Diagnosing pulmonary hypertension due to left heart disease using diastolic echo markers: The National Echo Database of Australia (NEDA) PH-LHD predictive formula

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Chapter 4. Summary, Key Findings, Recommendations and Future Directions

4.1. Summary
This thesis is written to contribute to the body of knowledge in managing patients with PH which is a serious and common health problem (2). In the chapter 2, the pathophysiology of PH, its classification and underlying aetiologies were described in detail. Among the 5 PH groups as per the 2013 Nice Classification(10), group 1 or pulmonary arterial hypertension (PAH) has the specific advanced therapy targeting at pulmonary vasculature. The prognosis of PAH patients has much improved because of this advanced therapy. However, there is no evidence that the advanced therapy is beneficial for PH patients due to other causes such as left heart (group 2) and lung diseases (group 3) (1). Multiple studies have suggested that PH-LHD (pulmonary hypertension due to left heart disease) is the most common cause (2, 13). Systolic or diastolic left ventricular failure and left sided valvular diseases can lead to PH-LHD. Owing to the aging population and higher prevalence of risk factors such as diabetes and hypertension in the general population, the prevalence of HFpEF has increased dramatically. PH due to HFpEF is a particularly challenging diagnosis as the left ventricular diastolic dysfunction may not be easily recognised. It is estimated that around 50% of HFpEF patients will develop PH (33). In a cross-sectional survey of 2042 randomly selected residents older than 45 years in Minnesota between 1997 to 2000, 20.8%, 6.6% and 0.7% of population had mild, moderate and severe diastolic dysfunction (34). Even in the absence of clinical syndrome of congestive heart failure, the moderate and severe diastolic dysfunction were associated with significant increase in all-cause mortality in this study.

The physiology of pulmonary circulation and the concept of PVR were also explained in chapter 2. The PVR is an important parameter which can determine the underlying pathophysiology of PH and RHC is the gold standard method to measure it. It is calculated as transpulmonary gradient (TPG) divided by the cardiac output (CO). TPG is the pressure difference between the mean pulmonary arterial pressure and left atrial pressure represented by PCWP (pulmonary capillary wedge pressure). The importance
of differentiating prePH (pre-capillary PH) vs postPH (post-capillary PH) by measuring PCWP and PVR using right heart catheterisation (RHC) was discussed. The risks and limitations of RHC (right heart catheterisation) were also discussed. I also described how important it is for PH patients to get correct diagnosis early in their disease process for better outcomes. The prePH patients have higher TPG and PVR (PVR>3WU) while postPH patients have elevated left heart pressure (PCWP) and low TPG and PVR. The PAH (pulmonary arterial hypertension) is a relatively rare form of PH where the specific advanced therapy is indicated. The advanced therapy includes vasodilators targeting the pulmonary vasculature such as endothelin receptor antagonists (e.g. mexitentan, bosentan and ambrisentan) and phosphodiesterase type 5 inhibitors (e.g. sildenafil and tadalafil). The diagnosis of PAH requires the presence of prePH which is defined as PCWP ≤ 15mmHg and PVR > 3WU in the absence of other causes of prePH (e.g. PH due to lung diseases, CTEPH (chronic thromboembolic PH) or other rare diseases (35). The postPH is mainly secondary to left heart diseases such as systolic and diastolic left ventricular failure and left sided valvular heart diseases (aortic and mitral). The management of postPH should be focused on correcting the underlying left heart diseases and advanced therapy or PAH approved therapy in not indicated.

It is not only impossible to do RHC in all PH patients but also such an approach is not necessary. A reliable echocardiographic marker which can differentiate different physiologies of PH is needed to improve PH evaluation. This will reduce the number of unnecessary RHC and will improve the utilisation of available resources by better selection of patients who require invasive tests. Researchers worldwide have been investigating for an ideal non-invasive way of estimating PVR with varying success as we described in the chapter 2. The original PVR_{echo} formula was described by Abbas et al in 2003 and it has been modified and improved by multiple researchers(36). The ePLAR (echocardiographic pulmonary to left atrial ratio) was introduced as a non-invasive surrogate of TPG (transpulmonary gradient) and its ability to differentiate between prePH and postPH was demonstrated in its pilot study involving 133 patients with PH(19). There were also studies investigating combined clinical and non-invasive investigations to identify left heart diseases among patients suspicious for PAH(31).
4.2. Key findings

Chapter 3 describes the current research in detail. This is a large real-world, single centre retrospective study involving 887 pairs of echos and RHCs. The data were automatically extracted from 2 data-bases (echo and RHC) minimising the humans error of manual data collection. The main finding was that the ePLAR provided good discriminatory power between prePH and postPH when compared with the current gold standard, RHC. There was a statistically significant difference in median ePLAR (IQR) values between prePH and postPH patients (0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s (P=0.003). It also performed better than previously published PVR_{echo} formulae(17, 18) in predicting the increased left atrial pressure (PCWP). The binomial logistic regression showed that ePLAR performed better than ejection fraction, age and mitral E velocity in predicting patients with postPH. The diastolic pulmonary gradient (DPG) has emerged as preferred marker to differentiate isolated post-capillary PH and combined pre-and post-capillary PH (1, 24). Therefore, DPG was used in our study to differentiate between the two groups in our study. The study also confirmed that the isolated post-capillary PH is the dominant physiology among patients who presented for RHC. In general, these patients will not benefit from the vasodilator therapy and RHC may not be necessary unless the patients were being worked up for heart transplant.

4.3. Recommendations and Future Directions

I do not believe that ePLAR or any other non-invasive surrogates of PVR will replace the role of RHC completely. RHC will still be the gold standard to confirm the diagnosis and to exclude significant elevation of left heart pressure (PCWP>15mmHg) in patients with PAH. However, in majority of PH patients, ePLAR may be a useful adjunct tool to other echo parameters in selecting appropriate patients who require invasive tests to further clarify the diagnosis. Development and validation of such a marker will be very useful in PH management and will lead to better resource management and early diagnosis for many patients.
Being a retrospective study, the study had inherent weaknesses such as incomplete data set and limited clinical information. These weaknesses limited our ability to investigate the accuracy of ePLAR to estimate the invasive PVR. Non-simultaneous performance of the RHC and echo for studied patients is also another limitation as the pressure measurements by both tests are dependent upon multiple factors such as fluid volume status and heart rate which are very dynamic in nature. A prospective study involving simultaneous echo and RHC in PH patients with different underlying aetiologies would be an ideal future study. A similar large retrospective study which includes comprehensive clinical information will also be a very useful study. There is also a possibility of further improving the ePLAR formula by including a surrogate for the cardiac output such as $TVI_{RVOT}$ (time velocity integral of blood flow through the right ventricular outflow tract) and testing it in the current data set or in a future prospective study.