Evaluation of Cardiac Reserve Using Echocardiography for The Detection of Mild Cardiac Dysfunction in Mice – A Review

Sanjay Kumar Mire [1], Deepak Kumar Sahu [1]

Abstract

Assessing cardiac reserve in mice through echocardiography is essential for early detection of subtle cardiac issues and understanding potential treatments. Despite challenges such as precise measurements, strain imaging stress-based cardiac reserve assessment (SIS-CRA) is used in this study, providing insights into the heart's functional capacity by measuring myocardial deformation and contractility. This technique aids in identifying cardiac abnormalities early, allowing for timely interventions. Stress echocardiography is particularly valuable in heart failure and cardiotoxicity studies, where cardiac reserve plays a crucial role. Beyond diagnostics, the paper explores applications in cardiovascular medicine and drug discovery, highlighting the method's revolutionary potential. Simulation analysis is incorporated to showcase its capability to improve research techniques and contribute to the detection of heart failure in mouse models.

Keywords: Cardiac, Echocardiography, Mild, Cardiac Dysfunction, Mice, Stress

Significance | Echocardiography-based strain imaging offers early detection of cardiac abnormalities, treatment, and research strategy.

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1. Introduction

This review discusses the challenges associated with using echocardiography to detect moderate cardiac dysfunction in mice. Despite echocardiography's common use in preclinical studies to evaluate heart function, the small size of mouse hearts poses difficulties in obtaining precise measurements. False-negative results may occur due to limited spatial resolution in detecting mild dysfunction. Variability in mouse physiology and genetics, along with differences in stressor responses, contributes to incongruent findings and reduces research reliability (Gupta et al,2022) The text emphasizes the limitations of echocardiography, genetic variability, and translational significance when assessing mild cardiac dysfunction in mice and highlights the need for cautious interpretation in therapeutic applications. Additionally, the paper introduces a strain imaging stress-based cardiac reserve assessment (SIS-CRA) method to improve research outcomes, monitor myocardial deformation, and enhance diagnostic and therapeutic potential in heart failure studies.

Using echocardiography to assess cardiac reserve in mice for diagnosing moderate cardiac failure is a valuable research strategy (Ljubojević-Holzer, S., 2022). Echocardiography is a common non-invasive imaging technique in preclinical research for evaluating heart health (Hammoudi, N., 2022). However, challenges arise in detecting moderate cardiac dysfunction in mice. Their small size and hearts make obtaining precise measurements difficult (Chambers, K. T., 2021). Echocardiography's spatial resolution may not be high enough to detect subtle changes in heart function in cases of mild dysfunction (Marshall, A. G., 2023), leading to potential false-negative results (Tu, Y., 2022).

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Assessing cardiac reserve faces challenges due to variations in animal physiology and genetics (Roh, J., 2022). Stressors used for evaluation may elicit different responses in mice with diverse genetic backgrounds or comorbidities, resulting in inconsistent findings (Gorelik, M., 2019). These variations reduce research reliability, making it challenging to define moderate cardiac failure in mice (Richards, D. A., 2019). Additionally, differences between mouse and human cardiac anatomy and physiology complicate the interpretation of echocardiographic data in mice (Villalba-Orero, M., 2022). Caution is necessary when applying findings from mouse studies to therapeutic applications, as discovered cardiac dysfunction may not be relevant or applicable to human circumstances (Ritchie, R. H., 2020).

While echocardiography is valuable in preclinical research, it is essential to consider its limitations, genetic variability, and translational significance when detecting mild cardiac dysfunction in mice (Obokata, M., 2020).

Echocardiography is commonly used to identify minor cardiac dysfunction in mice, employing various methods with inherent challenges (Wang, S., 2019). This non-invasive imaging technique is widely used in preclinical studies to assess heart function in small animals like mice (Lane-Cordova, A. D., 2019). Structural alterations indicative of cardiac dysfunction are often examined through measurements of heart size and wall thickness. Pumping efficiency can be quantified using methods such as ejection fraction and fractional shortening (Del Buono, M. G., 2019). Pulsed-wave Doppler and tissue Doppler imaging assess blood flow velocities and myocardial motion, providing insights into diastolic function and localized wall motion issues (Salhi, H. E., 2023).

Despite its utility, echocardiography has limitations in diagnosing moderate cardiac failure in mice (Li, Z., 2017). Obtaining precise and reproducible readings is challenging due to the small size and high heart rate of mouse hearts, requiring specialized equipment and expertise (Davis, M. B., 2020). Biological heterogeneity within genetically uniform groups adds complexity, necessitating large sample sizes for statistical significance. Substantial differences in cardiac physiology between mice and humans further complicate the transferability of findings. Sensitivity and specificity limitations of echocardiographic measures may result in false negatives or positives (Collins, K. A., 2003).

Researchers should be mindful of technological and biological obstacles associated with echocardiography when assessing cardiac reserve and diagnosing moderate cardiac dysfunction in mice. Careful consideration of experimental design, data interpretation, and the limitations of murine models is essential for results to be applicable to human heart disease.

The review aims to evaluate mouse cardiac reserve using strain imaging stress-based cardiac reserve assessment (SIS-CRA) through echocardiography. This method is employed for early detection of minor cardiac issues in experimental mice, facilitating timely understanding of heart dysfunction and potential treatments. Early identification can prevent the progression of heart disease in mouse models.

SIS-CRA is utilized to enhance study outcomes by monitoring myocardial deformation and contractility, providing insights into cardiac function. This approach improves researchers' understanding of mouse heart function and dysfunction, contributing to advancements in research methods and therapies.

The review emphasizes the broader applications of assessing cardiac reserve in mice, extending beyond cardiovascular care to include drug development. The research underscores the diagnostic and therapeutic potential of cardiac reserve assessment in heart failure and cardiotoxicity studies. Additionally, this strategy enhances research methods and aids in diagnosing heart failure in murine models, incorporating simulation analysis.

1. Literature Review

Recent advancements in novel methods and animal models have significantly advanced our understanding of heart function and disease, propelling cardiovascular research to new levels. Various research teams have explored diverse topics related to cardiac health, ranging from the impact of dietary treatments on coronary microvascular endothelial function to the complexities of heart failure in different contexts (Saraste, A., 2006).

Kwiatkowski, G. et al. investigated changes in coronary microvascular endothelial function and global cardiac performance markers in mice subjected to a high-fat diet (HFD) (Kwiatkowski, G., 2021). After four weeks of HFD, multiparametric cardiac MRI revealed a decline in systolic heart function, including reduced ejection rate, increased end-systolic volume, and decreased myocardial strain in diastole, ultimately leading to impaired ejection fraction.

Nguyen, I. T., et al. delved into the risk factors for heart failure with preserved ejection fraction (HFpEF), focusing on age, hypertension, type 2 diabetes, obesity, and gender differences (Nguyen, I. T., 2020). Their study explored cardiac phenotypes in lean and obese female ZSF1 rats, emphasizing the relevance of the female obese ZSF1 rat as an animal model for HFpEF with comorbidities.

Hollenberg, S. M. et al. highlighted sepsis-induced cardiomyopathy (PS-IC) as a leading cause of death in intensive care units, emphasizing the challenges in connecting myocardial abnormalities to therapeutic strategies and clinical outcomes (Hollenberg, S. M., 2021).

G. K. Thomas and colleagues developed high-sensitivity C-reactive protein (CRP) and used Doppler echocardiography to assess its link to changes in cardiac function and reserve post-exercise,

especially in individuals undergoing radiation for breast or lung cancer (Canada, J. M., 2020).

De Lucia, C. et al. introduced echocardiographic strain analysis (ESA) as a noninvasive and highly sensitive technology to assess left ventricular function in both animal models and humans. Strain imaging stress-based cardiac reserve assessment (SIS-CRA), proposed by Daniels, A. (2010), emerged as a promising technique with higher sensitivity and potential applications in various clinical settings. These innovations hold significant potential for enhancing our ability to detect, monitor, and treat cardiac issues as our understanding of the heart continues to advance.

2. An algorthm model to determine the cardiovascular health

Measuring cardiac reserves in mice can provide valuable insights into mild heart issues and various aspects of cardiovascular health. Simple imaging methods, like echocardiograms, show promise in this regard. The goal is to assess how well echocardiograms can serve as a tool to evaluate cardiac reserve in laboratory mice (Aref et al,2019). Researchers aim to establish a reliable and specific approach for early detection of minor cardiac abnormalities in mice. This approach could have implications for human cardiovascular studies and therapeutic treatments. The evaluation involves essential cardiac measures and reactions(Ghosh et al,2021).

The key objectives of disease classification systems are to provide nosographic systems based on unique features and suggest parameters for diagnostic workup. However, a single classification approach often doesn't effectively address both needs (Krittanawong et al ,2020). The European Society of Cardiology's policy statement on grouping cardiomyopathies has gained widespread endorsement in healthcare settings. It combines transthoracic echocardiography, assessment of cardiac phenotype, family history, and possible hereditary basis (Alaa et al,2019).

While this grouping method effectively categorizes various cardiomyopathies, it may not be the most suitable for distinguishing restrictive cardiomyopathy (RCM). Conventional ultrasound can differentiate between hypertrophic, dilated, and arrhythmogenic hearts due to shared morphology and functional characteristics (Nashif et al,2018). However, RCM's primary characteristic is hemodynamic, making it challenging to detect on ultrasound. RCM is characterized by significant wall hypertrophy or endomyocardial growth, leading to an immediate increase in pressure within the heart during the diastolic cycle, with minimal changes in filling volumes. According to ESC criteria, features of RCM include 'normal or decreased systolic and diastolic volumes' and 'normal ventricular wall thickness.' Despite its conceptual accuracy, a strict application of this classification may overlook health conditions that share similar physiology, as seen in various RCM types included in the same source (Maurovich et al,2021).

The provided equations and figures introduce various mathematical and experimental aspects related to cardiac research. The inclusion of classification systems and imaging techniques like transthoracic echocardiography and cardiac magnetic resonance provides a comprehensive overview of methodologies (Mezzatesta et al , 2019). This review shows the challenges associated with classification systems, emphasizing the need for precision and flexibility in grouping cardiomyopathies.

$$C(x,y) = \iint p(\mu) + g(x - \theta,\ ng - \emptyset)\, d\,\partial d\emptyset \qquad (1)$$

In the aforementioned equation (1), $p(\mu)$ is the input image of the heart that is convolved by the function named $g(x - \theta,\ ng - \emptyset)$ where $g(p - \theta)$ denotes the genetic and $ng - \emptyset$ denotes the non genetic component. $C(p,q)$ is the Cardiology component.

$$C_{\tau,\sigma}(x,y) = e^{-\left(\frac{x^2+y^2}{2}\right)} - \log[\cos\left(2\pi\frac{x}{\tau} + \sigma y\right)] \qquad (2)$$

The equation (2) denotes the cardiology component at the points τ, σ respectively. x, y be the vertices of the coordinates taken for the consideration.

The exploration of signal processing and efficiency metrics, such as amplitude, sensitivity, specificity, precision, and efficiency, offers a quantitative understanding of prediction accuracy and test performance. The use of mathematical models and experimental outcomes involving notopterol and tamoxifen highlights potential therapeutic applications and unveils underlying mechanisms in cardiac biology (Jiang et al,2020).

This review further discusses the complexities of mimicking heart failure with preserved ejection fraction (HFpEF) in animal models. Acknowledging the difficulties in reproducing clinical HFpEF, the proposed phenotyping approach aims to systematically analyze relevant phenotypes and adapt characterization based on specific HFpEF phenogroups (Khawaja et al,2012).. The importance of functional assessments in both ventricular and extra-cardiac tissues is emphasized, providing a foundation for developing credible animal models.

Electrocardiograms (ECGs) provide crucial clinical information and insights into the causes of cardiomyopathy. In infiltrative cardiomyopathies, the QRS complex voltages decrease due to the elongation between heartbeats, while they remain normal or increase in storage cardiomyopathies. Distinguishing hypertrophic cardiomyopathy (HCM) or other storage-related diseases from cardiac amyloidosis (CA) may be facilitated by assessing the gap between ventricular wall thickness and QRS region voltages in surface ECG (Zhang et al,2018).

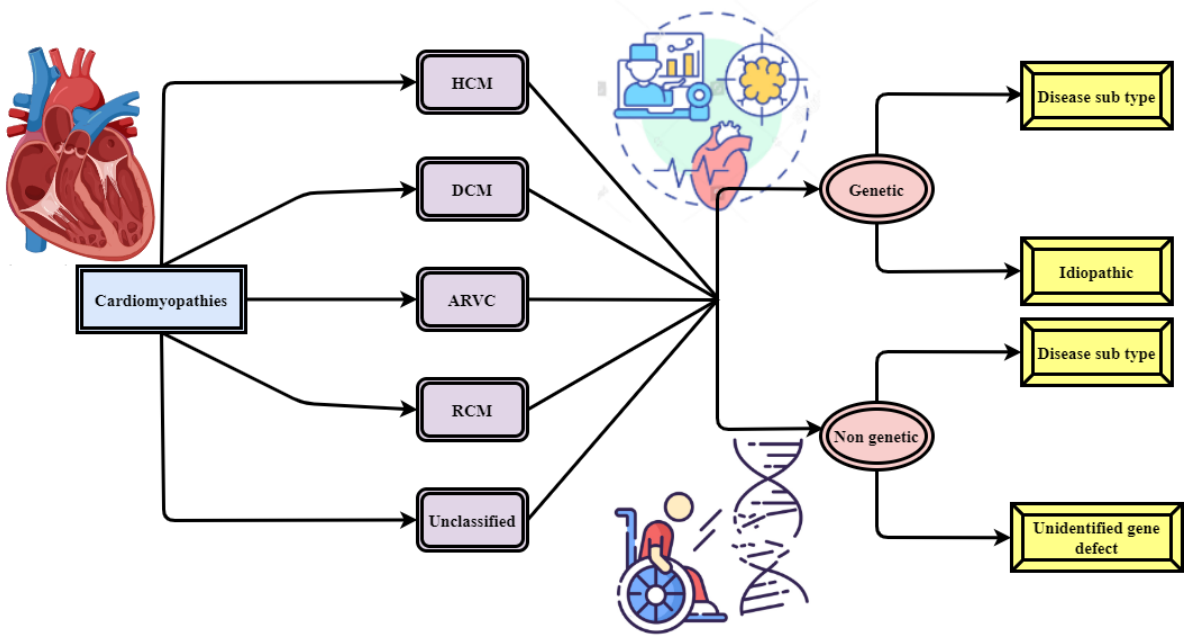

Figure 1. European Society of Cardiology, cardiomyopathies Policy statement.

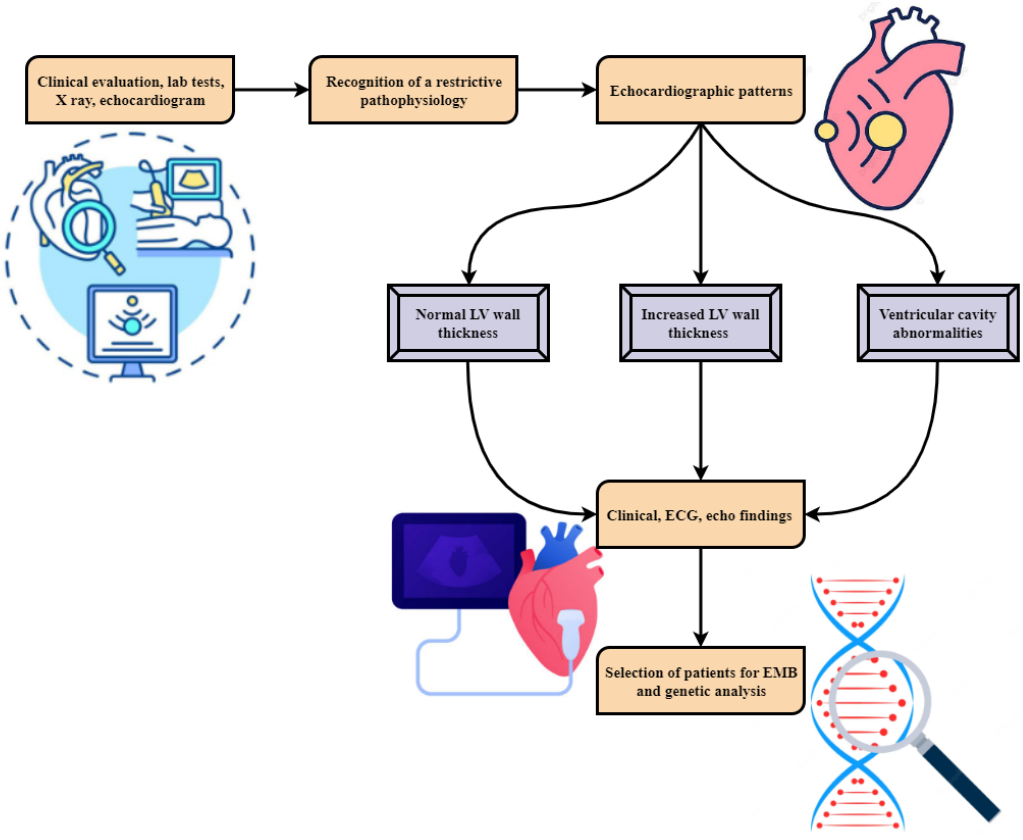

Figure 2. Medical evaluation and promote sensible EMB and genetic testing.

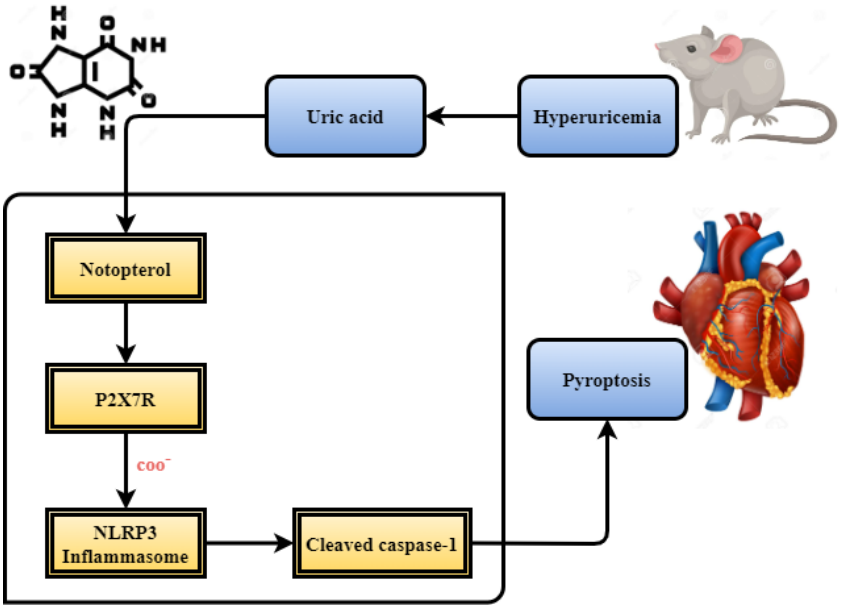

Figure 3. Illustration of Notopterol reduces pyroptosis and inflammation in hyperuricemic mice heart tissue.

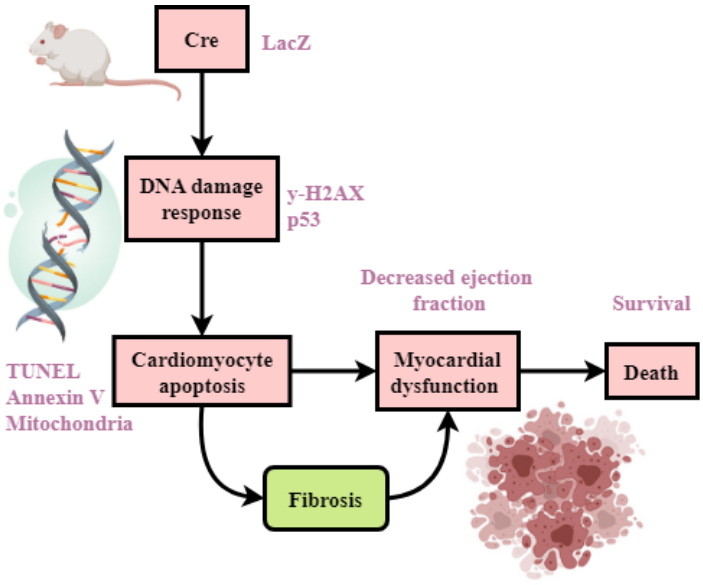

Figure 4. Injection of tamoxifen causes cardiac failure and death in MHC-MerCreMer mice through a loxP-independent damaging of DNA response.

Box 1. Predictive model/Algorithm of cardiac reserve assessment

Begin
Step1: Build the input image pyramid as I1(p, q) and I2(p, q).
Step2: Construct a fused pyramid of k levels from th-level input picture pyramids using a myocardial deformation-based fusion technique.
Step3: The second phase is repeated until all K levels of the fused image pyramid have been built.
Step4: Build the fused pyramid back into its original form, if (p,q).
Step 5: Heart failure issue is detected.
End

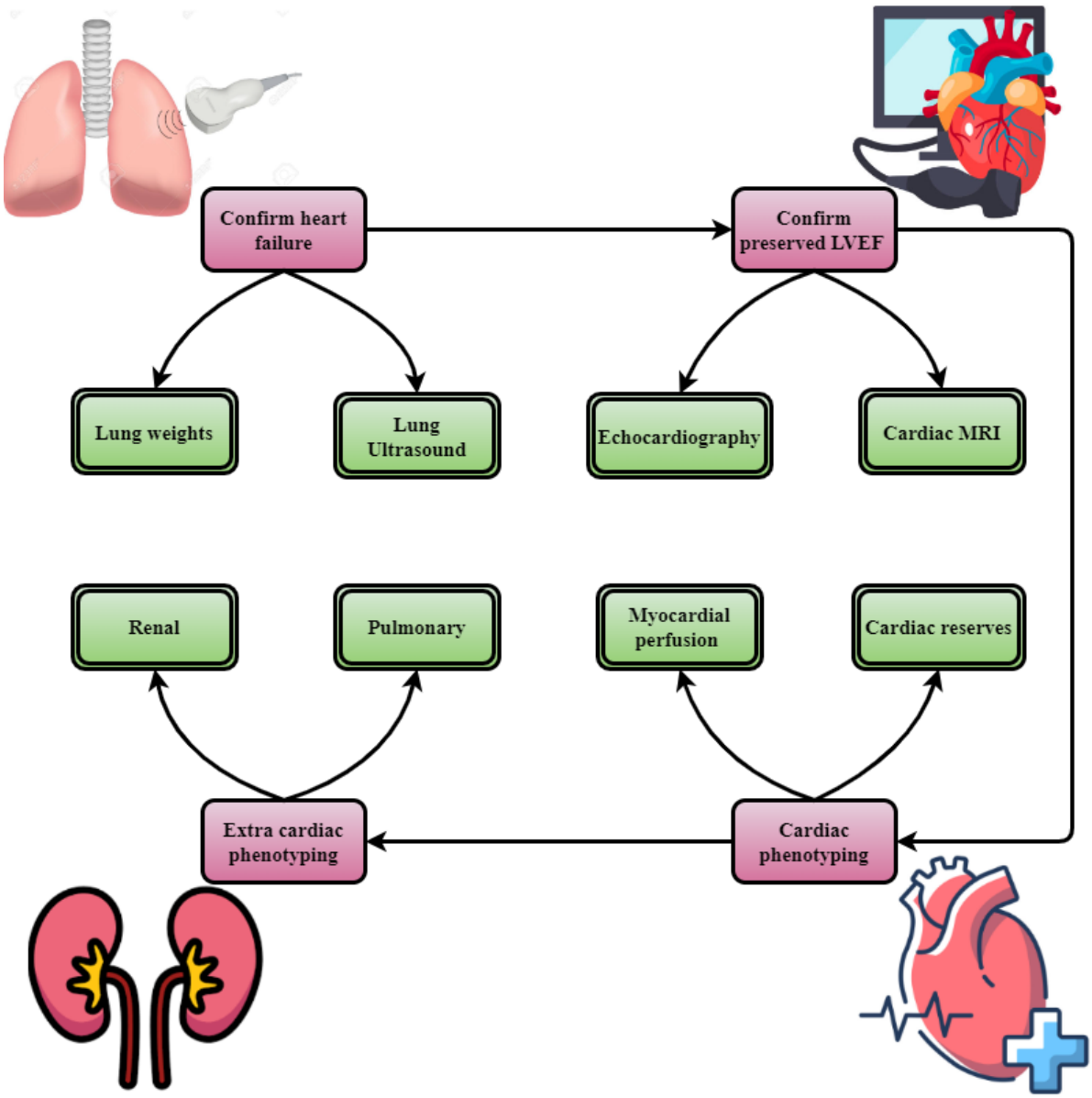

Figure 5. Building HFpEF models using a systematic, phenotype-based methodology.

Individuals suspected of having restrictive cardiomyopathy (RCM) should ideally undergo cardiac magnetic resonance (CMR) as part or measuring biventricular volumes, mass, and ejection fraction (Woodward et al,2017). CMR can detect myocardial edema through weighted imaging, intraventricular blood clots with early gadolinium enhancement, and myocardial interstitial changes in late gadolinium enhancement (LGE, often caused by fibrosis or amyloid deposits, sometimes alongside myocyte necrosis or extracellular swelling) (Badimon et al,2018).

Tissue changes in the myocardium can be assessed using native (pre-contrast) T1- and T2-mapping patterns, while gadolinium injection enables measurement of heart perfusion mapping and extracellular volume (ECV) mapping (Yang et al,2020). Transthoracic echocardiography, tailored to a suspected diagnosis, is recommended as the first-line screening (Figure 2). When considering endomyocardial biopsy (EMB) and genetic testing, early indicators of specific medical conditions should be explored to effectively utilize these diagnostic tools. Consider a two-class problem, where the plus sign (+1) represents the "positive" class and the minus sign (-1) represents the "negative" class. Take T(+) as the real deal, F(+) as the fake, T(-)as the real deal, and F(-)as the fake (Moons et al,2015).

$$\mathrm{Amp} = \frac{T(+) + T(-)}{T(+) + T(-) + F(+) + F(-)} \qquad (3)$$

The above equation (3) shows the amplitude which is denoted by Amp of the signal taken for consideration. It represents the rate at which actual data match those predicted.

$$\mathrm{Sen} = \frac{T(+)}{T(+) + F(-)} \qquad (4)$$

The sensitivity of a test measures how often positive results are returned and is represented by Sen which is shown in above equation (4).

$$\mathrm{Sp} = \frac{T(-)}{T(-) + F(+)} \qquad (5)$$

Equation (5) indicates the number of false-negative findings is the same as the specificity (Sp).

In mice with increased notopterol levels, there was a significant reduction in heart pyroptosis, improved exercise capacity, and reduced cardiac dysfunction. Urea treatment in cells induced this process, generating inflammation-inducing cytokines, while other cells controlled both reactions downstream (Vickers et al,2006). Notopterol effectively inhibited this process by blocking the signaling pathway (see Figure 3). Notopterol may be a potential treatment for alleviating pyroptosis and enhancing coronary circulation in animals with hyperuricemia (Rufibach et al,2009). The research findings are summarized, and a diagram illustrating the steps through which notopterol reduces pyroptosis and inflammation in the cardiac organs of hyperuricemic mice is provided. Notopterol decreased pyroptosis and inflammation in the ventricular tissue of hyperuricemic mice by reducing expression and inhibiting inflammasome activation. Symbols in the figure represent regulation, while activation or stimulation is depicted in Figure 3 (Mortazavi et al,2016).

Figure 4 shows that tamoxifen can induce acute toxicity in cardiomyocytes by stimulating nuclear Cre recombinase activity, independent of lox sites. High levels of Cre production in MHC-MerCreMer transgenic mice are associated with fatal heart failure (Arslan et al,2016). Cardiac fibrosis is linked to Cre activation with three administrations of >30 g tamoxifen/g body weight. Apoptosis of cardiomyocytes is linked to Cre induction at three dosages of tamoxifen greater than 30 ng/g body weight. Inducing Cre with three administrations of >30 g tamoxifen/g body weight triggers the DNA damage response (Christodoulou et al,2019). The study suggests that the response to DNA damage and apoptosis may lead to inflammatory processes causing cardiac fibrosis, representing initial responses of cells to recombination enzyme activity in cardiomyocytes. The proposed pathogenic approach to loxP-independent Cre impacts in cardiomyocytes is based on this understanding.

The equations (6) and (7) define precision (Prec) and efficiency (Eff) in predicting positive observations, respectively (Goldstein et al,2017). The study further discusses the toxicity of non-mammalian transgenes, such as fluorescent green proteins and Cre, in cardiomyocytes. Elevated Cre activity is found to be highly detrimental to cardiomyocytes, leading to impaired cardiac function. This study expands knowledge on the underlying mechanisms at the subcellular and tissue levels.

Cre has been shown to be harmful to proliferating, undifferentiated cells, and this study adds insulin-producing cells to the list of differentiated cells vulnerable to Cre toxicity (Goff et al,2014.). The findings suggest that Cre induces a DNA damage response even without loxP sites, potentially causing breaks in DNA at non-loxP sites. Previous research has established Cre toxicity as mutations in chromosomes during metaphase, particularly in spermatids (Jung et al,2013).

The vulnerability of additional myocardial cells, such as progenitor and stem cells, and ventricular fibroblasts in the embryonic and adult heart, to Cre toxicity is a relevant concern in cardiovascular science.

Creating animal models that accurately mimic heart failure with preserved ejection fraction (HFpEF) is challenging due to the condition's heterogeneity and chronic nature. Shortness of breath and exhaustion, the primary symptoms of HF, make simulation difficult, and various cardiac and extra-cardiac variables influence

HFpEF pathophysiology (Yang et al,2016). The proposed phenotyping approach aims to address this gap by creating reproducible and clinically relevant HFpEF animal models, acknowledging the complexity of the condition. Figure 5 illustrates the process of creating HFpEF models, emphasizing the need for systematic analysis and validation of clinically relevant phenotypes (Cook et al,2016). Please see Box 1. HFpEF is characterized by functional deficits in ventricular and extra-cardiac tissues. Diagnosis involves confirming maintained left ventricular ejection fraction and evaluating additional ventricular and extra-cardiac characteristics based on the phenotype being mimicked (Zhou et al,2016). The study proposes a broad characterization approach to capture crucial traits for specific HFpEF phenogroups, acknowledging the need for further extension to larger animals. Various diagnostic factors, including B-type natriuretic peptide (BNP), left ventricle (LV), magnetic resonance imaging (MRI), NT-proBNP, and pulmonary hypertension (PH), contribute to comprehensive phenotyping (Collaborators et al,2013).

In summary, this review provides a comprehensive overview of cardiac research methodologies, ranging from imaging techniques and mathematical models to experimental outcomes and the challenges associated with mimicking clinical conditions in animal models. The structural responses of the cardiovascular system will be evaluated using echocardiographic evaluates taken at base and under pressure. Researchers hope to find mild heart problems by evaluating statistics like ejection percentage, fraction shortening, and stress. This strategy has the ability to deepen the understanding of mice cardiology and has echoes in the prompt detection and treatment of cardiac dysfunction in mice as well as in humans.

3. Discussion

The comprehensive evaluation of heart function encompasses various methods, such as Ejection Fraction (EF) and Strain Imaging Stress-based Cardiac Reserve Assessment (SIS-CRA), each offering distinct insights. When these methods are synergistically employed, they collectively provide a more nuanced understanding of cardiac health, even uncovering subtle abnormalities that might otherwise go unnoticed, thereby enhancing overall patient care (Sharma et al,2020).

Strain Imaging Stress-based Cardiac Reserve Assessment (SIS-CRA), an advanced technique for assessing heart function and identifying moderate cardiac impairment, heavily relies on the integration of strain imaging analysis (Arunpradeep et al,2020). Strain imaging measures myocardial deformation, offering valuable insights into the mechanical characteristics and contractility of the heart. SIS-CRA combines strain imaging with EF monitoring, a standard measure of heart function, to quantify the heart's efficiency in pumping blood during stress conditions induced by exercise or pharmacological stress testing. Monitoring EF before and after stress enables the detection of alterations in heart function that may not be evident during rest, particularly revealing moderate dysfunction indicative of weakened cardiac reserve. The inclusion of EF in SIS-CRA significantly enhances its sensitivity to detect cardiac issues, contributing to more accurate diagnoses and individualized therapy approaches for cardiac diseases (Ravindhar et al,2019).

Furthermore, SIS-CRA incorporates analysis of cardiac output (CO), a crucial measure of heart efficiency, to provide a more comprehensive assessment. CO analysis, conducted during exercise or stress testing, allows researchers to observe changes in the heart's adaptive ability and reserve function (Patel et al,2023).Decreased CO after stress may signify moderate heart dysfunction and reduced cardiac reserve. This additional analysis enhances the sensitivity of SIS-CRA to detect cardiac anomalies, especially those that manifest during stress, leading to earlier diagnosis and personalized treatment plans (Kumar et al,2020).

Pressure-volume (PV) loops analysis is another integral component of SIS-CRA, offering a dynamic perspective on heart function. PV loops provide detailed insights into contractility and pump function throughout the cardiac cycle, facilitating the early detection of cardiac abnormalities during stress. By comparing data before and after stress, researchers can identify early signs of heart deterioration, enabling timely intervention and personalized treatment (Saravanan et al,2020).

Survival curve analysis, a unique aspect of SIS-CRA, adds a longitudinal dimension to the assessment, dynamically representing the influence of cardiac dysfunction on subjects' lifetimes. This analysis offers valuable insights into the physiological effects of mild cardiac abnormalities, quantifying the risk of mild dysfunction and its impact on patient outcomes. Integrating survival curve analysis into SIS-CRA enhances the clinical relevance of cardiac evaluations, bridging the gap between laboratory findings and real-world circumstances (Tarawneh et al,2019).

In summary, Strain Imaging Stress-based Cardiac Reserve Assessment (SIS-CRA) emerges as a holistic strategy for evaluating cardiac health. By combining various methods, including strain imaging, EF analysis, CO analysis, PV loops analysis, and survival curve analysis, SIS-CRA not only improves sensitivity and clinical relevance but also has the potential to optimize patient treatment. These findings underscore the importance of adopting a comprehensive approach to cardiac function evaluation for better patient care and outcomes.

4. Conclusion

The Strain Imaging Stress-based Cardiac Reserve Assessment (SIS-CRA) has become a crucial tool in experimental cardiology and

cardiovascular research, particularly in the assessment of cardiac reserve through echocardiography. This review emphasizes the significance of early detection of even minor cardiac issues in mice, paving the way for future treatment approaches. Despite challenges like obtaining precise measurements and interpreting complex data, along with establishing reliable baseline values, the benefits of SIS-CRA are substantial. By enabling therapeutic interventions at the earliest signs of cardiac dysfunction, this technique not only enhances research outcomes but also revolutionizes our understanding of cardiac function.

The value of SIS-CRA extends beyond the laboratory, finding notable applications in cardiology and drug discovery. Stress echocardiography proves effective in measuring cardiac reserve, especially in the realms of heart failure and cardiotoxicity research. The incorporation of simulation analysis provides new insights into identifying heart failure in murine models, indicating potential improvements in overall research methodologies. Consequently, the extensive research presented here contributes to both scientific progress and clinical practice, enhancing our understanding of cardiac function and suggesting a potential method for more effective diagnosis and prevention of cardiovascular problems.

Author Contributions

S.K.M. and D.K.S. conceptualized, wrote, and reviewed the article.

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Competing financial interests

The authors have no conflict of interest.

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