Am J Cardiovasc Dis 2021;11(5):635-641
www.AJCD.us /ISSN:2160-200X/AJCD0134846

Review Article

Hyperhidrosis: the neglected sign in heart failure patients

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Received April 30, 2021; Accepted October 15, 2021; Epub October 25, 2021; Published October 30, 2021

Abstract: Profuse sweating is a symptom often reported by cardiological patients and could be also an early phenomenon of adaptation or rather cardiac maladaptation in the context of incipient heart failure (HF). By definition, in HF patients the low cardiac output causing reduced renal blood supply and reduced pressure in the arterial baroreceptors activate compensatory mechanisms such as the RAAS and the adrenergic autonomic nervous system. The retention of fluids caused by the decompensation of heart-kidney system could generate a reactive hyperhidrosis and even anticipate an incipient decompensation and might prevent manifest volume overload. Moreover, in HF patients the overactive sympathetic nervous system generates an increase in the reabsorption of fluids in the kidney, on the other hand it generates a signaling to the sweat glands to induce a dispersion of fluids, with loss of sodium and chlorine at the glandular ductal level. Finally sweat gland production physiology during physical activity is also altered in HF patients. This review is focused on sweating and its pathophysiological role in heart failure. Although all the mechanisms underlying this phenomenon are not fully understood, there are interesting connections that might explain this fluid elimination as a wise and sophisticated way to prevent incipient heart failure crisis. Future research could be focused on studying new drugs that selectively would be able to promote fluid elimination by this specific way in patients suffering from heart failure.

Keywords: Heart failure, sweating, physiology

Introduction

Profuse sweating is a symptom often reported during cardiological outpatient visits or emergency department admission; although extremely debilitating, it is often neglected by clinicians, and not investigated and treated [1].

Although this manifestation may be a sign of vagal hyperactivation in patients with acute coronary syndrome [2] or cardiac arrhythmias [3], sweat crisis could be also an early phenomenon of adaptation or rather cardiac maladaptation in the context of incipient heart failure (HF).

While the etiology and the pathophysiology of the classical signs of HF (i.e. peripheral edema and pulmonary congestion) are now well known and explained, profuse sweating development, in the course of acute HF and/or in paroxysmal episodes in patients with chronic HF, is still unclear. Sweating could be an attempt of reducing cardiac work and therefore can be considered as an early index of volume overload such as peripheral edema, turgor of jugular veins or acute pulmonary oedema.

The pathophysiology underlying profuse sweating and what may be its cause, its role and its effect within the complex nosological picture of HF, remains to date a subject that is still poorly investigated and clarified. Aim of this review is to elucidate the pathophysiological connections between hyperhidrosis and heart failure, suggesting a particular attention to consider hyperhidrosis as a related sign of heart failure.

History. First observations and the first studies; where do we stand?

In 1952 Berger and Steele described an abnormal low sweat sodium concentration in 2 patients with HF; they believed that an exces-

sive secretion of a desoxycorticosterone-like hormone in presence of congestive HF could suppress sodium excretion through kidneys, colon, sweat and the salivary glands [4].

In 1953 Slavich et al. reported that patients with HF sometimes might develop anticipatory clinical manifestations such as insomnia, yawning, periodic nocturnal breathing and sweat crisis. Above all, the latter was associated with cardiac asthma or pulmonary edema, but also isolated and anticipatory with respect to severe cardiorespiratory crisis. Therefore, it was defined as "diaphoretic asystole" and assumed a clinical meaning equivalent to an incipient paroxysmal dyspnea in decompensated HF [5]. In their manuscript authors defined a complex picture of this "water drain" with the presence of paleness and peripheral cooling, with associated malaise, profound asthenia, agitation and restlessness; all within a framework of respiratory difficulty. The attacks lasted from 15-30 minutes to a few hours with the emission of sweat mostly located to the neck, upper limbs and the upper half of the trunk. As etiological explanation for this phenomenon, authors suggested a complex endocrine-neurovegetative interaction, probably involving complex reflex arcs regulated by higher nerve stations, such as the diencephalic.

On the same line, in 1957 Haugen described the case of a patient hospitalized for HF with associated profuse sweating but in the absence of noticeable peripheral edema despite a picture of reduced urinary output. The authors hypothesized that an aldosterone-mediated mechanism had favored the elimination of fluids through skin sweating, in order to balance the fluid overload and failure of renal output [6].

In 1963 Morgan and Nadas, on the basis of the hypothesis of Haugen, conducted an observational clinical study focused on the association between sweating and the absence of peripheral edema in patients with HF. Taking into consideration a group of pediatric patients with congenital heart disease and HF, they were able to observe the same combination: profuse sweating and absence of edema. In this study, however, it was hypothesized that the neurovegetative hyperactivation was the predominant pathophysiological mechanism, unlike what Haugen proposed regarding the aldosterone-mediated hormonal mechanism [7].

Anatomy and physiology of sweat glands. Evidences and hypothesis

The sweat glands are exocrine glands typical of mammals, essential for human and animals mechanism of acclimatization, that adapt to numerous conditions. Their main functions is thermo-regulation and maintenance of water balance [8]. There are 3 types of gland: eccrine, apocrine and apo-eccrine. The most widespread sweat glands in the human body are eccrine: they are innervated by cholinergic fibers of the sympathetic nervous system and secrete sweat in response mainly to the stimulus with acetylcholine. On the other hand, apocrine and apo-eccrine glands play a minor role in overall sweat production as they are limited to specific regions of the body.

From the anatomical point of view, they are simple tubular glands-glomerular shaped, opening onto skin surface. The glomerular part of the gland produces a primary (aqueous) sweat secretion, isotonic compared to plasma (sodium and chlorine concentration of about 142 and 104 mEq/L). The chemical composition can vary during transit through the glandular duct [9] in response to the thermoregulation need.

Sweat gland and the autonomic nervous system

The Autonomic Nervous System (ANS) provides extensive innervation to internal organs through very thin fiber networks. There are afferent fibers (viscero-sensitive) and efferent fibers (motor-secretory) which regulate, among others, the processes of sweating and thermoregulation: the latter are so involved in the modulation cardio-circulatory, respiratory, gastrointestinal, endocrine, and urovescical function. The ANS is activated through various centers located in the spinal cord, brainstem and hypothalamus, a structure that constitutes the floor of the diencephalon (consisting of epithalamus, dorsal thalamus, subthalamus and hypothalamus). The activation of the dorsal preoptic area, located in the anterior hypothalamus, transmits impulses to the posterior hypothalamic area, where signals from central and peripheral thermoreceptors are also integrated. These signals propagate along the spinal cord and the sympathetic-cholinergic efferent pathways, regulating both production and

dispersion of heat through sweating of the entire body [10].

Sweat gland and renin-angiotensin-aldosterone system (RAAS)

Aldosterone is a steroid hormone secreted from the adrenal cortex, which acts on classical target tissue such as kidney, colon and sweat/salivary glands to promote unidirectional sodium transport [11, 12]. Sodium reabsorption is controlled by Na-K-ATPase activity, which is influenced by plasma aldosterone concentration and/or sweat gland sensitivity to aldosterone. Kirby and Convertino [13] demonstrated eccrine gland responsiveness to aldosterone, as represented by sweat sodium reabsorption, which may be increased through exercise and heat acclimation. Moreover Yoshida et al. showed that individual variations in the sweat NA concentration response to an increase in the sweating rate during exercise were correlated with resting aldosterone, but not to the normal increase in aldosterone concentration during exercise: therefore, the genomic may have a stronger impact on inter-individual variations in sweat sodium concentration [14].

Sweat gland and regular physical exercise

In case of increased request, such as during physical activity, sweat glands can also respond to the adrenal glands catecholamines. Those molecules cause a significant increase in cells metabolic processes, through a chemical thermogenesis that enhances warmth production, dispersed 50 times greater than the values at rest. Increasing body temperature, cutaneous vasodilation favors the dispersion of heat, and the gland significantly increases the secretion of water, in order to reduce body temperature. The isotonic secretion produced by the convoluted section does not undergo large variations in composition but the subsequent absorption of sodium and chlorine at the ductal level is drastically reduced, with the direct consequence of an important reduction in the reabsorption of water, which ultimately results in the abundant loss of fluids and electrolytes in the skin [15].

Sweating pathophysiology in heart failure

Cystic Fibrosis is a classic example of the pathophysiological importance of sweating for human homeostasis. CFTR gene codes for an ATPase superfamily of transmembrane channel, essential for the coupled functioning of sodium-chlorine reabsorption of the sweat gland.

In case of genetic mutation such as in patients with Cystic Fibrosis, the channel is non-functional, consequently it loses the capacity to reabsorb these ions [16]. Multi-modality cardiac imaging, especially recent echocardiographic techniques, evidenced diastolic and/or systolic ventricular dysfunction in cystic fibrosis leading to the concept of a cystic fibrosis-related cardiomyopathy [17].

Heart failure, sweating gland and kidney homeostasis

By definition, in HF patients the cardiac output is not sufficient to meet the demand of body and organs. Consequently, reduced renal blood supply and reduced pressure in the arterial baroreceptors activate compensatory mechanisms such as the RAAS, and the adrenergic autonomic nervous system; this entails retention of fluids in the kidney, with the ultimate aim of volume overload. The described mechanism finally results in an excessive accumulation of fluids in the vascular compartment, with subsequent inevitable extravasation in the extravascular spaces: all this determines the known clinical manifestations [18].

The role of kidney as a cornerstone of the relationship between sweat glands and heart failure is attractive. Fluids overload in heart failure could theoretically be compensated by the simultaneous hyperactivation of sweat glands. In some cases, this physiological response could even anticipate an incipient decompensation and might prevent manifest volume overload: specifically, the increased sweat glands activity could actually lead to the elimination of an amount of liquids as high as 3000 ml per hour [19]. Based upon these premises different studies reported hyperhidrosis as a common symptom of heart failure in pediatric and adult patients [6, 7].

However, it must be considered that in the current therapeutic management of heart failure drugs with a direct influence on the autonomic nervous system and/or on the RAAS are often used. Therefore, the activity of the sweat glands could be affected both directly and through

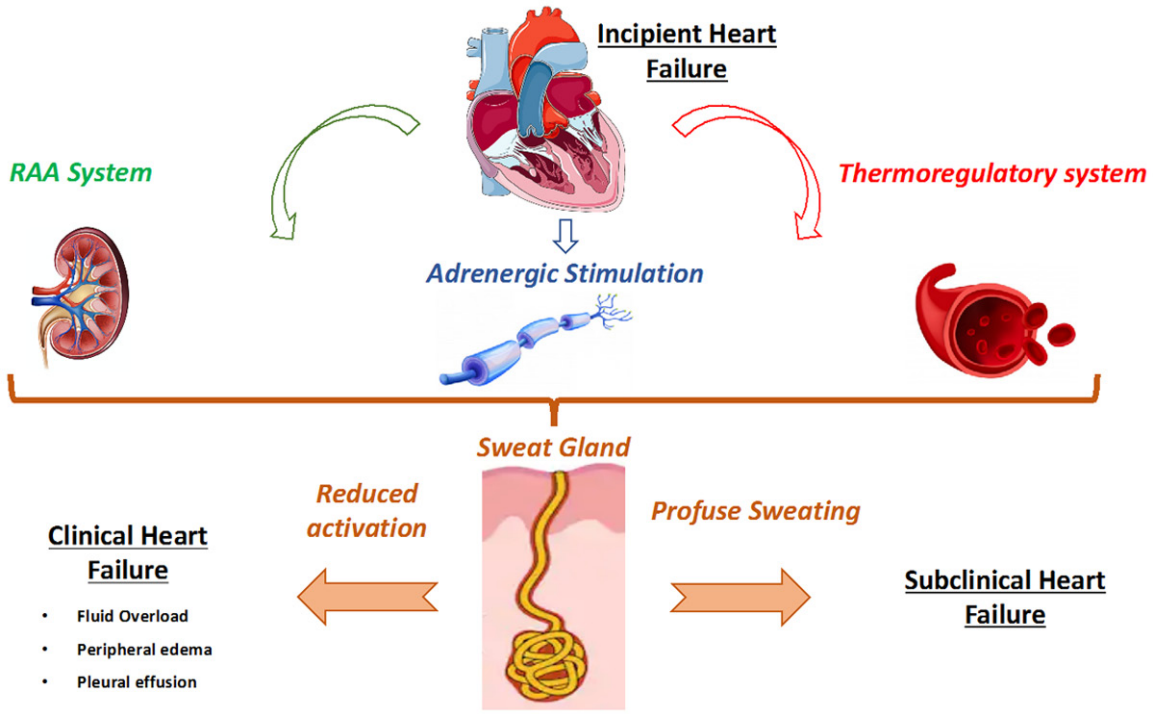

Figure 1. The role of the sweating gland in heart failure patients.

indirect negative modulation, as occurs in cases where blood pressure is significantly reduced by the treatment.

The role of sympathetic activation

The sympathetic nervous system is overactive in congestive HF. While this stimulation generates an increase in the reabsorption of fluids in the kidney, on the other hand it generates a signaling to the sweat glands to induce a dispersion of fluids, with loss of sodium and chlorine at the glandular ductal level. Interestingly, the prognostic value of sympathetic activation in heart failure patients is closely linked to the occurrence of life-threatening cardiac arrhythmias and sudden death, a finding that once again underlines the clinical relevance of neurogenic mechanisms in the development and progression of cardiac arrhythmic events [20-22]. Therefore, based upon the data presented it might wonder whether changes in sweating can be considered as a marker of adaptation or an early sign of decompensation in patients with heart failure. Furthermore, it would be interesting to evaluate in prospective studies whether the ability to increase sweating could be a positive prognostic factor as it would allow avoiding fluid retention or on converse a negative prognostic factor being a marker of sympathetic nervous system overactivation.

The role of the sweating gland in heart failure patients is summarized in **Figure 1**.

Thermoregulation in heart failure patient: the role of the sweat gland during stress

HF patients have an increase in morbidity and mortality during warm months [23]. Moreover, HF patients are encouraged to perform physical activity outside of formal rehabilitation programs, which can take place under a range of environmental conditions, including outdoors in a warm environment. As seen before, at the same time as temperature changes, human thermoregulatory system maintains core body temperature (Tc) as steady as possible through a continuous balance of vasomotor regulation and sweat production. Heat dissipating response is also secondary to the functioning of the cardiovascular and the autonomic system, which, if altered during warm stimuli, could lead to ineffective heat dissipation. Thus, this malfunction can hypothetically concur to the excess of morbidity and mortality during the hottest months in HF patients [24].

Table 1. Role of Thermoregulation during Stress in HF patients

	Year	Number of patients	NYHA Class	LVEF (%)	Type of Stress	Findings in HF patients during exercise	Reference
Cui et al.	2005	14 (HF) vs 14 (CON)	II-III	32±6	Tube-lined suit perfused with hot water	Similar WBSR, lower CVC increase	X
Green et al.	2006	7 (HF) vs 7 (CON)	II-III	27±2	Temperature-controlled room	Similar Tc and Ts elevation, lower CVC rise	X
Cui et al.	2013	9 (HF) vs 9 (CON)	II-III	<40	Tube-lined suit perfused with hot water	Similar Tc rise and SSNA, significantly lower CVC elevation	X
Benda et al.	2015	14 (HF) vs 14 (CON)	I-III	35±8	Incremental Cycling test	Similar increase in Tc, lower Ts rise	X
Balmain et al.	2016	10 (HF) vs 8 (CON)	I-II	N/A	Incremental Cycling test	Lower Tc, Ts and CVC increase and lower WBSR	X
Balmain et al.	2017	10 (HF) vs 10 (CON)	I-II	N/A	Incremental Cycling test	Greater Tr rise, similar WBSR and LSR but lower CVC elevation	X

CVC = Cutaneous Vascular Conductance; HF = Heart Failure; LSR = Local Sweat Rate; SSNA = skin sympathetic nerve activity; Tc = core Temperature; Tr = rectal Temperature; Ts = skin Temperature; WBSR = Whole-Body Sweat Rate.

In the past years several studies investigated this balance between sympathetic nervous system, vasoactive response and sweat production in heath failure patients during stress in a hot regulated climate (usually tube-lined suit perfused with hot water or temperature-controlled room) or during exercise (usually incremental cycling test). In these studies, rectal temperature was usually selected as an index of Tc. Whole-body sweat rate (WBSR) value was based on pre- and post-exercise weight while local sweat rate (LSR) was calculated as the product of vapor concentration of affluent air and flow rate. Cutaneous vascular conductance (CVC) was measured using a Laser-Doppler flowmetry. Finally, skin sympathetic nerve activity (SSNA) was assessed in only one study [25] by using microneurography from the peroneal nerve and the skin blood flow (forearm Laser-Doppler).

In a pioneer study in early 2005, Cui et al. observed that, compared to control, HF patients have similar WBSR but significantly CVC rise to both whole body and local heating obtained wearing a warm suit; this to demonstrate a reduced cutaneous vasodilator response during stress [26]. On the same line of research, Green et al. got same results utilizing a temperature-controlled room: skin temperature (Ts) and Tc didn't differ between cases and controls, but CVC rose significantly less in HF patients [27]. In another study, Cui et al. investigated the role of SSNA, responsible of skin flow control during passive heat stress with the use of a water-perfused suit: HF patients and controls had similar increase in Tc and the same SSNA, while again CVC was reduced in HF patients; from these results Authors deduced that attenuated vasodilator response was not due to an impairment of nerve stimulation to skin [25]. Benda et al. firstly introduced an active stressor, utilizing an incremental cycling test: they showed that increase of Tc was similar in the two groups, but Ts was lower in HF patients [28]. In the same way, Balmain et al. found a lower elevation of CVC and a lower WBSR during physical exercise, with non-different rise in Tc and Ts [29]. Notably, metabolic heat production and evaporative requirements for heat balance were lower in HF patients, reflecting their impaired functional response to stress. Authors therefore demonstrated an impairment of peripheral circulation to dissipate heat in HF patients. Again Balmain et al. designed a second study in which cases and controls were similar in age and body mass index and reached the same heat production during exercise [30]. Again, HF patients show a reduced CVC elevation, without any difference in WBSR and local sweat rate LSR; on contrary of previous studies, the rise of Tc was higher in HF patient compared to control, demonstrating an impaired distribution in heat production and between internal and external temperature.

To conclude, from these studies it follows that Tc and sweating response didn't vary significantly between healthy people and HF patients. Otherwise, the expected increase in skin blood flow was impaired in HF in all the studies. Notably, sweat grands direct contribution was less evaluated, most of them found no differences in the whole-body and local sweat rate.

These studies are summarized in **Table 1**.

Expert considerations

This review is focused on sweating and its pathophysiological role in heart failure. Although the main mechanisms underlying this phenomenon are not fully understood, there are interesting connections that might explain this fluid elimination as a wise and sophisticated way to prevent incipient heart failure crisis. Future research could be focused on studying new drugs that selectively would be able to promote fluid elimination by this specific way in patients suffering from heart failure. Moreover it could be of particular interest to observe the possible correlations between heart failure biomarkers and enhanced versus normal sweating in heart failure patients. Finally, this manuscript cites studies published over 70 years ago, when there was probably a more careful evaluation in clinical details which overcame the diagnostic tools nowadays available. During daily clinical practice, it could happen very often to correlate intense paroxysmal sweating to heart failure or angina equivalent; therefore we personally invite all the readers to consider unjustified sweating as a specific sign of heart failure.

Disclosure of conflict of interest

None.

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