International Journal of Cardiology 219 (2016) 186–194

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Pathophysiology of cancer therapy-provoked atrial fibrillation

Wan-Li Cheng [a], Yu-Hsun Kao [a,b], Shih-Ann Chen [c,d], Yi-Jen Chen [a,e,*]

[a] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[b] Department of Medical Education and Research, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[c] School of Medicine, National Yang-Ming University, Taipei, Taiwan
[d] Division of Cardiology and Cardiovascular Research Center, Taipei Veterans General Hospital, Taipei, Taiwan
[e] Division of Cardiovascular Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 13 May 2016
Accepted 11 June 2016
Available online 14 June 2016

Keywords:
Atrial fibrillation
Cancer surgery
Chemotherapy
Proinflammatory cytokines

ABSTRACT

Atrial fibrillation (AF) occurs with increased frequency in cancer patients, especially in patients who undergo surgery or chemotherapy. AF disturbs the prognosis of cancer patients and challenges therapeutic outcomes of cancer treatment. Elucidating the mechanisms of cancer-induced AF would help identify specific strategies for preventing AF occurrence. In addition to concurrent risk factors of cancer and AF, cancer surgery, side effects of anticancer agents, and cancer-associated immune responses play critical roles in the genesis of AF. In this review, we provide succinct potential mechanisms of AF genesis in cancer patients.

1. Introduction

Onco-cardiology is an innovative term commonly used to describe the close link between cancer and cardiovascular diseases [1]. One of the critical issues in managing cancer is the development of atrial fibrillation (AF) during or after cancer treatment [2]. AF is the most common sustained cardiac arrhythmia, which is an important risk factor for stroke, heart failure (HF), myocardial infarction, dementia, and mortality [3–7]. In addition to traditional risk factors of AF (hypertension, HF, myocardial ischemia, chronic pulmonary disease, diabetes, thyroid dysfunction, chronic kidney disease, and renal failure), cancer is also closely related to the genesis of AF, since there are many concurrent risk factors that contribute to the occurrence of both cancer and AF [8–12]. In addition, both cancer progression and cancer therapy can increase the frequency of AF [2,13,14]. Development of AF during cancer treatment is a poor prognostic factor, and affects outcomes of malignant diseases and challenges therapeutic strategies [15]. The pathophysiology of cancer therapy-provoked AF is complicated by multiple cellular and molecular interactions. As shown in Fig. 1, mechanisms of cancer-provoked AF include cancer surgery (acute and chronic sequels), chemotherapies (structural and electrical effects), and the cancer immune system. This review elucidates potential mechanisms of cancer-induced AF and provides clues for preventing AF during cancer treatment.

* Corresponding author at: Division of Cardiovascular Medicine, Wan Fang Hospital, Taipei Medical University, 111 Hsin-Lung Road, Sec. 3, Taipei 116, Taiwan.
E-mail address: a9900112@ms15.hinet.net (Y.-J. Chen).

2. Postoperative AF (POAF) in cancer

POAF frequently occurs after cancer surgery [16–18]. It was connected with increased intensive care utilization and hospital length of stay, morbidity, mortality, hospital readmissions, and long-term risk of stroke [17]. Besides, the prevalence of POAF was 16%–46% following cardiothoracic surgery and was 0.4%–12% following non-cardiothoracic surgery [19]. In lung cancer, AF is most frequently seen during thoracic surgery, especially pulmonary resection [20]. Numerous studies in patients undergoing lung cancer surgery reported incidences of AF ranging 5.6%–23% [16,21–23]. Previously, thoracic surgery was demonstrated to be an important risk factor for the occurrence of AF [24]. Furthermore, mortality after a pneumonectomy increased in lung cancer patients experiencing POAF [24]. In addition, systematic lymph node dissection during a right pneumonectomy in lung cancer patients was also related to the occurrence of AF [25]. Besides, POAF also occurred in 12.6% of colorectal cancer patients who underwent an elective colectomy, as well as in 9.2% of esophageal cancer patients who underwent an esophagectomy [26,27]. AF after an esophagectomy was suggested to be a marker for postoperative morbidity and mortality [28]. In a case–control study, the prevalence of AF was 2-times higher among patients admitted for colorectal or breast cancer surgery compared to patients undergoing non-cancer-related surgery [29]. Thus, we need to understand the mechanisms of POAF formation in cancer patients.

Factors facilitating POAF after cancer therapy can be classified as acute factors directly associated with surgery and chronic factors that reflect a progressive process of remodeling such as aging, hypertension,

http://dx.doi.org/10.1016/j.ijcard.2016.06.009
0167-5273/

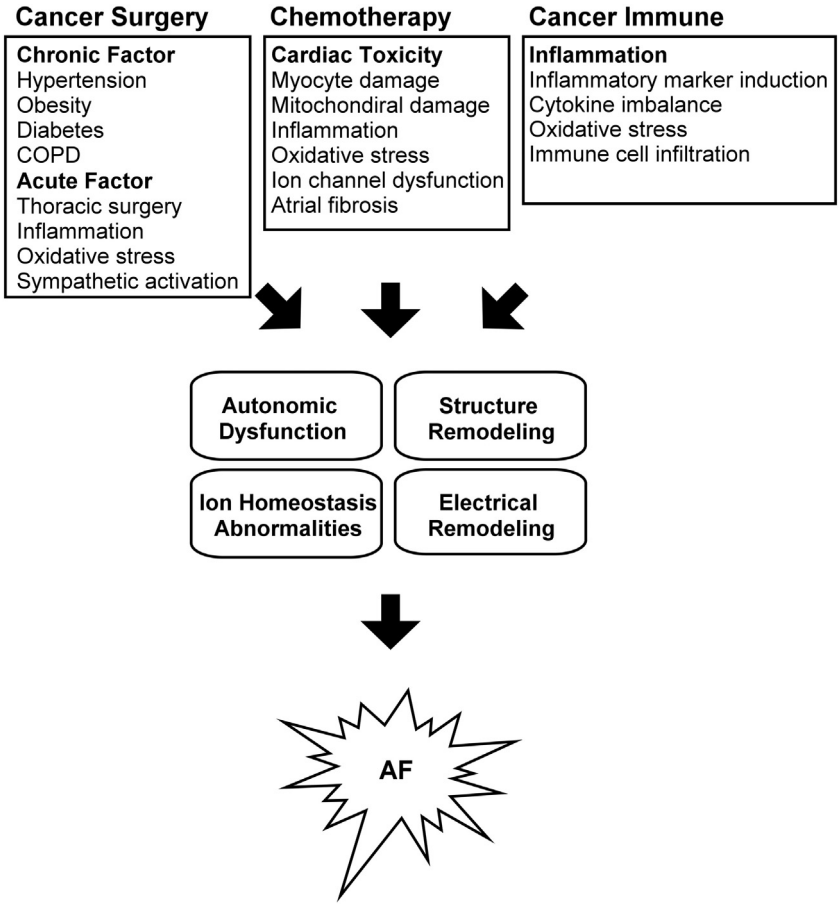

Fig. 1. A schematic illustration of the mechanisms of atrial fibrillation (AF) in cancer. COPD, chronic obstructive pulmonary disease.

diabetes, obesity, and chronic obstructive pulmonary disease (COPD) [8–12].

2.1. Acute factors facilitating POAF in cancer therapy

POAF in cancer is closely linked to thoracic surgery, systemic inflammation, oxidative stress, and sympathetic activation [30]. In lung cancer, POAF is one of the most common cardiac arrhythmias observed in the early postoperative period after lung surgery or resection [18,31]. Recent results demonstrated that pulmonary vein (PV) stumps in AF patients with a pneumonectomy history are electrically active and are frequently sites of active firing [32]. It is well established that PVs are the main trigger site in patients with AF [33–35]. Besides, there are functional relationships that exist between cardiac autonomic effects and PVs in arrhythmogenesis. Discharges of the nerves that proceed to the PVs and interconnect with intrinsic ganglionated nerve plexuses are suggested with potential triggers of AF in human [36]. Furthermore, catheter ablation of AF is feasible in patients with PV stumps, and long-term success rates of this procedure are similar to those of patients without a pneumonectomy undergoing the same procedure [32]. In addition, numerous reports also identified similarities between the time course of POAF occurrence after surgery and activation of proinflammatory cytokines, which suggests an inflammatory component in the mechanism triggering POAF [37–41]. The time course of POAF corresponds to changes in induction of inflammation, such as C-reactive protein (CRP) [37], interleukin (IL)-2 [42], IL-6 [10,38], IL-8 [43], and macrophage migration inhibitory factor (MIF) [44]. In lung cancer patients, induction of CRP and IL-6 was detected after thoracic surgery [45,46]. Several investigations suggested that infiltration of immune cells and proteins that mediate the inflammatory response in cardiac tissue and circulatory processes is associated with AF [47]. Moreover, AF after an esophagectomy may be modulated by sympathovagal nerve injury following surgical trauma [48,49], which plays a vital role in the genesis of AF. Following a lung lobectomy, atrial KCNE1 (potassium channel subunit) down-regulation was identified, which suggested an increased outward current in atrial myocytes, shortened atrial action potentials, and enhanced susceptibility to POAF [50]. Furthermore, a strong relationship was observed between postoperative hypoxia and AF after surgery for esophageal carcinoma [51]. Ma et al. hypothesized that factors predisposing one to postoperative hypoxia (like COPD) could play a role in the development of AF [49]. Recently, evidence supported the pathogenic role of oxidative stress induction in POAF and suggested that further development of therapies targeting oxidative stress pathways is warranted to prevent POAF [52]. Thus, it is important to decrease acute factor-induced POAF in cancer surgery.

2.2. Chronic factors facilitating POAF in cancer therapy

POAF is also a common complication after a lung resection or esophagectomy, and seems to be associated with old age, a male gender, a history of heart disease, hypertension, and a preoperative brain natriuretic peptide (BNP) level of ≥30 pg/mL [9,53,54]. POAF with esophageal and junctional cancer is common, and was linked to age, diabetes, cardiac disease, and neoadjuvant therapy [30]. Previously, obesity was suggested to be an independent predictor of new-onset AF in cardiac surgery patients [55]. Furthermore, obesity was reported to be a powerful risk factor for the occurrence of POAF after isolated coronary artery