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Review Article

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Adequacy of Ambulatory Hemodynamic Assessments for Reducing All-Cause Mortality in Individuals With Heart Failure

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ABSTRACT

Heart failure (HF) as a syndrome which is *normally* associated with significant reduction of cardiac output has evolved to include conditions such those of moderate and preserved ejection fraction. While the prevalence of HF in the population is increasing, it is not HF with reduced ejection fraction that is driving the trajectory upward for mortality. There is some evidence to suggest that a better understanding of the pathophysiology, novel pharmacological strategies, devices, as well as remote monitoring of the hemodynamics seem to account for a reduction in the cardiovascular mortality and re-hospitalization in some cohorts with HF. However, the all-cause mortality associated with HF has not been reduced significantly by the current interventions. To explore the potential approaches needed for the strategies and avenues to reduce all-cause mortality in patients with HF, it would be helpful to evaluate the evidence in the literature directed at the care of patients with chronic/acute decompensated HF. It is evident that ambulatory measurements of pressures and volume are pivotal in a better management of HF but unless the interventions extend to an improvement in the renal function, the chances of reducing all-cause mortality seems modest. Therefore, future directions of interventions must not only be directed at close monitoring of pressures and volume simultaneously in HF patients but also at improving renal function. Moreover, it is clear that venous congestion plays a detrimental role in the deterioration of renal function and until measures are in place to reduce it, all-cause mortality will not decrease.

Keywords: Heart failure; Venous congestion; Renal circulation; Telemedicine; Pharmacotherapy

INTRODUCTION

The landscape for heart failure (HF) as a syndrome is rapidly changing. Over the past two decades, HF as a syndrome that is associated with reduced cardiac output has evolved to become a condition that encompasses preserved ejection fraction (i.e., "normal" cardiac output). While the prevalence of HF in the population is increasing, it is not the HF with reduced ejection fraction (HFrEF) that is driving the trajectory upward for morbidity and mortality.[1,2] In fact, the prevalence of HFrEF seems to have stabilized with a slight downtrend while cohorts with preserved ejection fraction (HFpEF) are following an upward trend world-wide.[1,2] HF seems

to have a bimodal epidemiology based on the ejection fraction with the males being affected more than females in the "reduced" cohort while females seem to outnumber the males in the "preserved" group.[2] It is estimated that close to 60 million people suffer from HF,[2,3] and within this population approximately 50% have HFpEF.[4] Moreover, while the mortality associated with better diagnosis and treatments of HF has been decreasing, all-cause mortality seem to be stagnant or possibly increasing.[2] A number of reasons including a better understanding of the pathophysiology, novel pharmacological strategies and approaches, devices, as well as remote and careful monitoring of the hemodynamics seem to account for a significant reduction in the cardiovascular mortality and re-hospitalization in some of the cohort with HF.[5,6] The use of devices for ambulatory monitoring of cardiovascular function (e.g., cardiac contractility modulation, cardiac resynchronization therapy, left ventricular assisted devices, pressures and volumes) have been found to be of great benefit in the guided management of individuals with HF.[6,7] Nonetheless, the all-cause mortality for the most part seems not to be reduced significantly by the current interventions and the care available to individuals with HF. Therefore, the main aim of this review will be to address avenues relating to pressure and volume monitoring that need exploring in order to further reduce mortality associated with not only the cardiovascular system but also those of all-causes.

PATHOPHYSIOLOGY

Earlier discussions had centered on arterial under filling due to the diminished cardiac output (i.e., HF with reduced ejection fraction; HFrEF), and the activations of the sympathetic nervous system, renin-angiotensin-aldosterone system, the release of vasopressin, and other neurohormonal factors in response to baroreceptor reflex activation as well the structural changes with the cardiovascular systems.[8] HF has since transformed to include HFpEF, and HF with moderate ejection fraction, and with clinical evaluations that center on the alterations in the pathophysiology of the cardiac chambers (i.e., left/right atria and ventricles), as the imaging modalities have improved, and the overall assessments of hemodynamics via remote monitoring as well as factors such B-type natriuretic peptide (BNP) or amino-terminal pro B-type natriuretic peptide (NT-proBNP) and deficiencies in iron have come to play.

To explore the potential of approaches needed for the strategies and avenues to reduce all-cause mortality in individuals with HF, it would be most helpful to first examine the evidence in the peer-reviewed literature directed at the care of individuals with chronic/acute decompensated HF. Accordingly, monitoring of hemodynamics, blood chemistry and renal function coupled with appropriate pharmacological interventions may offer the best avenue directed at significantly reducing all-cause mortality in individuals with HF.

CARDIO-RENAL INTERACTION

A critical marker of deteriorating cardiovascular system in HF is renal dysfunction and more commonly described in the literature as "worsening renal function" (WRF). Ordinarily, reduced renal function (i.e., normally assessed as reduction in estimated glomerulus filtration rate [eGFR]) was ascribed solely to a reduction in the cardiac output, and reduced flow to the kidneys. However, an interesting and insightful longitudinal study by Anderson et al.[9] showed that reduction in jugular venous pressure correlated positively with reduction in body weight, and diuresis in individuals with congestive HF. Since, there has been ample evidence from clinical investigations linking deterioration in renal function as a consequence of venous congestion. In a sub-analysis (n=2,680) of the Candesartan Heart Failure Assessment of reduction in Mortality and Morbidity (CHARM), it was revealed that renal function can be considered as an independent high risk for death, cardiovascular death, and hospitalization in HF patients with reduced or preserved ejection fraction.[10] It seems that the majority of the individuals admitted for acute decompensated HF have a significant renal impairment and as such the renal dysfunction is not entirely due to left ventricular dysfunction or reduced cardiac output, and is predominantly the result of an increase in venous pressure.[11]

Evidence was also presented to suggest no correlation between renal insufficiency and cardiac index, leading to the further suggestion that reduced eGFR is not due to poor arterial flow.[12] However, it has been found that the occurrence of WRF in individuals with HF can be linked to more than one prognostic entity. For example, while significant reductions in arterial blood pressure can accentuate WRF, a deterioration in the renal function causing death can occur in the absence of significant reduction in blood pressure.[13] Nonetheless, it also seems that a combination of low systolic blood pressure and high central venous pressure lead to a lower eGFR, and this is associated with WRF in HF individuals.[14] Moreover, heart rate has also been directly and independently linked to WRF in individuals with HF.[15] Of importance is a distinction that has to be made between transient, persistent and no WRF in individuals while bearing in mind that the mechanisms associated with renal dysfunction in HF are multifaceted, and include factors such as overall hemodynamics, state of renal perfusion, venous congestion and the neurohormonal activation and the release of catecholamines, angiotensin II, vasopressin,

and other humoral factors. Accordingly, it has been reported that individuals with persistent versus transient or no WRF, as assessed by changes in serum creatinine levels, show a significantly higher rate of mortality in c cohorts with HF.[16]

More importantly is the association of the impairment in the renal function and all-cause mortality. Evidence has been presented (n=3,605) to indicate that renal dysfunction (eGFR<60 mL/min) is a strong predictor of all-cause mortality in individuals with HF.[17] Moreover, the routine use of loop diuretics and the aldosterone receptor antagonist, spironolactone, in individuals with HF with renal dysfunction may further have detrimental effects on kidney function.[17] Further, WRF as a cause of hospitalization in individuals (n=20,063) with HF is an independent risk factor for re-admissions and mortality in individuals with HFrEF or HFpEF.[18] In individuals with HFpEF, persistent-versus non-WRF was significantly associated with all-cause death, and all-cause-death or re-hospitalization.[19]

Damman et al.[20] had suggested that an increase in central venous pressure leads to reduction in GFR. Moreover, the elevation in central venous pressure was independently linked to all-cause mortality. This has led to the suggestion that an increase in the central venous pressure and the ensuing impairment in renal function are independently related to all-cause mortality.[20] Essentially congestion has been tagged as a major risk factor in HF with the emphasis that an elevation in venous pressure and possibly ascites are strong independent risk factors of all-cause mortality, hospitalization, and death from pump failure.[21,22] Reduction in BNP has been suggested to lead to decongestion in individuals with HF.[23] Hence, reduction in the diameter of inferior vena cava, and lowered pulmonary arterial wedge pressure (PAWP) and weight loss have been linked to reduction in venous pressure and associated with diuresis and improved renal function in individuals with HF.[23] This would suggest that in order to reduce all-cause mortality in individuals with HF, it would be prudent to alleviate significant elevations in venous system, and attempt to reduce venous congestion.

It seems that while cardiac index is not associated with risk of death, elevated PAWP and right atrial pressure appear to be so in individuals with acute HF.[24] Moreover, analysis of the clinical data indicates that cardiac index does not have to be lower for individuals to develop WRF.[25] In addition, there is a lack of dissociation between cardiac index and different metrics such as changes in hemoglobin, creatinine, and blood urea nitrogen levels as well as the blood urea nitrogen to creatinine ratio. Thus, suggesting that cardiac index is not the main instigator for the renal dysfunction in individuals with HF.[25] While evidence has been provided to further support the idea that changes in GFR are not directly linked to cardiac index, it has been suggested that WRF is less frequent if central venous pressure is less than 8 mmHg.[26] Accordingly, in examining the effects of right ventricular function and venous congestion with respect to cardio-renal integration in decompensated HF, Testani and colleagues[27] have suggested that the right ventricular function is an important surrogate of renal function. Thus, in individuals with right ventricular dysfunction a reduction in cardiac output can lead to improvement in renal function as a summation of hemodynamics that then manifest as a reduction in venous congestion due to decrease in the workload placed on a dysfunctional right ventricle.[27] More recently, a longitudinal study of 15-year follow-up (n=2,677) of kidney function of individuals with chronic HF has revealed that a decline in eGFR is influenced by several factors including age, sex, diabetes, and left ventricular ejection fraction with significant impact on survival.[28] In addition, the decline in eGFR was found to be significantly associated with all-cause mortality (p<0.001) and cardiovascular death (p<0.001).[28]

HEMODYNAMIC MONITORING AND INTERVENTIONS

Vascular pressure

In a comparative study of the merit of physical exam to a host of hemodynamic parameters in individuals with chronic HF, Stevenson and Perloff[29] found that an increase in PAWP (≥35 mmHg) does not necessarily lead to pulmonary rales. Hence, a suggestion that hemodynamic monitoring may provide a better diagnostic and prognostic value than just assessment of physical signs. However, they also noted that while a high cardiac index was associated with lower PAWP, a higher PAWP was not associated with lower cardiac index.[29] The current interpretation of the latter observations would be the presence of two population of individuals with chronic HF (e.g., HFrEF and HFpEF). Robust long-term evaluation of the hemodynamic parameters as an approach is becoming a novel avenue to strategically treat individuals with cardiovascular-related disorders, and is becoming increasingly more promising with the advent of new technologies and more sophisticated and precise remote monitoring (**Table 1**). Much earlier, such a notion had led Nathan et al.[30] to undertake a study of the ambulatory measurements of pulmonary arterial pressure (PAP) in individuals with HF. The strategy was to detect and combat dyspnea using pharmacological interventions. Of interest was the fact that dyspnea did not always correlate with elevation in PAP.[30] Further strides were also made in the measurements of ambulatory PAP for better insight of the dynamics of this parameter, and its prognostic value in the guided management of the individuals with HF. There are clearly nuances in the ambulatory measurements of hemodynamics

Table 1. Vascular pressure and management of individuals with heart failure

PAWP	Modest correlation with cardiac index
Pulmonary arterial pressure	Influenced by diurnal cycle
Right atrial pressure	Correlates well with PAWP regardless of increase in right ventricular pressure
Pulmonary arterial systolic pressure	Strongly correlates with PAWP and subject to changes with use of diuretics and/or vasoactive drugs
Remote monitoring right atrial pressure	Useful for guided management of individuals with heart failure

PAWP = pulmonary arterial wedge pressure.

especially PAP in relation to dyspnea. For example, Gibbs et al.[31] in angina-free individuals with chronic HF, showed diurnal variations in PAP was associated with a nocturnal rise in latter pressure in these individuals (i.e., there are other sources that increase PAP than posture). There is evidence to suggest no correlations between heart rate and either systolic or diastolic PAP, and dissociation between dyspnea and changes in PAP.[32] Nonetheless, in studying the relationship between right atrial pressure, pulmonary arterial systolic pressure and the PAWP in individuals with advanced HF, Drazner et al.[33] noted a robust correlation between the right atrial pressure and PAWP regardless of an elevation in the right ventricular pressure. In addition, pulmonary arterial systolic pressure strongly correlated with PAWP while treatment with diuretics and/or vasodilators produced simultaneous changes of pulmonary arterial systolic pressure and PAWP.[33] Thus, the vision that future clinical investigations would further extend the value of long-term ambulatory hemodynamics in individuals with chronic HF, and allow for optimal care and pharmacological treatments that would reduce cardiovascular mortality, re-hospitalization and all-cause mortality, and as well as a better quality of life has become the focus of telemedicine and personalized medicine.

Historically, attempts have also been made to further refine the assessment of PAP in a number of clinical investigations using the right ventricular pressure,[34-36] with the outcome being labelled as the estimated pulmonary diastolic arterial pressure (ePAD) based on values obtained from the right ventricular pressure at maximal of dP/dt.[34-36] Primarily, the expectation being that such an approach would provide information on the right ventricular end-systolic and end-diastolic pressures leading to a more in-depth assessment of the ambulatory hemodynamic data that could be captured over the course of longer periods of time, i.e., one year.[37,38]

Using implantable monitoring devices, the assessment of increases in the right ventricular pressure as a surrogate of volume-overload were evaluated.[39] Significant increases in right ventricular systolic pressure (25%) and heart rate (11%) were noted prior to hospitalization in individuals with HF, leading to the suggestions that ambulatory pressure measurements using implantable hemodynamic devices, long-term, may be helpful in providing guidance in day-to-day clinical care and management of individuals with HF.[39] However, evidence from a number of clinical investigations attempting to provide guided therapy using implantable continuous hemodynamic monitoring did not provide favorable outcomes. In individuals with advanced HF (left ventricular ejection fraction < or ≥50% stratified to two groups), randomized controlled trial post-six months resulted in the end-point of HF-related events, emergency and urgent clinic visit frequency requiring iv therapy not being different in control (n=140) versus the optimal-therapy (n=134) group.[40] Further, in individuals with diastolic HF (NYHA III/IV), continuous hemodynamic monitoring of right ventricular systolic and diastolic pressures, dP/dt (max. & min.) and ePAD with modifications of medications such as diuretics to adjust for volume (intervention; n=34) compared to control (n=36), did not significantly result in reduced HF-related events.[41] As well, in randomized controlled clinical studies in individuals with HF using wireless devices to monitor PAP while making therapeutic adjustments to lower the latter pressure did not increase survival rate in the intervention versus control groups even though the treated group had a significantly lower pressure x days at six months.[42] Notwithstanding the latter findings, in an observational investigation of physician-directed, self-remote monitoring of left atrial pressure with an optimal range of 10–18 mmHg resulted in improvements in a cohort of chronic HF individuals following adjustments to medications.[43] In the latter investigation an increase in the use of diuretics and lower use of angiotensin converting enzyme inhibitors/angiotensin receptor type$_2$ antagonists and β-blockers resulted in significant increases in the left ventricular ejection fraction ($p<0.001$) and cardiac index ($p=0.010$), while PAWP ($p=0.013$) was reduced, no changes in eGFR ($p=0.46$) or BNP ($p=0.21$) were observed (n=35) over the course a twelve month period.[43] Remote monitoring of PAP in individuals with HFpEF (n=119) and HFrEF (n=430) in a treatment or control resulted in significantly better outcomes in the former group. In essence, changes in pharmacological managements (increase/decrease in use of loop or thiazide diuretics, nitrate and hydralazine dosing in reducing PAP) in the treatment (T) compared to control (C) groups resulted in significant reductions in hospitalization of individuals with left ventricular ejection fractions, ≥40% (T, n=62 vs. C, n=57; $p<0.0001$), ≥50% (T, n=35 vs. C, n=31; $p<0.0001$) and <40% (T, n=208 vs. C, n=222; $p=0.0010$) over the course of 17.6 months follow-up.[44] PAP guided management of individuals with functional NYHA Class III overall resulted in 48% reductions in admissions to hospital for HF ($p<0.0001$) and 21% reduction in all cause admissions ($p=0.0034$)

while mortality alone was not significantly (p=0.17) reduced.[45] Varma et al.[46] also found that remote monitoring of PAP in individuals with HF (NYHA III) and making adjustments to medications in treatment (T) compared to control (C) cohorts produced favorable outcomes in a course of a six month period. In the two cohorts with HF, reductions in PAP over time (T; n=76: −413.2±23.5 mmHg-days vs. C; n=76: 60.1±88.0 mmHg-days; p=0.0023) resulting in significant reductions in HF-related hospitalization (p=0.0280), death and HF hospitalization (p=0.0223) but no significant impact on the overall mortality (p=0.3813).[46] In patients with NYHA Class II and IV and elevated BNP or NT-proBNP, ambulatory monitoring of PAP produced similar findings as those from a clinical study by Abraham and colleagues;[47] a reduction in the primary endpoint HF hospitalization with no benefits on all-cause mortality at 12 months.[47] In the latter, data adjusted for coronavirus disease 2019 supports PAP monitoring and guided management of individuals with HF.[46] More recently, Brugts et al.[48] reported some interesting findings in individuals with chronic HF (NYHA III) that were being monitored remotely for PAP at 3, and 6 months and thereafter every 6 months up to 4 years. There were two cohorts in this investigation, the remotely hemodynamic monitored (n=176) and standard groups without hemodynamic monitoring as the control (n=172) arms and subject to pharmacological interventions. At 12 month, the mean PAP was significantly (p<0.0001) lower (24.9±9.4 mmHg) than baseline (33.3±10.6 mmHg; mean ± SD). In addition, NT-proBNP was found to be significantly lower from the baseline in monitored cohort (median: 2,377 pg/mL vs. 1,708 pg/mL; p=0.013) but not standard non-monitored (median: 1,907 pg/mL vs. 1,607 pg/mL, p=0.81) cohort. Further, the outcomes of this investigation in the monitored compared to the standard treatment using Kaplan Meier curve, for time-to-first HF-hospitalization revealed significant reductions for HF hospitalization (p=0.041) in the former group but no significant impact on, for-time-to-first cardiovascular mortality (p=0.48) or for-time-to-first all-cause mortality (p=0.85) between the cohorts.[48] This further indicates that quantitative assessment of pressure, and even BNP are not adequate to significantly reduce all-cause mortality in individuals with HF.

In an attempt to provide a suitable quantitative metric of health measure based on remote hemodynamic monitoring of individuals with HF, Zile et al.[49] tested the value of the product of an increase in ePAD (P) over time (T), days, in connection to HF-related events (i.e., P × T mmHg.days). The analysis involved plotting ePAD increases from baseline to peak over days relative to HF-related events, and attempting to identify the numerical increase of the product P × T that could be closely linked with transitioning from chronic HF to acute decompensated HF and its circumstances. Here, it was noted that other factors contributed to this quantitative measure such as eGFR. Of interest, was the fact that P × T was significantly greater when eGFR was larger than 60 mL/min/1.73m^2 (i.e., P × T=256±136 mmHg.days eGFR ≥60 mL/min/1.73m^2 vs. P × T = 196±123 mmHg.days eGFR <60 mL/min/1.73m^2; mean ± SD; p<0.05).[49] Thus, the analytics seem to point to an increase in both extravascular and intravascular volumes as a tipping point for the balance of chronic compensated HF to acute compensated HF. Further, the analysis seem to suggest that the renal function becomes worse, once diastolic filling pressure is significantly increased. While the outcome of such analysis seems to reinforce the importance of the cardio-renal interaction (as discussed earlier), it also suggests that measurement of pressure over time may not be the pragmatic prognostic entity for predicting worsening cardiovascular status, and that the extravascular and intravascular volumes need to be more carefully monitored for better health outcomes in individuals with chronic HF. In essence, measurements of pressures in a system with large capacitance (i.e., systemic venous and pulmonary system) may not provide a holistic picture of the functionality of the body. Thus, it is pivotal to attempt and achieve remote assessments of as many components of the hemodynamics in the body in order to reduce not only cardiovascular-related deaths but also all-cause mortality in individuals with chronic HF. Remote measurements of ePAD and venous tone simultaneously may offer a better assessment of the health status of individuals with chronic HF. Experimental evidence suggests the possibility of remote and accurate monitoring of the cross-sectional area of the inferior vena cava in real-time with wireless implantable devices as a reliable marker of venous function.[50] Moreover, it was reported that changes in inferior vena cava area are more sensitive than the corresponding filling pressure as an indicator of volume overload and fluid redistributions.[50] In clinical investigation, noninvasive venous waveform analysis has been found to have a higher sensitivity in predicting HF hospitalization, and has an excellent correlation (r=0.93) with PAWP measurements.[51] More recently, it has been reported that PAP monitoring and guided therapy improves quality of life of individuals with HFrEF.[52] Further, a meta-analysis of three clinical trails seem to suggest remote hemodynamic monitoring reduces hospitalization and mortality but there are a number of limitations associated with the latter analysis, and hence the findings may not readily translate into real-world outcomes.[53] In addition, some evidence has become available to indicate that ambulatory hemodynamic monitoring and guided therapy could offer a cost-effective avenue for health care professionals to optimize care for individuals with chronic HF while improvements in the quality of life have also been noted.[54,55] Taken together, a timely approach for accurate and reproducible assessments of both pressures and volume changes in the circulatory system may provide for a more robust avenue of saving lives in some individuals with chronic HF.

Intrathoracic impedance

Assessment of volume accumulation in individuals with HF is an important facet of the syndrome, and a critical sign of well-being and health of the individual's with dysfunctional cardiovascular-renal system. Thus, it would be prudent to find a reliable and reproducible remote method of assessing fluid accumulation in the body, and this premise led Yu et al.[56] to evaluate intrathoracic impedance in individuals with HF in attempt to determine fluid accumulation in the lungs as a prognostic index of the health of the cardio-lung circulatory system. The theory underpinning this approach is that when electrical current is passed across the chest between points, lower impedance will occur following the accumulation of fluids in the lungs, consequently giving a much better conductance of the current that is being transmitted; and it could be quantified in ohms as a unit of assessment. Accordingly, an inverse correlation (r=0.61; p<0.001; n=33; NYHA III/IV) was found to exist between impedance in lungs and PAWP measurements made in the cardiac care unit in individuals with HF.[56] However, Vanderheyden et al.[57] only found a modest correlation (−0.48±0.25) of intrathoracic impedance and ePAD in individuals with HF where sample size was relatively small (n=16) during the course of an investigation for six months (**Table 2**).

There has been mixed evidence with regards to the usefulness of the measurements of intrathoracic impedance as a link to viable predictive positive outcomes of appropriate endpoints. Accordingly, earlier observational investigations confirmed the prognostic value of intrathoracic impedance with modest sensitivity (32–60%) and positive predictive values (38–60%).[58-60] Further, a prospective investigation (n=156; 44±26 months) in evaluating the sensitivity of intrathoracic impedance and weight gain, indicated fluid index was significantly (p<0.001) more sensitive than daily weight (76.4% vs. 22.5%).[61] In addition, in the latter study, it was noted that unexplained death rate per patient-year was significantly (p<0.001) lower while monitoring by intrathoracic impedance (1.9) than daily weight (4.3).[61]

There are a number of clinical investigations that have not provided positive outcomes using such a metric in conjugation with telemedicine for predicting deterioration in the health of the population with chronic HF, and leading to the suggestion of high inter-patient variability curtailing the robust prediction of decompensation in individuals with HF.[62] For example, in a clinical investigation in individuals with chronic HF (n=335), attempting to provide better outcomes (14.9±5.4 months) using audible alerts due to changes in conductance, the use of implantable intrathoracic impedance did not provide a positive outcomes either for death, hospitalization for HF, or hospitalization for cardiovascular events.[63] Similar findings were reported by Domenichini et al.[64] in two groups of individuals (treated, n=41 vs. control, n=39) of no significant differences for primary endpoint of HF hospitalization or secondary endpoint of admissions to emergency room and unscheduled visits to heart clinic or quality of life in individuals with chronic HF (NYHA II/III) as well as mortality in the cohorts in course of one year. As well, remote fluid monitoring (n=87) versus control (n=89) did not lead to significant reductions in HF-related hospitalization (p=0.551), or mortality (p=0.512) after one year in individuals with HF (left ventricular ejection fraction=32±11%).[65] Moreover, a larger randomized clinical study (fluid alert n=505 vs. no alert n=497) followed for an average of 1.9 years, did not lead to significantly (p=0.13) reduced composite all-cause mortality and cardiovascular hospitalization between the two groups.[66]

A limited number of studies have reported modest positive outcomes with the remote monitoring of intrathoracic impedance in individuals with HF. Wintrich et al.[67] in the OptiLink HF Study (n=1,002 in four groups), reported positive outcomes of significant reduction, in remotely monitored versus usual care, for cardiovascular death or first HF hospitalization but only in individuals contacted appropriately. In contrast, there were no significant differences with fluid monitoring compared to usual care for cumulative incidence of cardiovascular death, or cumulative incidence of all-cause mortality. Perhaps it is also important to note that the total number of fluid alerts were not found to be an independent risk predictor of the primary endpoint.[68] Further, a sub-analysis of OptiLink HF Study, in individuals with or without chronic kidney disease revealed that intrathoracic impedance monitoring independently reduced (p=0.006) rate of primary events (i.e., risk of cardiovascular and HF hospitalization) in patients with chronic kidney disease versus without the disease.[68] In addition, fluid monitoring reduced (p=0.003) all-cause mortality in individuals with but not without chronic kidney disease.[68]

Pharmacological strategy

A premise for hemodynamic and fluid monitoring of individuals with chronic HF is to attempt to optimize pharmacotherapy and personalized medicine to improve well-being. Thus, remote monitoring and lowering of ePAD or fluids by suitable adjustments of

Table 2. Intrathoracic impedance in management of individuals with heart failure

Intrathoracic impedance as an index of lung fluids	Modest correlation with estimated pulmonary diastolic arterial pressure
Comparison of intrathoracic impedance versus body weight	Intrathoracic impedance more sensitive than body weight
Prognostic value of intrathoracic impedance	Modest sensitivity and modest positive predictive value
Value of remote intrathoracic impedance monitoring	Good correlation in individuals with heart failure and chronic kidney disease

medications would be expected to lead to better outcomes, and while this has been the case in certain conditions, the exact positive nature of the outcomes has been challenging to decipher.

Earlier findings had suggested that withdrawal of diuretic furosemide in individuals with ejections fraction of less than 27%, and no history of hypertension may benefit functionality of the cardiovascular system.[69] The positive outcome noted in the latter investigation could be due to overzealous use of the diuretic producing substantial reductions in right ventricular pressure as result of large decrease in venous return (due to extensive reduction in volume) compromising central hemodynamics in a state of low cardiac output. Evidence exists to suggest that in individuals with acute decompensated HF, low efficacy of diuretics was associated with a poor survival rate. Moreover, the possibility of differential outcomes with the use of diuretics associated with mortality in individuals with HFrEF compared to those with HFpEF has been noted.[70] It also seem evident that forward flow (i.e., cardiac index) has no correlation with the efficacy of loop diuretics in individuals with acute HF.[71]

The use of pharmacological agents to reduce volume-overload and congestion in the state of acute HF has provided some benefits. Meta-analyses seem to provide some inconsistent outcomes regarding WRF in individuals with acute HF with use of vasopressin V2 receptor antagonist, tolvaptan, as an add-on to diuretics. Ma et al.[72] have suggested tolvaptan as an add-on therapy in individuals with acute HF did not reduce incidence of WRF or all-cause mortality but reduced body weight. In contrast, the outcome of meta-analysis by Wang et al.[73] seem to suggest that tolvapan improves WRF, reduces body weight and improves dyspnea but not all-cause mortality and re-hospitalization. Notwithstanding the two mentioned analysis, Luo et al.[74] seems to suggest that the use of a lower dose (7.5–15 mg/d) than higher dose (30 mg/d) of tolvaptan significantly reduces incidence of WRF. Nonetheless, none of the analysis suggests that such an intervention significantly reduces all-cause mortality.

The outcomes from the meta-analysis by Cao et al.,[75] suggest that the use of sodium glucose co-transporter 2 inhibitors in individuals with advanced chronic kidney disease could attenuate progressive decrease in eGFR in comparison to treatment with placebo. In addition, the outcomes from another meta-analysis revealed the use of sodium glucose co-transporter 2 inhibitors caused a higher volume of diuresis while combined with a lower dose of loop diuretics resulted in reduced all-cause death in individuals with acute HF.[76] However, more evidence will be needed to confirm such outcomes. Taken together, survival in individuals with chronic HF leading to acute HF seem very connected to functionality of the kidneys, and unless measures are in place to improve renal function, the likelihood of survival in such individuals is dramatically reduced (**Figure 1**).

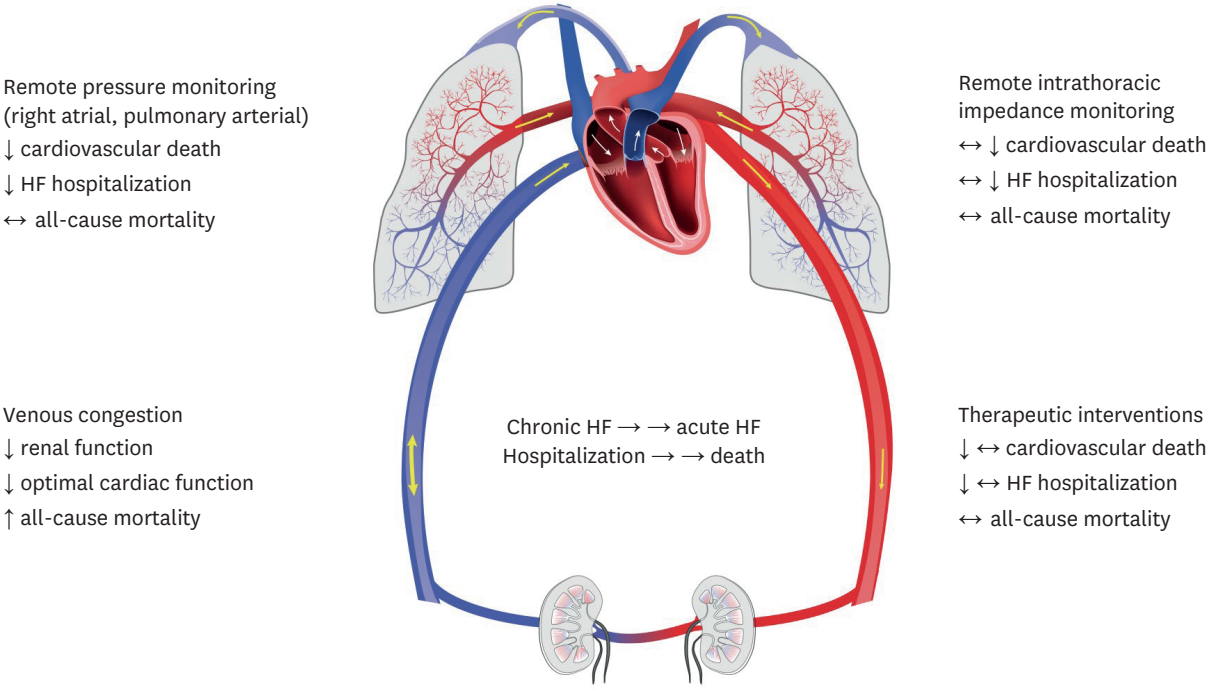

Figure 1. Hemodynamic assessments and potential outcomes in individuals with HF.
HF = heart failure.

FUTURE DIRECTION

While the ambulatory measurements of pressures and volume are of excellent value in individuals with chronic HF, it seems that unless the ensuing interventions lead to improvements in eGFR and renal function, the chances of reducing all-cause mortality appear to be relatively modest. Accordingly, future directions for interventions must not only be directed at the close monitoring of pressures and volume simultaneously but also be squarely aimed at improving renal function. Moreover, it is quite evident that venous congestion plays a detrimental role in WRF and until measures are in place to reducing such congestion in individuals with HF then failure of the cardiovascular-renal axis will lead to death in such a population.

STATEMENTS AND DECLARATIONS

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Conflict of Interest

The author has no financial conflicts of interest.

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