Sildenafil improves cardiac function in a rat model of cancer cachexia

1)Musolino MV. 2)Carresi CC. 3)Gliozzi GM. 4)Bosco BF. 5)Nucera NS. 6)Giancotta GC. 7)Tavano TD. 8)Scarano SF. 9)Scicchitano SM. 10)Maiuolo MJ. 11)Maretta MA. 12)Oppedisano OF. 13)Palma PE. 14)Muscoli MC. 15)Mollace MV.

Institute of Research for Food Safety & Health (IRC-FSH)

Introduction: Cachexia is a complex metabolic disorder occurring in late stages of chronic disease including cancer and characterized by involuntary weight loss caused by an ongoing wasting of skeletal muscle with loss of adipose tissue. Cachexia also affects the cardiac muscle. As a consequence of the atrophy of the heart, cardiac function is impaired. Anti-cachectic therapy in patients with cancer cachexia is so far limited to nutritional support. Sildenafil, a selective inhibitor of the enzyme phosphodiesterase-5 (PDE5), has been shown to induce myocardial protective effects and to improve energy balance in a variety of experimental model. Sildenafil ameliorates the wasting process and the heart function, in the Yoshida hepatoma tumor model, probably modulating inflammation and down- regulating autophagy.

Study design and methods: In this study the effects of sildenafil were tested in cachectic tumour-bearing rats (Yoshida AH-130). Rats were treated daily with 30mg/kg of sildenafil for a period of 16 days. Body weight and composition were assessed at baseline and at the end of the study. Cardiac function was analyzed by echocardiography at baseline and at day 11.

Results: Treatment with 30mg/kg/d of sildenafil attenuated the loss of body weight and the wasting of fat mass. Administration of 30mg/kg/d of sildenafil protected the heart from general atrophy. Tumor-bearing rats displayed cardiac dysfunction, as indicated by the significant impairment of the left ventricular ejection fraction (LVEF) and the left ventricular fractional shortening (LVFS). In contrast, sildenafil improved cardiac dysfunction. Western blotting analysis showed an up-regulation of eNOS and iNOS in the hearts of tumor-bearing rats. Some autophagic markers (Beclin-1 and LC3) were also up-regulated in the hearts of cachectic animals. Sildenafil was able to down- regulate eNOS and iNOS as well as the autophagy in the hearts of tumor-bearing rats. Although sildenafil did not reduce the loss of lean body mass, it protects from adipose tissue depletion.

Conclusions: Sildenafil treatment in the Yoshida hepatoma model showed an attenuation of fat tissue loss in animals with progressive weight loss in cancer cachexia. Moreover, the drug led to an improvement of cardiac function. While mounting evidence supports the implication of the iNOS/NO pathway in muscle wasting, many questions remain unanswered. Larger studies with longer follow-up and molecular analysis are required to verify whether sildenafil could ameliorate cardiac wasting and function by modulating inflammation and autophagy.