Non-intuitive findings from the MEMS-HF haemodynamic substudy

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This article refers to 'Effects of remote haemodynamic-guided heart failure management in patients with different subtypes of pulmonary hypertension: insights from the MEMS-HF study' by B. Assmus et al., published in this issue on pages 2320–2330.

It's the little details that are vital. Little things make big things happen.

Quote from John Wooden, United States college basketball coach whose teams won a record 10 national championships including seven in a row.

Treatment algorithms targeted to lowering pulmonary artery pressures (PAP) monitored from the CardioMEMS wireless implantable system (St. Jude Medical Inc., Sylmar, CA, USA) have yielded dramatic benefit for patients with New York Heart Association (NYHA) class III symptoms and recent heart failure-related hospitalizations (HFH). In the prospectively randomized CHAMPION trial, HFH over an average 18-month follow-up were 37% lower among the algorithm-treated patients compared to controls ($p = 0.0001$).[1] During an average 13-month open access follow-up, HFH among patients previously randomized in the CHAMPION trial decreased by 48% after PAP-guided algorithms were utilized ($p = 0.001$).[2] Similarly, in the MEMS-HF study, 1-year annualized HFH decreased by 38% after device implantation and application of PAP treatment algorithms.[3] CHAMPION and MEMS-HF algorithm-treated patients also enjoyed improved quality of life. There were few device-related complications, 1.4% in CHAMPION and 1.7% in MEMS-HF. The clinical benefits were in addition to the guideline-directed medical therapy that all patients received.
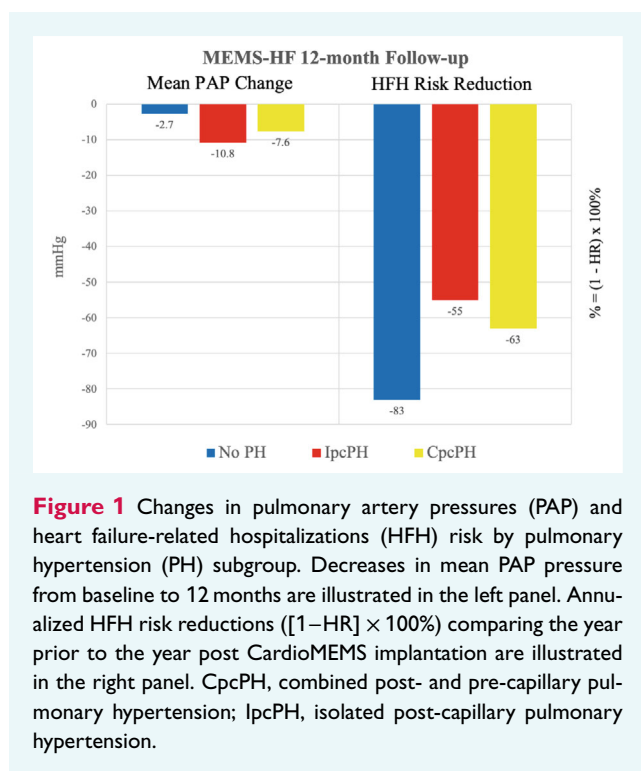
Paradoxically, the average absolute decreases in PAP with PAP-guided algorithms were small even though they made 'big things happen'. In CHAMPION, the sustained reduction in mean PAP averaged −1.6 mmHg in the algorithm-treated patients versus 0.0 mmHg in the controls ($p = 0.0351$).[4] In MEMS-HF, the reductions were larger but only −3.3 mmHg after 6 months and −5.0 mmHg after 1 year ($p < 0.0001$).[3]

In this context, identifying subgroups of patients for targeted PAP-guided therapy could be useful. In this issue of the Journal, Assmus and colleagues present a subgroup analysis of the MEMS-HF trial.[5] They analysed haemodynamic tracings obtained at the time of CardioMEMS implantation and divided patients into three groups based on the presence or absence of pulmonary hypertension (PH) and by the type of PH: isolated post-capillary (Ipc) or combined post- and pre-capillary (Cpc). They found reductions in PAP in all three groups, especially in the groups with PH. From baseline to 1 year, mean PAP decreased −2.7 mmHg in patients without PH ($p = 0.03$), −10.8 mmHg in patients with IpcPH ($p < 0.001$), and −7.6 mmHg in patients with CpcPH ($p = 0.005$). These results were partially expected since the patients without PH had the lowest initial PAP and were, at least partially, boundary-limited for subsequent pressure decreases. Quality of life improved in all three groups, especially in the groups with PH. Although HFH declined in all three groups, the greatest decrease occurred in patients without PH who had the smallest decreases in PAP and the smallest improvements in quality of life. Annualized HFH rates fell from 1.558 to 0.261 for patients without PH ($p < 0.0001$), from 1.528 to 0.686 for patients with IpcPH ($p = 0.0018$), and from 1.655 to 0.618 for patients with CpcPH ($p < 0.0001$). The respective hazard ratios were: 0.17, 0.45, and 0.37. This large discrepancy between the small decrease in PAP and the very large decrease in HFH in patients without PH is surprising and not intuitive. However, as Assmus and colleagues acknowledge this finding is more hypothesis generating than definitive. The decreases in mean PAP and the reductions in the risk of HFH in the subgroups at 12 months are illustrated in *Figure 1*.

The authors speculate that patients with heart failure and PH may have remodelled pulmonary vasculature thereby limiting the effects of a CardioMEMS associated decrease in PAP. This hypothesis would explain the relative effects on HFH only in the CpcPH subgroup and would not explain the larger benefit in quality of life for patients with versus without PH. An alternative explanation is that the patients without PH were clinically

Figure 1 Changes in pulmonary artery pressures (PAP) and heart failure-related hospitalizations (HFH) risk by pulmonary hypertension (PH) subgroup. Decreases in mean PAP pressure from baseline to 12 months are illustrated in the left panel. Annualized HFH risk reductions ([1−HR] × 100%) comparing the year prior to the year post CardioMEMS implantation are illustrated in the right panel. CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension.

improving and that their HFH rates were already declining as they entered the MEMS-HF trial. The average number of days from the last hospitalization to device implantation was longer and more widely dispersed in patients without PH than in patients with IpcPH or CpcPH (100.1 ± 111.6 days vs. 66.4 ± 78.9 days, and 65.8 ± 71.6 days). However, overall HFH immediately prior to trial entry were high and similar between the three groups (84−90% within 6 months) making an improving clinical condition among the patients without PH unlikely as a primary explanation. Nevertheless, in the absence of a control group for comparison, the authors cannot completely exclude an unusual patient mix in the group without PH. Furthermore, the number of patients in each subgroup was small, 106 out of the 234 MEMS-HF patients had baseline haemodynamic tracings of sufficient quality for analysis including only 31 patients without PH. Thus, the authors cannot exclude the possibility that the large reduction in HFH in this group represents a statistical sampling aberration.

The prospectively randomized GUIDE-HF trial extended the potential heart failure target population for CardioMEMS PAP monitoring from only patients with NYHA class III symptoms and a recent HFH to NYHA class II or III symptoms and a recent HFH or elevated natriuretic peptide level.[6] Although the results were confounded by the COVID-19 pandemic, GUIDE-HF demonstrated a trend toward a greater reduction in HFH rates among patients with NYHA class II symptoms than patients with NYHA class III symptoms (hazard ratios 0.72 vs. 0.87). GUIDE-HF found

no difference in benefit regardless of entry based on recent hospitalization or elevated natriuretic peptide level. GUIDE-HF also showed no benefit among patients with NYHA class IV symptoms, presumably because their disease had progressed to the point that HFH could not be avoided. Neither CHAMPION or GUIDE-HF demonstrated a reduction in mortality from CardioMEMS PAP-guided therapy.

The strategy for PAP-guided therapy is based on a time window lasting up to several days between increases in PAP and subsequent decompensation leading to HFH.[7,8] This window of opportunity is relatively brief, and the increase in PAP may be modest. Nevertheless, the benefit is based on the 'little details' essential to the algorithms, frequent and timely medication adjustments responding to the monitored PAP rather than large absolute reductions in PAP. In the CHAMPION trial, algorithm-treated patients received 2468 medication changes compared to 1061 changes for controls. Most of the medication changes (78.4%) were directed at relieving volume overload – adjustments in loop diuretics, thiazide diuretics, and nitrates. These interventions flatten a patient's haemodynamic course and reduce the risk of hospitalization but do not alter the ultimate course of the disease or reduce the risk of death. Based on CHAMPION, MEMS-HF, and GUIDE-HF, benefit from algorithm-driven therapy may occur in any NYHA class II or III symptomatic patient at risk for HFH and irrespective of the presence or subtype of PH at baseline as Assmus and colleagues' data suggest.

Conflict of interest: none declared.

References

1. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costano MR, Stevenson LW, et al.; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;**377**:658−66.
2. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: completed follow-up results from the CHAMPION randomised trial. *Lancet*. 2016;**387**:453−61.
3. Angermann CR, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett ME, et al. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). *Eur J Heart Fail*. 2020;**20**:1891−901.
4. Benza RL, Raina A, Abraham WT, Adamson PB, Lindenfeld J, Miller AB, et al. Pulmonary hypertension related to left heart disease: insight from a wireless implantable hemodynamic monitor. *J Heart Lung Transplant*. 2015;**34**:329−37.
5. Assmus B, Angermann CE, Alkhlout B, Asselbergs FW, Schnupp S, Brugts JJ, et al. Effects of remote haemodynamic-guided heart failure management in patients with different subtypes of pulmonary hypertension: insights from the MEMS-HF study. *Eur J Heart Fail*. 2022;**24**:2320−30.
6. Lindefeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF); a randomized controlled trial. *Lancet*. 2021;**398**:991−1001.
7. Zile MR, Bennett TD, Sutton MSJ, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure. Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;**118**:1433−41.
8. Abraham WT, Perl L. Implantable hemodynamic monitoring for heart failure patients. *J Am Coll Cardiol*. 2017;**70**:389−98.