

HEART FAILURE**HF-INDUCED DIAPHRAGMATIC ATROPHY AND WEAKNESS**

A central neurohormonal pathway that activates ventilatory overdrive triggers the development of diaphragmatic atrophy and weakness in the setting of heart failure (HF), independently of pulmonary oedema or lung remodelling. This finding was reported by Foster and coworkers in *Sci. Transl. Med.*, and emphasizes the importance of designing HF drugs that target both respiratory and cardiovascular dysfunction to improve outcomes.

Dyspnoea and exertional fatigue in patients with advanced HF have been attributed to diaphragmatic remodelling and dysfunction, but the incipient causes of diaphragmatic weakness are not clear. Foster and colleagues sought to identify how diaphragmatic weakness develops using mouse models of pressure overload-induced HF. Transverse aortic constriction of male mice resulted in progressive diaphragmatic weakness, even in the absence of pulmonary oedema; this decline in diaphragmatic strength was associated with increased fibrosis and atrophy.

Given that the cause of atrophy was not related to changes in lung mechanics and chemical drive, the investigators explored the possibility that a neurohormonal mechanism might be involved in decreased diaphragm function. Angiotensin II and β -adrenergic signalling stimulated ventilatory overdrive to induce a state of chronic diaphragmatic hyperactivity via receptors that were contained within the blood–brain barrier. This finding was noteworthy, given that conventional pharmacological agents used to treat HF do not cross this barrier. Furthermore, although increases in ventilatory drive were shown to enhance diaphragmatic function, chronic activation resulted in inhibition of protein synthesis and eventual diaphragmatic weakness.

“Our findings establish the cause of diaphragm weakness and mechanisms by which it could be treated with appropriate therapy,” conclude the investigators. “Translating our study to improve clinical outcome in HF patients requires careful consideration of both drug class and type, in addition to titration for respiratory efficacy.”

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ORIGINAL ARTICLE Foster, A. J. *et al.* Central-acting therapeutics alleviate respiratory weakness caused by heart failure-induced ventilatory overdrive. *Sci. Transl. Med.* **9**, eaag1303 (2017)