Stressing the Importance of Cardiac Assessment in Pheochromocytoma*

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The complexities of catecholamine physiology have intrigued physicians and the public alike for centuries. Epinephrine was isolated in 1897 by John Jacob Abel (1), and in parallel in 1901 by the Japanese scientist Jokichi Takamine (2), who called it adrenaline. Quickly the positive inotropic and chronotropic effects of catecholamines were appreciated and exploited, but by the second half of the 20th century the adverse effects of chronic exposure were increasingly recognized, including their roles in hypertension and heart failure (HF), eventually yielding β-adrenoceptor blockers as HF therapy.

More recently the notion that short-term effects of catecholamines are temporary and reversible has been challenged. Acute HF in the context of adrenergic “storms” has highlighted that high circulating catecholamine levels can either be toxic or cause acute negative inotropic effects. However, the long-term effects of these acute surges in endogenous or exogenous catecholamines and associated acute adrenergic crises are poorly understood.

One patient cohort characterized by high circulating catecholamine levels, including sudden surges with adrenergic crises, are patients with a pheochromocytoma (3). Pheochromocytoma is a syndrome of catecholamine excess consequent to neoplastic growth of chromaffin cells of the sympathetic nervous system, classically in the adrenal medulla.

The precise biochemistry depends on the cell lineage and tumors can release combinations of norepinephrine, epinephrine, or dopamine alongside numerous other hormones. The intermittent secretion of catecholamines by tumor cells makes single point-of-care testing of plasma or urine for catecholamines or their breakdown products unreliable and diagnosis challenging. Collection of urine over 24 h for urinary metanephrines increases sensitivity, but corroboration from other techniques (including suppression testing, functional nuclear imaging with 123I-metaiodobenzylguanidine, or cross-sectional anatomical imaging in combination with positron emission tomography) is required for accurate diagnosis.

Traditional thinking purports that surgery is curative for the majority of these patients and their cardiovascular physiology returns to normal after tumor resection, with long-term follow-up targeted to detecting recurrence, metastatic disease, or tumors in the contralateral adrenal gland. However, Ferreira et al. (4) challenged this standard view in this issue of the Journal. The authors recognized that catecholamine toxicity is known to cause histopathological evidence of acute and chronic myocardial inflammatory changes (5), and hypothesized that pheochromocytoma produces significant unrecognized cardiac toxicity, both acutely and (more importantly) at long-term follow-up after surgical “cure.” They applied advanced cardiac magnetic resonance (CMR) imaging to assess cardiac function in a cohort of patients before or following surgical resection of pheochromocytoma.

The authors recruited 125 patients in 3 study groups. The pheochromocytoma group (n = 60) comprised 29 patients in whom the tumor was recently diagnosed, scanned 2 (interquartile range [IQR]: 1 to 4) months after diagnosis (referred to as...
the “newly diagnosed” cases), and another 31 historic cases studied 51 (IQR: 27 to 83) months after surgical resection (the “previously diagnosed” cases). Eighteen patients (62%) in the newly diagnosed group and 5 patients (16%) in the previously diagnosed group underwent a second scan, respectively, at 12 ± 5 months and 25 ± 10 months after the initial examination. These cohorts are used to characterize acute and chronic cardiac phenotypes in pheochromocytoma, in comparison to healthy (n = 51) and hypertensive (n = 14) controls. The authors reported CMR cardiac phenotypes from cine images in standard planes for left ventricular ejection fraction (LVEF) and ventricular mass; tagged cine sequences for strain and strain rate; and myocardial tissue characterization using late gadolinium enhancement (LGE) and native (pre-contrast) T1 mapping.

In the newly diagnosed group, there was evidence of systolic (reduced global LVEF and impaired peak systolic circumferential strain) and diastolic (diastolic strain rate) impairment. These functional changes were accompanied by focal LGE in a nonischemic pattern in 59% of patients and elevated myocardial T1 compared with healthy and hypertensive controls, assessed both as mean T1 and proportion of myocardium with T1 meeting established criteria for myocarditis. Global LVEF improved by the second scan (median: 12 months), while the deformation parameters show no significant change, suggesting a persistent, subclinical abnormality of myocardial function. The observed LGE is persistent but nonprogressive. The total area of abnormal T1 reduced at late follow-up but remained elevated compared to healthy controls, whereas the reduction in mean T1, a subtler parameter, was not significant.

The previously diagnosed group had preserved global systolic function (LVEF 67 ± 5%) comparable to controls, but persistent, subtle abnormalities of systolic and diastolic function by deformation parameters. Nineteen percent have LGE, which may reflect persistent fibrosis from the previous catecholamine exposure, given the absence of other confounding cardiovascular diseases. This group exhibited a larger area of myocardium with abnormal T1 compared to normal and hypertensive controls, though again mean T1 showed no difference.

Considering these findings together, the authors concluded that pheochromocytoma causes an acute catecholaminergic myocarditis, with elevated T1 and patchy subendocardial LGE accompanied by global LV dysfunction. It partially resolves after tumor resection but leaves chronic LGE, indicating focal replacement fibrosis, and a T1 abnormality that might represent diffuse interstitial fibrosis, with subclinical abnormalities of LV function. Interestingly, LV hypertrophy was not seen in these patients, distinguishing these findings from those of hypertension alone.

This is the first systematic report of long-term cardiac effects of this rare tumor, and we congratulate the authors on their success in completing the study. Recruitment took 5 years across 3 centers to enroll 60 pheochromocytoma patients, demonstrating the rarity of the condition and difficulty studying it. Applying state-of-the-art CMR techniques provided unique insight into this illness’s long-term cardiac sequelae.

This paper raised several questions. First, we should consider what these CMR findings actually represent. There is a continuum of myocardial changes in response to high catecholamine exposure (from acute cardiomyocyte swelling, contraction band necrosis, and inflammatory infiltrate—through reactive interstitial fibrosis—to chronic replacement fibrotic change), and neither the native T1 mapping nor the LGE defines specifically any of these as distinct categories. In the acute and chronic phases, the signals from either technique could represent myocardial inflammation (leaky capillaries and increased myocardial water content) or fibrosis (expanded extracellular volume). Based on a prior histopathological study (5) and preclinical insights from acute catecholamine challenges, the LGE and T1 changes seen acutely predominantly represent active catecholaminergic myocarditis (perhaps with some fibrosis developing depending on chronicity); late post-tumor resection they represent focal (LGE) or diffuse (T1) fibrosis. Novel CMR techniques including post-contrast T1 mapping and extracellular volume mapping could be informative, but ultimately biopsy or post-mortem specimens are required to confirm the underlying histopathology and what these CMR signals represent.

Second, the specific biochemical nature of the catecholamine excess may be relevant but was not explored in this study. Pheochromocytomas can secrete an array of hormones, most commonly epinephrine, norepinephrine, and dopamine, usually with one being the dominant catecholamine. The authors did not report the patients’ biochemical results; it would be interesting to compare the cardiac effects of different catecholamines separately. Endogenous catecholamines affect the heart and circulatory system differently due to varying relative potencies for α- and β-adrenoceptors and also can activate distinct subcellular signalling pathways depending on their concentrations. This holds particular relevance at high concentrations and
sudden surges in circulating concentration boast a different impact than chronic moderate elevation. Preclinical pharmacological studies demonstrated that high concentrations of epinephrine, but not norepinephrine, can activate the β2-adrenoceptor, switching coupling from the Gs to Gi secondary messenger pathway (6,7). This stimulus trafficking to Gi results in a profound negative inotropic effect, particularly in the cardiac apex where density of β2 receptors is greatest, but importantly is cardioprotective, limiting apoptosis. Conversely, norepinephrine excess exerts no protective effect. Therefore, the acute and chronic cardiac effects of a pheochromocytoma may vary depending on the precise cocktail of catecholamine exposure and its pattern of release by the tumor. Further studies are needed to compare their relative effects on regional as well as global abnormalities in the myocardium and those with versus without persisting LGE and higher levels of T1 abnormalities.

Finally, and most importantly, the clinical significance of these findings remains to be determined. As surrogate biomarkers, abnormal CMR findings raise the question of the relevance of current and future functional pathophysiological abnormalities. It would be interesting to correlate these imaging findings with other established biochemical cardiac biomarkers (brain natriuretic peptide or cardiac troponin) and with functional assessment such as cardiopulmonary exercise testing to unmask limitations in cardiac performance.

But most important is the impact on morbidity and mortality. Abnormalities during the acute phase may affect acute complications and cardiovascular risks during surgery and post-operative recovery. Persisting abnormalities could lower the threshold for developing HF or arrhythmias in the context of future myocardial stressors (e.g., hypertension, myocardial infarction, cardiotoxic cancer therapy). Long-term clinical outcomes for this and future cohorts of pheochromocytoma patients are needed to clarify if heightened morbidity or mortality is associated with these structural and functional cardiac abnormalities seen on CMR, and to guide the optimal clinical management for patients post-resection.

Ferreira et al. provided a detailed account of the myocardial CMR phenotype in patients with pheochromocytoma before and after tumor resection, highlighting an unrecognized complication of this condition, preponderant in patients previously thought to be cured. Further studies are required to relate the observed CMR phenotypes to myocardial histopathology, subgroups determined by biochemical catecholamine signatures, and long-term cardiovascular outcomes of these patients to help guide the optimal acute and long-term clinical approach. Even in 2016, we continue to understand more about the impact of these fundamental stress hormones upon cardiovascular pathophysiology and, no doubt, there is still more to learn.

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**KEY WORDS** catecholaminergic myocarditis, pheochromocytoma