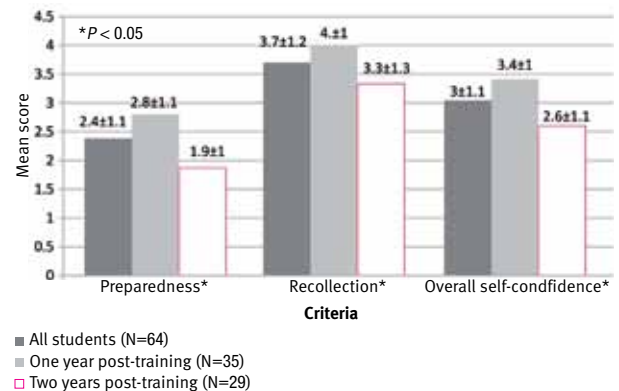
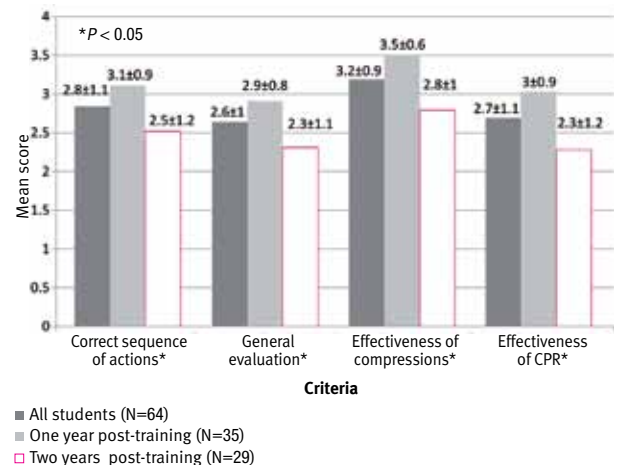


Figure 2. Examiners' evaluations of OSCE performance

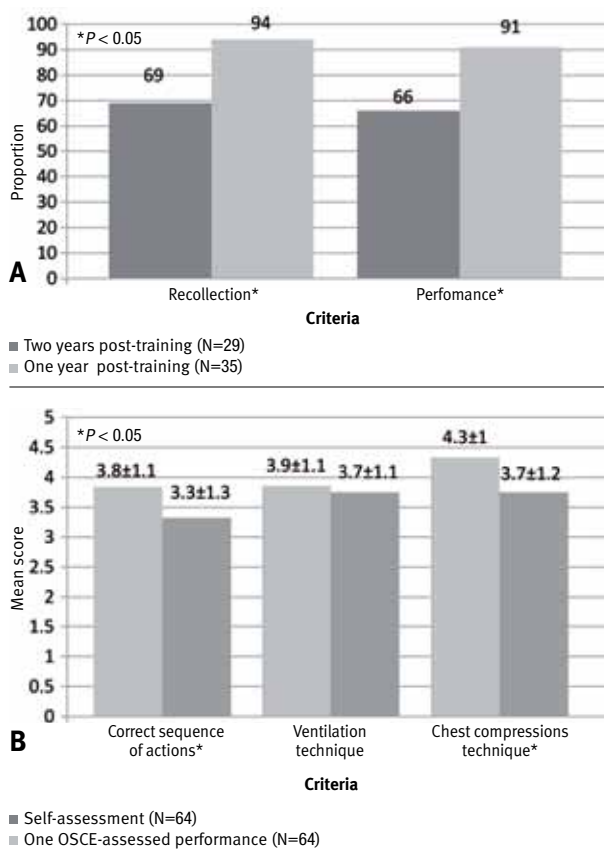


grade in the chest compression technique score compared to the 2 year group [Table 1]. Examiners' ratings of OSCE performance categories were significantly higher in the 1 year group compared to the 2 year group [Figure 2].

SELF-REPORTED VERSUS OSCE ASSESSED PERFORMANCE

A significantly higher rate was found in the 1 year group for correctly answering the question and performing de facto the ventilations:compressions ratio that they had been taught [Figure 3A]. Of those who knew the correct ratio, 85% implemented it during the OSCE in both years. In a comparison of specific questions in the questionnaire relating to self-assessed performance versus integrated scores, or examiners' assessment of those skills following stratification to the same 5 Likert-type categories scale, students correctly estimated their performance in ventilation technique and underestimated their performance in chest compressions technique and sequence of CPR actions [Figure 3B].

Figure 3. [A] Recollection versus performance of ventilations: compressions ratio. **[B]** Self versus OSCE-assessed performance



THE PERCEIVED OPTIMAL INTERVAL BETWEEN REFRESHER TRAININGS

When asked about the optimal interval between refresher trainings, overall 81% of the students answered 1 year intervals, 17% answered 2 year intervals, and only 2% answered 3 or 4 year intervals. When comparing the 2 year group to the 1 year group, a non-significant tendency was found for members of the 2 year group to choose training once a year (91% vs. 71% respectively, $P = 0.08$). Furthermore, for the question relating to the students' willingness to participate in a refresher training, 82% of all students marked 5 or 6 (out of 6, 6 being the most positive). The mean score was 5.45, higher in the 2 year group than the 1 year group (5.7 vs. 5.2 respectively, $P < 0.05$).

DISCUSSION

The current study demonstrates that self-reported preparedness, recollection and confidence of preclinical medical students in delivering CPR are clearly insufficient 1 year after the initial training, and significantly and unacceptably lower 2 years post-training. These findings are consistent with previ-

ous studies demonstrating that self-assessed confidence in delivering CPR after training significantly and quite rapidly decreases, both among medical students and lay responders [15,16]. The reduced confidence, preparedness and recollection could often result in decreased willingness and hesitation to initiate bystander CPR [16,17]. However, refresher training or actively participating in a cardiac arrest resuscitation attempt increases confidence in resuscitation skills and thus performance and willingness to initiate CPR [16-18].

Nevertheless, Wynne et al. [19] previously reported a disparity between confidence and competence in CPR training. They did not find a correlation between the amount of training and perceived confidence, and noted that a rise in confidence is not necessarily reflected by a rise in competence [19]. We agree that additional factors not fully controlled by additional training – i.e., artificial training situations and fear of “the real thing” – could affect performance.

The results of the OSCE in the present study demonstrate that the CPR skills of preclinical medical students deteriorate to what may well be considered unacceptable levels as early as 1 year post-training, and even worse 2 years post-training with only 50% of the students passing the test. This finding is consistent with previous reports showing rapid deterioration of skills post-training in laypersons, preclinical and clinical medical students, as well as professionals [13-16,20,21]. Considering individual skills, a low proportion of correct performance was seen for checking safety, pulse check, airway opening, rescue breathing, and ventilation technique. However, chest compressions were performed adequately by a relatively high proportion of students in both years. This is consistent with Frkovic et al. [14] who reported that 1 year post-training the number of first or second-year medical students who were able to check pulse, open and check airway and check safety declined to 45%, 69%, 64% respectively, while 82% performed adequate chest compressions. Additionally, more rapid deterioration of skills in airway opening and rescue breathing than chest compression technique was previously reported by Woollard et al. [22] in lay volunteer responders and by Nicol et al. [13] in interns. By contrast, Grzeskowiak [7] compared the performance of first and sixth-year medical students and reported 72% retention for opening the airway and checking for breathing skills, but only 50% retention for compressions technique. This finding could possibly be explained by the fact that the later years of the curriculum concentrate on advanced resuscitation techniques. Similar to the findings of Frkovic et al. [14], we found that both the knowledge and performance of ventilations:compressions ratio were relatively high 1 year post-training. Nevertheless a significant decay is evident in this skill and knowledge 2 years post-training in our study. This is consistent with the findings of Nicol et al. [13] in fifth-year students prior to refresher and advanced first-aid training.

Another important finding is that students correctly estimated their performance in ventilation technique but underestimated their performance in chest compressions technique and sequence of CPR actions. This further supports the previous statement that self-confidence and thus willingness to perform bystander CPR is impaired, possibly even more than the actual knowledge and performance. When well-prepared (after the CPR classes or on the day of the final exam) first and sixth-year students were asked to evaluate their own ability to perform CPR, self-estimations were very high, higher than their performance in the written and practical exam [7]. This, in our opinion, means that the self-confidence is high immediately after training yet decreases significantly as time passes.

It has been suggested that the physical skill-based components may deteriorate in a more predictable fashion following training than the reduction in knowledge. Moreover, Moser and Coleman [23] suggest that CPR skills appear to decline at a faster rate than knowledge, with a significant decline in CPR skills occurring as early as 2 weeks post-training. This is supported by the finding that theoretical CPR knowledge retention in airline cabin crew 12 months post-training was high, but there was an inability to meet the standard passing criteria in CPR skill performance [24]. This is related to another important finding of the current study; namely, most students were interested in refresher training and thought that the optimal interval between such training courses should be 1 year. This was more prominent in the 2 year group. Although the optimal interval between courses is unknown, updated 2010 CPR guidelines emphasize the need to move toward more frequent assessment and reinforcement of skills [17]. The optimal timing and method for this assessment and reinforcement are not known. Thus, due to the limited resources for frequent traditional refresher methods that include lectures and “hands-on training,” many innovative concepts to reduce the decay of skills and knowledge were recently introduced. Examples of such concepts include, among others, virtual online CPR simulations and viewing of a reminder video clip using a mobile phone [10,16]. It is clear that any refresher CPR training method should be based on a balance between cost and effectiveness.

LIMITATIONS

A few limitations of our study should be mentioned. First, the sample size was relatively small and might have prevented reaching statistical significance in several parameters; we believe that research with a larger sample should be conducted. Second, because this study included subjects who were trained before publication of the 2010 CPR guidelines, assessments of CPR skills were performed according to the 2005 CPR guidelines [5].

CONCLUSIONS

Preparedness, recollection, self-confidence and CPR skills of preclinical medical students deteriorate within a year of

CPR training. The decay is significantly more prominent, to an unacceptable level, 2 years post-training. In some areas the deterioration of skills is more prominent (e.g., checking safety, pulse check, airway opening, rescue breathing and ventilation technique). Hence, a refresher training course within no more than a year from training is warranted.

Acknowledgments

The authors are grateful to the students and CPR instructors who willingly participated in the study and to Dr. Keren Dopelt for her assistance in the statistical analysis of the data.

Correspondence author:

Dr. A. Shiyovich

Dept. of Internal Medicine, Soroka University Medical Center, Beer Sheva 84101, Israel

Fax: (972-8) 681-2202

email: arthur.shiyovich@gmail.com

References

- Zheng ZJ, Croft JB, Giles WH, Mensah GA. Out-of-hospital cardiac deaths in adolescents and young adults in the United States, 1989 to 1998. *Am J Prev Med* 2005; 29 (5 Suppl 1): 36-41.
- Fuchs T, Torjman A, Galitzkaya L, Leitman M, Pilz-Burstein R. The clinical significance of ventricular arrhythmias during an exercise test in non-competitive and competitive athletes. *IMAJ* 2011; 13 (12): 735-9.
- Canetti M, Feigenberg Z, Caspi A, et al. Out-of-hospital resuscitation in Israel 2000. *Harefuah* 2004; 143 (11): 785-9, 839 (Hebrew).
- Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. *Circulation* 1997; 96 (10): 3308-13.
- 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; 112 (24 Suppl): IV1-203.
- Tipa RO, Bobirnac G. Importance of basic life support training for first and second year medical students – a personal statement. *J Med Life* 2010; 3 (4): 465-7.
- Grzeskowiak M. The effects of teaching basic cardiopulmonary resuscitation – a comparison between first and sixth year medical students. *Resuscitation* 2006; 68 (3): 391-7.
- Graham CA, Scollon D. Cardiopulmonary resuscitation training for undergraduate medical students: a five-year study. *Med Educ* 2002; 36 (3): 296-8.
- Das M, Elzubeir M. First aid and basic life support skills training early in the medical curriculum: curriculum issues, outcomes, and confidence of students. *Teach Learn Med* 2001; 13 (4): 240-6.
- Creutzfeldt J, Hedman L, Medin C, Stengard K, Fellander-Tsai L. Retention of knowledge after repeated virtual world CPR training in high school students. *Stud Health Technol Inform* 2009; 142: 59-61.
- Suzuki A, Suzuki Y, Takahata O, et al. A survey of 3,303 6th-year medical students from 36 universities concerning knowledge of resuscitation – more than 80% of medical students can not perform standard cardiopulmonary resuscitation? *Masui (Jpn J Anesthesiol)* 2001; 50 (3): 316-22.
- Luscher F, Hunziker S, Gaillard V, et al. Proficiency in cardiopulmonary resuscitation of medical students at graduation: a simulator-based comparison with general practitioners. *Swiss Med Wkly* 2010; 140 (3-4): 57-61.
- Nicol P, Carr S, Cleary G, Celenza A. Retention into internship of resuscitation skills learned in a medical student resuscitation program incorporating an Immediate Life Support course. *Resuscitation* 2011; 82 (1): 45-50.
- Frkovic V, Sustic A, Zeidler F, Protic A, Desa K. A brief reeducation in cardiopulmonary resuscitation after six months – the benefit from timely repetition. *Signa Vitae* 2008; 3 (2): 24-8.
- Lo BM, Devine AS, Evans DP, et al. Comparison of traditional versus high-fidelity simulation in the retention of ACLS knowledge. *Resuscitation* 2011; 82 (11): 1440-3.

16. Ahn JY, Cho GC, Shon YD, Park SM, Kang KH. Effect of a reminder video using a mobile phone on the retention of CPR and AED skills in lay responders. *Resuscitation* 2011; 82 (12): 1543-7.
17. Bhanji F, Mancini ME, Sinz E, et al. Part 16: Education, implementation, and teams: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122 (18 Suppl 3): S920-33.
18. Price CS, Bell SF, Janes SE, Ardagh M. Cardio-pulmonary resuscitation training, knowledge and attitudes of newly-qualified doctors in New Zealand in 2003. *Resuscitation* 2006; 68 (2): 295-9.
19. Marteau TM, Wynne G, Kaye W, Evans TR. Resuscitation: experience without feedback increases confidence but not skill. *BMJ (Clin Res Ed)* 1990; 300 (6728): 849-50.
20. Anderson GS, Gaetz M, Masse J. First aid skill retention of first responders within the workplace. *Scand J Trauma Resusc Emerg Med* 2011; 19: 11.
21. Hamilton R. Nurses' knowledge and skill retention following cardiopulmonary resuscitation training: a review of the literature. *J Adv Nurs* 2005; 51 (3): 288-97.
22. Woollard M, Whitfield R, Newcombe RG, Colquhoun M, Vetter N, Chamberlain D. Optimal refresher training intervals for AED and CPR skills: a randomised controlled trial. *Resuscitation* 2006; 71 (2): 237-47.
23. Moser DK, Coleman S. Recommendations for improving cardiopulmonary resuscitation skills retention. *Heart Lung* 1992; 21 (4): 372-80.
24. Mahony PH, Griffiths RF, Larsen P, Powell D. Retention of knowledge and skills in first aid and resuscitation by airline cabin crew. *Resuscitation* 2008; 76 (3): 413-18.

Capsule

An interleukin 17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy

Although angiogenesis inhibitors have provided substantial clinical benefit as cancer therapeutics, their use is limited by resistance to their therapeutic effects. While ample evidence indicates that such resistance can be influenced by the tumor microenvironment, the underlying mechanisms remain incompletely understood. Chung and team have uncovered a paracrine signaling network between the adaptive and innate immune systems that is associated with resistance in multiple tumor models: lymphoma, lung and colon. Tumor-infiltrating T helper type 17 (T_H17) cells and interleukin-17 (IL-17) induced the expression of granulocyte colony-stimulating factor (G-CSF) through nuclear factor κB (NF-κB) and extracellular-related kinase (ERK) signaling, leading to immature myeloid cell

mobilization and recruitment into the tumor microenvironment. The occurrence of T_H17 cells and Bv8-positive granulocytes was also observed in clinical tumor specimens. Tumors resistant to treatment with antibodies to vascular endothelial growth factor (VEGF) were rendered sensitive in IL-17 receptor (IL-17R)-knockout hosts deficient in T_H17 effector function. Furthermore, pharmacological blockade of T_H17 cell function sensitized resistant tumors to therapy with antibodies to VEGF. These findings indicate that IL-17 promotes tumor resistance to VEGF inhibition, suggesting that immunomodulatory strategies could improve the efficacy of anti-angiogenic therapy.

Nature Med 2013; 19: 1114

Eitan Israeli

Capsule

The toxicity of anti-prion antibodies is mediated by the flexible tail of the prion protein

Prion infections cause lethal neurodegeneration. This process requires the cellular prion protein (PrP^C), which contains a globular domain hinged to a long amino-proximal flexible tail. Sonati et al. describe rapid neurotoxicity in mice and cerebellar organotypic cultured slices exposed to ligands targeting the α1 and α3 helices of the PrP^C globular domain. Ligands included seven distinct monoclonal antibodies, monovalent Fab₁ fragments and recombinant single-chain variable fragment mini-antibodies. Similar to prion infections, the toxicity of globular domain ligands required neuronal PrP^C, was exacerbated by PrP^C overexpression, was associated with calpain activation and was antagonized by calpain inhibitors. Neurodegeneration was accompanied by a burst of reactive oxygen species, and was suppressed by antioxidants. Furthermore, genetic ablation of the superoxide-producing enzyme NOX2 (also known as CYBB) protected mice from globular domain ligand toxicity. The authors also found that neurotoxicity was prevented by deletions of the octapeptide repeats within the flexible tail. These deletions did not

appreciably compromise globular domain antibody binding, suggesting that the flexible tail is required to transmit toxic signals that originate from the globular domain and trigger oxidative stress and calpain activation. Supporting this view, various octapeptide ligands were not only innocuous to both cerebellar organotypic cultured slices and mice, but also prevented the toxicity of globular domain ligands while not interfering with their binding. The authors conclude that PrP^C consists of two functionally distinct modules, with the globular domain and the flexible tail exerting regulatory and executive functions, respectively. Octapeptide ligands also prolonged the life of mice expressing the toxic PrP^Cmutant^Δ, PrP(Δ94–134), indicating that the flexible tail mediates toxicity in two distinct PrP^C-related conditions. Flexible tail-mediated toxicity may conceivably play a role in further prion pathologies, such as familial Creutzfeldt-Jakob disease in humans bearing supernumerary octapeptides.

Nature 2013; 501: 102

Eitan Israeli