# The effects of foot reflexology on agitation and extubation time in male patients following coronary artery bypass surgery: a randomized controlled clinical trial

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# ABSTRACT

**Background and purpose:** This study examined the effects of foot reflexology on agitation and extubation time of male patients following coronary artery bypass graft surgery. **Materials and methods:** In this randomized three-arm controlled clinical trial, participants (n=120) were randomly assigned to the intervention, placebo, or control groups. The intervention group received foot reflexology massage for 15 minutes. Agitation was assessed using the Richmond Agitation- Sedation Scale before the intervention (Time 1) and immediately (Time 2) and 10 minutes after the intervention (Time 3). Extubation time was measured as the time from gaining full consciousness to endotracheal extubation. **Results:** Agitation reduced in all groups from Time 1 to Time 3 (p<0.05); however, the intervention group showed a significantly higher reduction at Time 2 (p<0.001) and Time 3 (p<0.001). Also, extubation time was significantly shorter in the intervention group (p<0.01). **Conclusion:** Foot reflexology may be introduced as a nursing intervention to facilitate the weaning process in the cardiac ICUs.

Keywords: agitation, coronary artery bypass graft, extubation time, foot reflexology, nursing

# Highlights

- Foot reflexology was found effective in reducing patient agitation following CABG.
- Foot reflexology also decreased extubation time in these patients.
- Nurses can apply foot reflexology to facilitate the weaning of patients from mechanical ventilation in the cardiac ICUs.

### **1. Introduction**

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and is projected to remain so by 2030 [1]. As the main feature of CVD, coronary artery disease (CAD) is characterized by narrowing or blockage of the coronary arteries supplying the myocardium. Coronary artery bypass graft (CABG) is a common type of cardiac surgery and a treatment of choice for patients who have significant narrowings and blockages in their coronary arteries. **CABG** is a major surgery requiring general anesthesia and mechanical ventilation support [2], and therefore, it is associated with significant physical and psychological stressors, such as having tubes in the nose and mouth, chest tubes, cannulas, catheters, insufficient sleep, pain, fear of death, loss of control, and communication issues. These stressors can agitate the patients and increase their anxiety [3, 4]. Evidence shows that agitated patients are at increased risk of self- extubation, requiring re-intubation [5, 6]. In addition, agitation and anxiety increase patients' needs for opioids and benzodiazepines [5], the interventions that can have significant adverse effects, such as respiratory depression, hypotension, urinary retention, and nausea and vomiting [7].

Both agitation and medications that are used for its treatment, such as opioids and benzodiazepines, can delay weaning from mechanical ventilation [8], and increase the risk of postoperative complications, mortality, the length of hospitalization, and health care costs [9, 10]. Ventilator-associated pneumonia is one of the most common nosocomial infections in the ICUs, affecting 10–30% of mechanically ventilated patients [11], and it is known that prolonged intubation can increase the risk of this infection in CABG patients [12]. An intubation time longer than 12 hours has also been linked to increased risk of delirium and hemofiltration post cardiac surgery. Therefore, early weaning from mechanical ventilation is a key goal in managing these patients [13].

Non-pharmacological therapies may offer a safer alternative to or are used in conjunction with medications to reduce patients' anxiety and agitation during mechanical ventilation, improve their comfort level, and promote a healing environment [14]. Stay et al. (2005) found that acupressure therapy, a form of massage therapy, was effective in improving the symptoms of dyspnea and anxiety in patients who required prolonged mechanical ventilation [15]. Examples of other non-pharmacological therapies that seem to be useful in reducing patients' anxiety during mechanical ventilation include music intervention [16] and animal-assisted interactions [17]. Thus, by decreasing patient agitation and anxiety, non-pharmacological therapies may have the potential to reduce the length of ventilation and the associated complications.

Reflexology is a non-pharmacological intervention, which involves the application of pressure to the reflex zones on the feet or hands with specific thumb, finger, and hand techniques to promote wellness in the corresponding body structures, organs, or glands [18]. The beneficial effects of reflexology have been demonstrated in various health conditions, such as pain [19], anxiety [19, 20], sleep disorders [21], mood disorders [22], and quality of life [23]. Ebadi et al. (2015) found that foot reflexology was effective in shortening the length of weaning time in patients post open-heart surgery. However, a systematic review of the relevant studies failed to support the use of reflexology for medical conditions [24]. Evidence

is scarce on the effectiveness of foot reflexology in weaning from mechanical ventilation in patients post CABG. This study aimed to investigate the effectiveness of foot reflexology on agitation and extubation time in patients post CABG surgery. We hypothesized that foot reflexology would reduce the agitation as well as the extubation time of patients following CABG surgery.

#### 2. Materials and Methods

This was a three-arm parallel design randomized controlled clinical trial conducted between February 2017 and June 2017 in the intensive care unit of a tertiary referral cardiac hospital in Iran. Primary outcomes included patient agitation and extubation time. All participants were male and candidate for non-urgent CABG. As the massage provider was male, the cultural and religious confines limited the inclusion of female participants in the study. Patients were excluded from the study if they needed emergency CABG, had a previous history of CABG, mechanical ventilation, mental disorder, such as depression or anxiety (based on their medical records), previous history of foot reflexology, or foot disorder (such as corns and calluses, former scar, neuropathy). Patients were also excluded if they had intraaortic balloon pump, pacemaker, addiction to the alcohol or narcotic drugs, chronic pain such as arthritis, deep vein thrombosis, low consciousness level, severe visual disorders, selfextubation, lack of hemodynamic stability, received inotropic and vasopressor agents, or analgesic injection or nerve-muscle blockers after admission to the ICU, or were extubated during the intervention. Also, patients who underwent valve repair or valve replacement in addition to CABG were excluded to ensure that surgery type did not affect the study outcomes, as surgery time and recovery can vary for different cardiac surgeries [25]. The total sample size for this study was 120 participants; 40 participants were assigned to each study arm. In Babayan et al.'s (2014) study, foot reflexology resulted in a mean

difference of 1.48 and a standard deviation of 2.07 in the pain level of patients during the removal of their chest tubes. Using these values and assuming a significance level of 5% and a power of 80%, a sample size of 31 participants in each study arm was calculated sufficient to test the study hypotheses. Figure 1: CONSORT flowchart demonstrates the number of patients who were screened, enrolled, assigned to each arm, followed up, and included in the final analysis.

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, R.TBZMED.REC.1395.931, and registered in the Iranian Registry of Clinical Trials (IRCT2016110125937N3). Patients received information about the study while they were awaiting their surgery in the cardiac surgery ward of the participating hospital. Those interested were screened against the study inclusion and exclusion criteria. Eligible patients signed the consent form and were enrolled in the study. The participants were assured of the confidentiality of their provided information and were free to withdraw from the study at any time.

A block randomization scheme with a block size of six was used to allocate participants to one of the three study arms: intervention, placebo, or control. The randomization scheme was generated using computer software. Each allocation was written on a piece of paper, placed in a separate opaque envelope, and sequentially numbered. The process was completed by an independent person. The researcher who delivered the interventions was informed of the allocations only at the patients' bedside.

#### 2. 1. Intervention

Participants in the intervention group received foot reflexology massage on their feet in the supine position in bed. The placebo group received a superficial heel touch in the same position, based on the study by Ebadi et al. [26]. During the heel touch, the researcher held

the patient's heel gently in his hand. No pressure was applied to the feet in order to evade nerve stimulation. This technique enabled the researchers to control for the possible placebo effect. Participants in the control group received routine care. Foot reflexology for the intervention group and heel touch for the placebo group was provided when the patients regained their complete consciousness in the ICU. The researcher who provided foot reflexology massage had been trained by a professional reflexologist for one year, and the techniques used were based on a reference text [27]. The points on the sole of the foot, which are believed to be linked to stress reduction, were selected. The selected reflex points included the solar plexus (referred to as the relaxation point), the hypothalamus gland, the hypophysis gland, and the adrenal gland. To provide food reflexology, the researcher first washed his hands, lubricated them with olive oil and warmed them up by rubbing the hands together. He informed the patient about the procedure before applying reflexology massage or superficial heel touch, depending on the patient's group allocation. Reflexology massage or heel touch was applied for 15 minutes in one session, first on the right foot, and then on the left. The massage started with relaxation movements on both feet, which included rotating the foot, stretching the Achilles tendon, and opening and stretching the chest of the foot. Each of these techniques was applied for one minute before providing reflexology massage. When rotating the foot, the heel was held with the opposite hand, and the metatarsal arch with the hand of the same side, and clockwise and counterclockwise rotations were applied several times. Then, the heel was pulled and released with the opposite hand in the same position. Next, the fingers of both hands were placed on the top of the foot in a way that the fingertips were located towards the base of toes in zone three (the longitudinal area that begins from above the head, passes through the eyes and reaches the middle fingers and toes), and both thumbs were placed under the metatarsal arch in this area. Then, the pressure was applied by gliding the thumbs outwards. In the next stage, foot reflexology massage was provided on the

selected points on both feet, which took 12 minutes altogether. Massaging of the solar plexus included applying and releasing pressure on the point and applying rotational pressure with the thumb. Massaging of the hypothalamus gland, pituitary gland, and adrenal gland was performed by applying rotational pressure with the thumb [27]. The locations of the reflex points were selected based on the book by Keet [28].

### 2.2. Data collection tools

# 2.2.1. Demographic and clinical data

Data on the demographic and clinical characteristics of the participants were collected using a researcher-developed questionnaire and through an interview with the participants and using their medical records. This questionnaire included questions on age, body mass index, marriage status, educational level, job, economic status, place of residence, disease history, history of smoking, duration of CABG, and the number of grafts.

# 2.2.2. Richmond Agitation- Sedation Scale (RASS)

The Richmond Agitation- Sedation Scale (RASS) was used to assess the participants' level of agitation. The RASS is a validated and reliable tool, developed by a team of multidisciplinary researchers with the aim of assessing patient agitation and level of sedation in the ICU. This is a 10-point scale with scores ranging from +4 (combative) to -5 (unarousable). Scores from +4 to +1 assess the level of agitation; score 0 indicates alertness and calmness, and scores from -1 to -5 measure the level of sedation. The validity of the RASS for ICU practice has been confirmed by its strong correlations with the Sedation–Agitation Scale (r=0.78, p< 0.0001), Ramsay Sedation Scale (r =- 0.78, p<0.0001), and Glasgow Coma Scale (r=0.79, p< 0.0001). The scale has also shown excellent inter-rater reliability when used by five groups of

health care professionals (r=0.956; kappa=0.73) [29]. The Persian version of the RASS is available, and the tool has been validated on Iranian adult ICU patients [30].

The time interval between regaining full consciousness (GCS 15) in the ICU and endotracheal extubation was considered as extubation time, which was measured by a chronometer and recorded in minutes. In the setting of this study, the GCS levels of all patients who are admitted to the ICU from the operation room are frequently measured by the ICU nurses. We found no statistically significant difference in the time of regaining consciousness after admission to the ICU between the groups (p>0.05). In this hospital, all patients are admitted to the ICU from the operation room on synchronized intermittent mandatory ventilation (SIMV) mode and remain on this mode until they regain complete consciousness. The ventilation mode may be changed later, depending on the patient's condition. Extubation is performed when the patient is on continuous positive airway pressure (CPAP) mode.

The researcher scored patients' agitation by observing their gestures and movements and adapting them to the RASS. The same researcher completed all the measurements. The agitation levels of the participants were assessed when they regained complete consciousness in the ICU before intervention (Time 1) and immediately after (Time 2) and 10 minutes after foot reflexology massage or heel touch (Time 3). Time 2 and Time 3 measurements for the control group were carried out 30 minutes and 40 minutes after baseline measurement (Time 1).

# 2.3. Data analysis

Data analysis was conducted using the IBM SPSS Statistics version 21. Descriptive statistics were used to summarize the demographic and clinical data, and one-way ANOVA, Fisher's test, or Chi-square test were applied to examine differences between the groups. The

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significance level was considered less than 0.05. The ordinal logit link function was used to analyze the data on agitation. As the data on extubation time was not normally distributed, the non-parametric tests of Kruskal-Wallis and Mann-Whitney U were applied. The correlation between agitation scores at Time 3 and extubation time was assessed using the Spearman rho. All participants who were randomized received the intended treatment and included in the analysis.

#### 3. Results

The demographic and clinical characteristics of the participants are shown in Table 1. The groups were similar in the demographic and clinical characteristics at baseline. The mean age of participants was 56.50±7.99 years.

The agitation scores decreased significantly from Time 1 to Time 3 in all the three groups (p<0.05). Generalized estimation equations (GEE) showed the significant effect of time on the agitation level of the participants (p<0.001). The Kruskal-Wallis test demonstrated no significant difference in the agitation scores between the groups at baseline (Time 1) (p>0.05); however, the agitation scores were significantly different between the groups at Time 2 and Time 3 (p<0.001). The results of the GEE analysis indicated that the reduction in the agitation scores was higher for the intervention group compared to the placebo group (p<0.001). In the intervention group, agitation level reduced by 1.844 scores, 95% CI -2.768 to -0.921, while the reduction was only 0.822 scores, 95% CI -1.792 to 0.147 for the placebo group (Table 2).

In addition, the result of the Kruskal- Wallis test showed a statistically significant difference between the groups in extubation time (p<0.001). Comparing the groups two by two using the Mann- Whitney and Bonferroni correction, extubation time was significantly lower in the intervention group compared to the placebo and control groups (72.62±15.93, 83.62±16.36,

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84.00 $\pm$ 19.91, respectively; p<0.01). No significant difference was observed between the placebo group and the control group in extubation time (p>0.05) (Table 3). There was found a statistically significant correlation between agitation scores at Time 3 and extubation time (rho=0.20, p<0.05).

### 4. Discussion

This study examined the effects of foot reflexology massage on agitation and extubation time in male patients following CABG. The results showed that foot reflexology was effective in reducing patients' agitation and extubation time. Although the agitation scores on the RASS reduced by time in all the groups, the reduction was significantly higher in the group that received foot reflexology. Apart from the statistical significance, the clinical significance of the results is also apparent. At Time 3, 31 (77.5%) participants in the intervention group had zero agitation on the RASS, while this was observed only in 15 (37.5%) and 10 (25.0%) participants in the placebo and control groups, respectively. In other words, participants in the foot reflexology group had 2.06 times and 3.1 times higher chance of having no agitation in Time 3 compared to the placebo and the control groups, respectively. Inconsistent with our findings, Kavei et al. (2015) found that foot reflexology massage had no statistically significant effect on the agitation of patients following open-heart surgery [32]. This inconstancy may be related to the time when foot reflexology was provided. In Kavei et al.'s study, foot reflexology was performed when patients had not yet regained their complete consciousness, while participants in our study were completely conscious when they received foot reflexology massage. This may indicate that patients gain benefits from foot reflexology if they are awake and can sense the massage. There is a need for further research to test if the time of foot reflexology or patients' consciousness level affects the response to foot reflexology massage.

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Foot reflexology was also effective in reducing the time to extubation in the current study. Participants in the intervention group stayed an average of 11 minutes and 11.38 minutes less on mechanical ventilation compared to those in the placebo and control groups, respectively. In awake mechanically ventilated patients, instead of sedation, foot reflexology may help reduce ventilation time and its associated complications, such as pneumonia, length of hospital stay, or delirium [9, 10, 12, 31]. Similar to our study, Ebadi et al. (2015) reported that foot reflexology was effective in shortening weaning time in patients following openheart surgery [26]. In Ebadi et al.'s (2015) study, participants received 20 minutes of foot reflexology one hour after admission to the ICU regardless of their level of consciousness. Further, the researchers did not provide a clear definition of weaning time.

Overall, the beneficiary effects of foot reflexology for CABG patients have not been widely studied, and studies that have examined the health benefits of foot reflexology on different patients' groups have reported mixed results. The time when foot reflexology is applied and how the techniques are used may affect the outcomes. Future studies should identify the right time and the most effective foot reflexology techniques to be used for different health conditions.

We found a statistically significant correlation between agitation scores and extubation time. This may suggest that foot reflexology exerted its effects on extubation time by reducing patient agitation. Agitation is a known barrier to successful extubation. In practice, when anxiety or agitation is the reason for delaying extubation, an anxiolytic agent, preferably, dexmedetomidine, is administered to facilitate extubation by sedating the patient [32]. Dexmedetomidine does not suppress the respiratory system; however, it may cause other side effects, such as bradycardia, hypotension, and discontinuation syndrome [33]. Using nonpharmacological methods, such as foot reflexology, can be a safer alternative to medications in the management of patient agitation before extubation.

# 4.1. Limitations

This study recruited only male participants from a single center; future research should consider including female participants, and recruit from multiple sites to increase the generalisability of the findings. In this study, nurses who assessed the patients' GCS level and doctors who ordered extubation were blind to the study allocations; however, the researchers who measured the agitation of the patients and applied the interventions were not blind to the groups. Further, we did not collect data on the amount of blood loss during surgery or in the ICU or analgesic medications used in the operating room, factors that may have affected the study results. It is also recommended that future research examine other important outcomes, such as length of hospital stay and patient acceptance and satisfaction.

#### **5.** Conclusion

This study found that foot reflexology was effective in reducing agitation and extubation time in male patients following CABG. This non-pharmacological option can be introduced as a nursing intervention to relieve patient agitation and facilitate weaning from mechanical ventilation in the ICUs.

# References

- 1. Mathers CD, Loncar D: **Projections of global mortality and burden of disease from 2002 to 2030**. PLoS medicine 2006, **3**(11):e442.
- 2. Yuh DD, Vricella LA, Yang S, Doty JR: Johns Hopkins Textbook of Cardiothoracic Surgery, Second Edition: McGraw-Hill Education; 2014.
- 3. Dessotte CAM, Rodrigues HF, Furuya RK, Rossi LA, Dantas R: **Stressors perceived by patients in the** *immediate postoperative of cardiac surgery*. Rev Bras Enferm 2016, **69**(4):694-703.
- 4. Nesami MB, Shorofi SA, Jafari A, Khalilian AR, Tabari SZ: **The relationship between stressors and** anxiety levels after CABG in Sari, Iran. Iranian Red Crescent Medical Journal 2016, **18**(5).
- 5. Freeman S, Yorke J, Dark P: **Patient agitation and its management in adult critical care: A integrative review and narrative synthesis**. Journal of clinical nursing 2018, **27**(7-8):e1284-e1308.
- 6. Mahmood SA, Mahmood OS, El-Menyar AA, Asim MM, Abdelbari AA-A, Chughtai TS, Al-Thani HA: Selfextubation in patients with traumatic head injury: Determinants, complications, and outcomes. Anesthesia, essays and researches 2019, 13(3):589.
- 7. Caughey GE, Gadzhanova S, Shakib S, Roughead EE: **Concomitant prescribing of opioids and benzodiazepines in Australia, 2012–2017.** The Medical journal of Australia 2019, **210**(1):39-40.
- 8. Tobar E, Gusmao-Flores D: Agitation During Prolonged Mechanical Ventilation and Influence on Weaning Outcomes. In: Noninvasive Mechanical Ventilation and Difficult Weaning in Critical Care. Springer; 2016: 265-273.
- 9. Hough CL, Caldwell ES, Cox CE, Douglas IS, Kahn JM, White DB, Seeley EJ, Bangdiwala SI, Rubenfeld GD, Angus DC: **Development and validation of a mortality prediction model for patients receiving 14** days of mechanical ventilation. Critical care medicine 2015, **43**(11):2339.
- 10. Adegunsoye A, Kress JP: **Weaning from Mechanical Ventilation**. In: Evidence-Based Critical Care. Springer; 2017: 273-280.
- 11. Safdar N, Dezfulian C, Collard HR, Saint SJCcm: Clinical and economic consequences of ventilatorassociated pneumonia: a systematic review. 2005, 33(10):2184-2193.
- 12. He S, Wu F, Wu X, Xin M, Ding S, Wang J, Ouyang H, Zhang J: Ventilator-associated events after cardiac surgery: evidence from 1,709 patients. Journal of thoracic disease 2018, 10(2):776.
- Kotfis K, Szylińska A, Listewnik M, Lechowicz K, Kosiorowska M, Drożdżal S, Brykczyński M, Rotter I, Żukowski M: Balancing intubation time with postoperative risk in cardiac surgery patients – a retrospective cohort analysis. Therapeutics & Clinical Risk Management 2018, 14:2203-2212.
- 14. Tracy MF, Chlan L: Nonpharmacological interventions to manage common symptoms in patients receiving mechanical ventilation. Critical care nurse 2011, **31**(3):19-28.
- 15. Tsay S-L, Wang J-C, Lin K-C, Chung U-L: *Effects of acupressure therapy for patients having prolonged mechanical ventilation support*. 2005, *52*(2):142-150.
- 16. Lee OK, Chung YF, Chan MF, Chan WM: **Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study**. Journal of clinical nursing 2005, **14**(5):609-620.
- 17. Hetland B, Bailey T, Prince-Paul MJJoh, Hospice pnJtojot, Association PN: Animal Assisted Interactions to Alleviate Psychological Symptoms in Patients on Mechanical Ventilation. 2017, **19**(6):516-523.
- 18. Williamson J: The Complete Guide to Precision Reflexology 2nd Edition: Andrews UK Limited; 2014.
- 19. Koras K, Karabulut N: **The Effect of Foot Massage on Postoperative Pain and Anxiety Levels in Laparoscopic Cholecystectomy Surgery: A Randomized Controlled Experimental Study**. Journal of perianesthesia nursing : official journal of the American Society of PeriAnesthesia Nurses 2018.
- 20. Quattrin R, Zanini A, Buchini S, Turello D, Annunziata M, Vidotti C, Colombatti A, Brusaferro SJJoNM: Use of reflexology foot massage to reduce anxiety in hospitalized cancer patients in chemotherapy treatment: methodology and outcomes. 2006, **14**(2):96-105.
- 21. Bakir E, Baglama SS, Gursoy S: **The effects of reflexology on pain and sleep deprivation in patients with rheumatoid arthritis: A randomized controlled trial**. Complementary therapies in clinical practice 2018, **31**:315-319.
- 22. Abbaszadeh Y, Allahbakhshian A, Seyyedrasooli A, Sarbakhsh P, Goljarian S, Safaei N: Effects of foot reflexology on anxiety and physiological parameters in patients undergoing coronary artery bypass graft surgery: A clinical trial. Complementary therapies in clinical practice 2018, **31**:220-228.
- 23. Özdelikara A, Tan M: **The effect of reflexology on the quality of life with breast cancer patients**. Complementary Therapies in Clinical Practice 2017, **29**:122-129.

- 24. Ernst E, Posadzki P, Lee M: **Reflexology: an update of a systematic review of randomised clinical trials**. Maturitas 2011, **68**(2):116-120.
- 25. Yuh DD: Johns Hopkins textbook of cardiothoracic surgery: McGraw-Hill Companies; 2014.
- 26. Ebadi A, Kavei P, Moradian ST, Saeid Y: **The effect of foot reflexology on physiologic parameters and mechanical ventilation weaning time in patients undergoing open-heart surgery: A clinical trial study**. Complementary therapies in clinical practice 2015, **21**(3):188-192.
- 27. James A: Hands on reflexology: a complete guide: Hodder & Stoughton; 2002.
- 28. Keet L: The Reflexology Bible: Godsfield; 2008.
- Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'neal PV, Keane KA, Tesoro EP, Elswick R: The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. American Journal of Respiratory and Critical Care Medicine 2002, 166(10):1338-1344.
- 30. Tadrisi S, Madani S, Farmand F, Ebadi A, AA KZ, Mirhashemi S, Haji Amini Z, Mottahedian Tabrizi E: **Richmond agitation–sedation scale validity and reliability in intensive care unit adult patients Persian version**. Journal of Critical Care Nursing 2009, **2**(1):15-21.
- 31. Chiang S-R, Lai C-C, Ho C-H, Chen C-M, Chao C-M, Wang J-J, Cheng K-C: **Prolonged mechanical** ventilation assistance interacts synergistically with carbapenem for clostridium difficile infection in critically ill patients. Journal of Clinical Medicine 2018, **7**(8):224.
- 32. Wiener-Kronish JP: **Critical Care Handbook of the Massachusetts General Hospital**: Wolters Kluwer Health; 2015.
- 33. Scott-Warren V, Sebastian J: Dexmedetomidine: its use in intensive care medicine and anaesthesia. BJA Education 2015, 16(7):242-246.