High-Frequency Echocardiography
— Transformative Clinical and Research Applications in Humans, Mice, and Zebrafish —

Louis W. Wang, MD; Scott H. Kesteven, BSc; Inken G. Huttner, MD; Michael P. Feneley, MD; Diane Fatkin, MD

Echocardiography is an invaluable tool for characterizing cardiac structure and function in vivo. Technological advances in high-frequency ultrasound over the past 3 decades have increased spatial and temporal resolution, and facilitated many important clinical and basic science discoveries. Successful reverse translation of established echocardiographic techniques, including M-mode, B-mode, color Doppler, pulsed-wave Doppler, tissue Doppler and, most recently, myocardial deformation imaging, from clinical cardiology into the basic science laboratory has enabled researchers to achieve a deeper understanding of myocardial phenotypes in health and disease. With high-frequency echocardiography, detailed evaluation of ventricular systolic function in a range of small animal models is now possible. Furthermore, improvements in frame rate and the advent of diastolic strain rate imaging, when coupled with the use of select pulsed-wave Doppler parameters, such as isovolumic relaxation time and E wave deceleration, have enabled nuanced interpretation of ventricular diastolic function. Comparing pulsed-wave Doppler indices of atrioventricular inflow during early and late diastole with parameters that describe the simultaneous myocardial deformation (e.g., tissue Doppler $e$ and $a$, global longitudinal strain rate and global longitudinal velocity) may yield additional insights related to myocardial compliance. This review will provide a historical perspective of the development of high-frequency echocardiography and consider how ongoing innovation will help future-proof this important imaging modality for 21st century translational research.

Key Words: Cardiac function; Echocardiography; Humans; Mice; Zebrafish

Echocardiography is an ultrasound-based imaging method that enables serial, in vivo structural and functional characterization of the heart. Studies are well-tolerated and can be performed in a relatively short amount of time, and the technology is generally readily available and affordable. Because of this, transthoracic echocardiography (TTE) has been widely used as a first-line investigation for the diagnosis of numerous cardiac disorders, including cardiomyopathies, valvular abnormalities and congenital heart defects.

Over the years, attempts to improve image resolution have been constrained by an unavoidable trade-off between higher transducer operating frequency and the resultant reduction in the depth of imaging field caused by frequency-dependent attenuation. This, together with the advent and increasing popularity of other phenotyping tools that have superior spatial resolution, such as cardiovascular magnetic resonance imaging (CMR) and cardiac computed tomography, have challenged the primacy of ultrasound as the cardiac imaging investigation of choice for clinical and research applications. Offsetting this perceived obsolescence are recent advances in high-frequency ultrasound, which has the key advantage of having the highest temporal resolution among all the existing in vivo imaging methods. This review will discuss the evolution of high-frequency echocardiography over the past 3 decades, and the successive technical advances that have led to major breakthroughs for examining cardiac structure and function in humans, mice, and zebrafish. This enabling technology has uniquely facilitated seminal studies that have not only provided deeper insights into normal cardiac physiology, but have also expanded the suite of animal models that can be used for mechanistic studies of human disease.

Fundamental Considerations of Ultrasound Wavelength and Frame Rate

Echocardiography utilizes the reflection of emitted high-frequency sound waves (i.e., ultrasound) to yield information relating to cardiac structure and function. Image resolution is directly influenced by the wavelength ($\lambda$) of the ultrasound beam, which inversely correlates with the depth of field and image quality. As with light-based
Applications of High-Frequency Echocardiography

M-mode imaging gives a time-and-motion display of an ultrasound wave along a single line, and has been used for real-time assessment of wall thickness, intracavity chamber diameter and heart rate. The unidimensional nature of M-mode imaging results in high frame rates and provides the highest temporal resolution of all ultrasound modalities.

Frequency-dependent attenuation remains the major disadvantage of high-frequency ultrasound. This limits depth of field and the ability to visualize deeper structures with sufficient clarity. This is represented by the formula:

\[ \text{Attenuation} = \alpha \times \text{depth} \times f \]

where \( \alpha \) represents the attenuation coefficient of the medium transmitting the ultrasound. High-frequency echocardiographic transducers, especially those with operating frequencies between 30 and 70 MHz, typically have a depth of field of \( \geq 10 \text{cm} \). Above 50 MHz, the depth of field is \( \leq 2 \text{cm} \), which precludes echocardiography in adult rodents, although it is still possible in zebrafish and neonatal mice, which have smaller body sizes.

**Figure 1.** Relationship between transducer frequency, lateral resolution, and depth of field. The operating characteristics (and year of introduction) of commonly used ultrasound (US) systems for small animal echocardiography are shown. When a curve of best fit (red dashed line) is plotted, there is an inverse relationship between frequency and lateral resolution. Although higher transducer frequencies result in improved lateral resolution, this is offset by a reduction in the effective depth of the imaging field because of frequency-dependent attenuation. As transducer frequencies increase above 70 MHz, there is diminishing improvement in lateral resolution, which appears to plateau around 30 µm with existing technologies. Clinical US systems used in humans operate at frequencies between 2 and 15 MHz because they require depths of field \( \geq 10 \text{cm} \). Above 50 MHz, the depth of field is \( \leq 2 \text{cm} \), which precludes echocardiography in adult rodents, although it is still possible in zebrafish and neonatal mice, which have smaller body sizes.

imaging modalities, ultrasound-based imaging is subject to Abbe’s law of diffraction-limited resolution, whereby 2 objects are distinguishable from each other if they are more than half a wavelength apart. The wavelength of the ultrasound beam is governed by the fundamental wave equation:

\[
\text{Velocity} (V) = \text{frequency} (f) \times \text{wavelength} (\lambda)
\]

with the velocity of ultrasound being relatively constant in tissues (\( \sim 1.540 \text{m/s} \)). Advances aimed at improving image resolution have sought to produce the smallest feasible ultrasound wavelength. The inverse relationship between frequency and wavelength means that the higher the transducer operating frequency, the smaller the wavelength of the ultrasound wave and the better the spatial resolution (Figure 1). Spatial resolution \( R \), defined as the minimal distance at which 2 ultrasound reflectors can be distinguishable from each other, is determined by the ultrasound wavelength and therefore, by the frequency of the transducer producing the ultrasound wave, according to the following 2 equations:

\[
(2) \quad R_{\text{axial}} = \frac{1}{2} \times \frac{V (\text{sound})}{f (\text{transducer})}
\]

\[
(3) \quad R_{\text{lateral}} = \lambda \times \frac{\text{focal distance}}{\text{diameter of transducer}}
\]

Temporal resolution, which is determined by frame rate (i.e., the number of still images visualized per second), is another important consideration in real-time live imaging. Frame rate is influenced by many factors, including (1) imaging depth, (2) scanning angle, (3) number of foci, (4) number of scan lines, and (5) the pulse repetition frequency. M-mode imaging gives a time-and-motion display of an ultrasound wave along a single line, and has been used for real-time assessment of wall thickness, intracavity chamber diameter and heart rate. The unidimensional nature of M-mode imaging results in high frame rates and provides the highest temporal resolution of all ultrasound modalities.

Frequency-dependent attenuation remains the major disadvantage of high-frequency ultrasound. This limits depth of field and the ability to visualize deeper structures with sufficient clarity. This is represented by the formula:
Biplane 5-MHz Transducer and Transesophageal Echocardiography (TEE): Advances for Imaging the Human Heart

Clinical TTE is usually performed using transducers with operating frequencies ranging between 2 and 5 MHz. The development of biplane 5-MHz transducers and the implementation of techniques for TEE were major advances that provided improved resolution of the deep, posterior structures of the heart by reducing the distance to the target of interest and the air-tissue interface. TEE has been used to gain detailed information about cardiac chamber size and function, valve morphology and function, and to detect cardiac developmental defects, tumors, and pericardial and aortic pathologies. It is frequently utilized intraoperatively to guide reparative procedures. One of the most common indications for TEE is in assessment of thromboembolic risk in patients with atrial fibrillation (AF). Expert consensus guidelines recommend that TEE is performed prior to electrical or pharmacological cardioversion of AF to detect thrombus in the main body or appendage of the left atrium.8,9 Seminal studies using TEE that were performed by our group and others in the 1990s also revealed “smoke-like” echoes (termed “spontaneous echocardiographic contrast”) in the left atrium of patients with AF. The presence of spontaneous echo contrast was found to strongly correlate with left atrial thrombus and risk of embolic stroke.9 The inverse association between left atrial thrombus and the magnitude of left atrial appendage blood flow velocity measured on pulsed-wave Doppler helped to establish that the increased thromboembolic risk in patients with AF was likely the result of poor atrial mechanical function and the resulting stasis of blood.10 A semiquantitative scoring system for grading left atrial appendage blood flow velocity is often used in clinical reports and provides a guide for anticoagulant use. The resolution of modern echocardiography systems is ~300 µm, but red cell aggregates as small as 50–100 µm (when measured on blood film) can occasionally be discerned on 2D B-mode TTE.11 These large intracavity aggregates (“snowflakes”) may be indicative of underlying hyperviscosity disorders and are often more noticeable on M-mode because of its higher temporal resolution.

Animal Studies

Application of High-Frequency Echocardiography for Assessment of Heart Function in Rodents

Animal studies have formed a cornerstone of cardiovascular research studies for many decades. Large-animal physiology studies involving dogs, pigs and sheep are able to use ultrasound transducers with equivalent frequencies to those used in human echocardiography because of the similar heart rates and anatomical sizes of their hearts. In contrast, imaging studies in small animals, particularly mice and rats, require substantially higher transducer frequencies. The development of high-frequency echocardiography not only provided a non-invasive method for measuring cardiac chamber size and structure in rodent models, which previously could only be measured during necropsy, but also uniquely enabled in vivo assessment of cardiac function.12,13 This technological advance coincided with a burgeoning interest in human genetics and a need for generation of models in small animals to study the roles of genes and selected genetic variants.

Early forays into murine echocardiography used techniques adapted from pediatric clinical use with 12–15-MHz transducers. After a period of time during which imaging techniques and anesthesia protocols were optimized, the publication of seminal methods papers using echocardiography in adult mice helped standardize the use of this important phenotyping tool.12,14 The development of dedicated devices in the early 1990s, such as the Humphrey ultrasound biomicroscope, allowed lateral image resolution that approached 65 µm, although this came at the expense of a limited penetration depth (~4–5 mm). The ultrasound biomicroscope made it possible to study neonatal mice, with novel insights gained into cardiomyopathic phenotypes and disease mechanisms. As an example, in a mouse model of hypertrophic cardiomyopathy, although it was known that homozygous α-MHC Arg403Gln animals died in the early neonatal period, serial echocardiography helped demonstrate that this was not because of massive hypertrophy, but rather, a severe dilated cardiomyopathy (DCM) and rapidly progressive heart failure (HF) in the days leading up to death.15

The technology of this instrument was then incorporated into the VS40 (VisualSonics, Toronto, Canada).16 It had a single transducer with a nominal center frequency of 40 MHz, a diameter of 3 mm, and a focal length of 6 mm. It had a lateral resolution of 50–100 µm and an axial resolution that ranged from 81 µm at 19 MHz to 28 µm at 55 MHz. However, the low frame rate of this instrument (4 frames/s [fps]) was an important limiting issue, and meant that sequential real-time visualization of all parts of a single cardiac cycle was not possible. Procedural times for echocardiographic studies were lengthy, typically lasting 30–45 min per examination.

VisualSonics launched a 2nd-generation system (Vevo 660; transducer 30–55 MHz) in 2003. Although providing comparable spatial resolution (lateral resolution 115 µm, axial resolution 55 µm), this new instrument provided a much faster frame rate (30 fps), which allowed characterization of ventricular structures as well as pulsed-wave Doppler interrogation of ventricular inflow and outflow.17 Further improvements to the frame rate (100 fps) and tissue Doppler and M-mode capabilities were incorporated into a 3rd-generation system, the Vevo 770, in 2006. Current systems (e.g., Vevo 2100, Vevo 3100, Vevo MD) now have significantly higher frame rates (300–400 fps; up to 1,000 fps in a narrow field of view) and the ability to conduct analysis of speckle-based deformation parameters.

Zebrafish Echocardiography

In recent years, the zebrafish has been rapidly gaining popularity as an animal model for diverse research applications. The bodies of embryonic and early larval zebrafish are transparent, allowing cardiac structure and function to be readily assessed using direct optical techniques. As a result of this, zebrafish have been used frequently to study cardiac developmental processes. This transparency is lost with age and, until recently, the use of adult zebrafish models had been severely hampered by a lack of tools for imaging the mature heart. The recent adaptation of high-frequency echocardiography for zebrafish imaging allowed, for the first time, real-time in vivo assessment of cardiac structure and function in adult fish. This transformative technology has been game-changing and has now opened up a new avenue of investigation to study adult-onset human heart disease in zebrafish models.
Indices of Myocardial Systolic Function in Small Animals

The utility of echocardiography stems from its ability to quantify a number of different parameters of ventricular systolic and diastolic function that can help provide insight into the contractile and relaxation properties of the myocardium in vivo. For many of these parameters, there are close similarities between humans and small animals. However, for some parameters, there are distinctive species differences that need to be taken into account.

Ejection Fraction (EF) The ventricular EF, the ratio of the stroke volume over the end-diastolic volume expressed as a percentage, is frequently used to gain an overall assessment of ventricular systolic function in humans and in small animals. Other indices of myocardial systolic performance, such as +dp/dTmax, preload recruitable stroke work, and end-systolic elastance are less commonly used, because they require invasive measurement of ventricular pressure, which is a terminal procedure in many small animals. High-frequency echocardiography allows the adoption of strain-based deformation parameters as well as detailed analysis of the pulsed-wave Doppler waveform, and this has now provided an alternative non-invasive method for estimating some of these indices.

Myocardial Strain Assessment The extent of myocardial strain, or deformation of the myocardial wall, has been used to quantify myocardial mechanical function. Ventricular wall strain (ε) is defined as the change in length of a deformed segment of interest relative to its original length:

\[ ε = \frac{L - L_0}{L_0} \]

where \( L \) is the final length and \( L_0 \) is the baseline length. During systole, the ventricular myocardium shortens in the longitudinal and circumferential dimensions, producing a negative strain, while at the same time, thickening in the radial direction, resulting in a positive strain. Strain rate (\( \dot{ε} \)) represents the time-derivative of strain, and measures the rate of deformation.26 In echocardiographic analyses, myocardial strain is assessed in separate wall segments, with global values (computed average of all segments) and peak values (highest value of any of the segments) able to be determined.

In human HF studies, it has been noted that systolic strain abnormalities can precede changes in conventional parameters such as the EF, suggesting that myocardial strain could be used to detect early disease.27 Two main methods of strain measurement have been used in clinical medicine and have been adapted for use in small animal studies: tissue Doppler-based imaging and speckle tracking-based imaging.28 Radial and circumferential strain in the ventricular short axis were favored initially in mice because they had superior clarity when compared with measurements taken in other views, and the entire cross-section of the left ventricle could often be observed without image drop-out. In a murine study, speckle-tracking strain echocardiography enabled identification of both acute and chronic left ventricular dysfunction following transverse aortic constriction, with circumferential strain showing better correlation with the development of cardiac fibrosis than radial strain.29 In another murine study, peak longitudinal strain and strain rate were able to detect changes in ventricular systolic function following myocardial infarction at an earlier time than conventional B-mode indices, and predicted the later development of adverse left ventricular remodeling.30 The different sensitivities of strain parameters may relate to the differential functional properties of the myocardial layers. Whereas circumferential and radial strain reflect the contractile properties of the mid-myocardium, longitudinal strain is a particularly sensitive marker of subendocardial myofiber dysfunction, which often occurs early in mechanical or ischemic stress.30 We have recently demonstrated that myocardial deformation indices can also be successfully measured in adult zebrafish (Figure 2).31

Maximum Aortic Acceleration (aortic\textsubscript{acc}) Maximum aortic\textsubscript{acc}, measured as the steepest tangent to the aortic pulsed-wave Doppler envelope (Figure 2), has been shown to be related to +P/dTmax.31 This is not surprising, given the close temporal relationship between maximal aortic\textsubscript{acc} and +P/dT in the cardiac cycle. The rationale behind using this parameter is the assumption that ventricular +P/dT\textsubscript{max} is equal to aortic +P/dT\textsubscript{max}, an assumption that is valid in the absence of any significant aortic stenosis.32 Maximal aortic\textsubscript{acc} has been shown to be sensitive to the inotropic state of the heart and is relatively insensitive to preload.33-38 However, unlike +P/dT\textsubscript{max}, it is significantly influenced by changes in afterload.39 Nevertheless, studies correlating maximum aortic\textsubscript{acc} and +P/dT\textsubscript{max} have shown...
that it can be used to noninvasively assess the contractile state of the left ventricle in humans.\textsuperscript{37,38} Maximum aortic\textsubscript{acc} has been observed to be lower in patients with critical coronary artery disease who had normal hemodynamic and angiographic indices of left ventricular systolic function, suggesting that this parameter may detect early myocardial impairment not otherwise detected by other conventional non-invasive indices in disease states.\textsuperscript{39} as well as day-to-day changes in ventricular function among HF patients.\textsuperscript{37} In an ideal world, Doppler measurements of maximum aortic\textsubscript{acc} offer an effective means to noninvasively assess short-term changes in left ventricular performance under conditions of varying preload, heart rate, and inotropic state. In practice, however, considerable measurement variability has limited its widespread applicability in both humans and small animals.

**Indices of Myocardial Diastolic Function in Small Animals**

Ventricular diastolic properties are important determinants of normal heart function, and abnormalities of these properties may contribute to various disease phenotypes. There are 4 phases of ventricular diastole: (1) isovolumic relaxation (IVRT), which represents the rate of early active relaxation, when the ventricle is relaxing but the atrioventricular valve has not yet opened, (2) early diastolic filling, which occurs with the opening of the atrioventricular valve, followed by a period (of varying duration, if present at all) of (3) diastasis, when there is relatively little flow, followed by (4) late diastolic filling resulting from atrial systole. These components of ventricular diastolic function are often studied in animal models using invasive techniques such as micromanometry, but can also be assessed noninvasively by echocardiography.

**Isovolumic Relaxation Time** IVRT is the time interval between the closure of the aortic valve and the opening of the mitral valve (Figure 2). It has been used as a measure of the rate of myocardial relaxation, which relates to the rate of calcium sequestration by the sarcoplasmic reticulum following cardiomyocyte excitation.\textsuperscript{40} IVRT has been used as a non-invasive surrogate for \( \tau \), a parameter that describes the time constant of ventricular relaxation.\textsuperscript{41} \( \tau \) can be estimated from echocardiographic parameters according to the formula:\textsuperscript{42}

\[
\tau (\text{Doppler}) = \frac{\text{IVRT (Doppler)}}{\ln P (\text{systolic}) - \ln P (\text{LA})}
\]

The major limitation of IVRT is that it is the result of multiple competing factors that can be altered under conditions of systolic and diastolic HF. IVRT is shortened by high heart rates, and by increased atrial pressure, which itself results in an earlier atrioventricular valve opening, and is lengthened with increasing age. IVRT has been used to assess diastolic relaxation in mice,\textsuperscript{43} and IVRT abnormalities have recently been reported in zebrafish with DCM.\textsuperscript{23}
Evaluation of Early and Late Diastolic Filling Measurement of the peak velocities of the early (E) and late (A) diastolic filling waves and the E/A ratio using pulsed-Doppler interrogation of blood flow through the atrioventricular annulus are used widely to assess diastolic ventricular function in both humans and small animals. Reduction in the peak E wave velocity indicates reduced early ventricular filling, and results in a reduced E/A ratio that typically characterizes the early stages of impaired diastolic relaxation. The peak A-wave velocity coincides with atrial systole, and may be influenced by atrial mechanical function, ventricular compliance and the diameter of the atrioventricular valve orifice. In healthy young humans, the E/A ratio is >1.0. This ratio reverses in older humans, as age-related reductions in ventricular relaxation and compliance necessitate an increased contribution of atrial contraction to ventricu-
lar filling. Human pulsed-wave Doppler signals are often noisy because of interference and distance of the region of interest from the ultrasound probe (Figure 2). In rodents, the E/A ratio is also generally E-dominant (Figure 2). Noise is less of an issue in rodents than in human Doppler tracings but it may be difficult to clearly differentiate E and A waves because of the high heart rates. In zebrafish, pulsed-wave Doppler tracings are remarkably clear, and in contrast to mice and healthy human adults, the E/A ratio is generally <0.30, with marked A-dominance (Figure 2).

Myocardial deformation in diastole (i.e., the rate of chamber expansion) can be assessed by ventricular parameters such as the tissue Doppler diastolic velocity, and the speckle-based global longitudinal diastolic strain rate and global longitudinal diastolic velocity. Combining ventricular inflow and strain characteristics provides useful information about ventricular relaxation and compliance properties, as exemplified by studies of the normal zebrafish heart (Figure 3). Detailed analysis of diastolic parameters may also be useful to distinguish between fundamental defects of left ventricular compliance and of atrial function. For example, in the setting of a reduced myocardial diastolic deformation response in late diastole, a primary atrial myopathy would be accompanied by reduced pulsed-wave peak A-wave velocity while preserved A-wave velocities would suggest impaired left ventricular compliance during late diastole (i.e., increased passive ventricular stiffness).

Limitations of Echocardiography in Small Animals

Variability, caused by biological, technical, and operator factors, is an important issue when performing echocardiographic studies in small animals. Although genetic and environmental factors can be more tightly controlled in animal models than in human subjects, there is still physiological variability within and between animals that can affect echocardiographic measurements. In contrast to humans, a distinguishing feature of echocardiography in small animals is the requirement for anesthesia to facilitate tolerability of the procedure and technical feasibility. Anesthetic agents can directly affect heart rate and myocardial contractile function, and can confound assessment of myocardial phenotypes. There is also a significant learning curve for acquiring high-quality images and for reproducible data analysis in small animals. Reproducible studies require a skilled operator. To facilitate repeatability and translatability of results between different institutions, steps should be taken to limit the effect of variability. This includes undertaking randomized and blinded studies that are adequately powered and standardized for age, sex and background strain, standardizing and minimizing anesthetic dose and duration, avoiding data collection during an operator’s learning curve, and assessing operator variability by reporting inter- and intraobserver agreement.

Specific care is needed when using deformation (strain) parameters in small animal echocardiography, as myocardial strain properties differ according to the muscle layers interrogated. Systems that calculate measurements based on 1 particular layer of the myocardium would vary from another system that evaluates a different layer. Variability of measurements performed on the same echocardiography machine can be improved by automation of strain protocols, but inter-vendor variability is still significant, and has been shown to complicate interpretation of results arising from different analysis programs. This remains a problematic area in small animal echocardiography.

Because of the anatomical factors, such as a relatively posterior position of the heart, and limited spatial resolution, assessment of atrial size is challenging in small animals. Size estimation of the irregular, bi-lobed single atrium in zebrafish is particularly problematic because geometric shape assumptions cannot be applied. Similarly, in the mouse, the anatomical position of the right ventricle often precludes accurate assessment of chamber size and function.

Future Directions

Achieving higher image clarity is an ongoing quest of ultrasound imaging. In the field of light microscopy and imaging, techniques such as photo-activated localization microscopy (PALM) and other methods of super-resolution have allowed greater resolution than would be expected according to Abbe’s law by spatial or temporal summation of standard resolution images in order to produce a super-resolved image. Similar ideas can be applied to sound waves to enhance the resolution of ultrasound. One promising technique is the use of signal-averaging of ECG-gated images obtained over multiple heart beats in order to produce a cine video image of improved resolution compared with original, unprocessed images. This concept, known as ECG-gated kilohertz visualization, has been used in certain high-frequency ultrasound systems to allow for increased temporal and spatial resolution imaging. The temporal resolution of B-mode images obtained using this method can reach up to 10,000 fps. Applied to clinical echocardiography, this may allow much better resolution of important structures such as cardiac valves, but will significantly increase study duration.

Translation of this idea from super-resolution light microscopy into ultrasound, however, is still in its formative stages. Point scatterers of ultrasound such as microbubbles, similar to the fluorescent point scatterers of light used in PALM, in combination with high frame rate ultrasound imaging (500 fps), have allowed characterization of intracranial blood vessels. One disadvantage with this technique for in vivo small animal scanning is that the requirement of summatiing multiple images would likely result in long scanning times. This technique also requires intravascular access, and is unlikely to be a practical option in many of the species used in preclinical research.

CMR measurements of cardiac dimensions and function have superior spatial resolution when compared with ultrasound, and are now considered the gold standard in human clinical research. Many of the modalities offered by echocardiography (including strain) have an analogous modality in CMR. Although rodent CMR has been reported, several factors limit its potential widespread use. On top of the considerable costs and physical requirements of installing the operating system, CMR studies often require deeper sedation or anesthesia than is required in echocardiography, an issue that may significantly confound studies of systolic and diastolic function. Temporal resolution in CMR remains lower than that of echocardiography and this is a very important limiting factor in rodent cardiac studies because of their very high resting heart rates.
Conclusions

Technological developments in cardiac imaging have facilitated high-quality in vivo cardiac phenotyping and have underpinned many new discoveries in cardiovascular medicine. Contemporary high-frequency echocardiographic systems, utilizing transducer frequencies of 40–70 MHz and B-mode frame rates in excess of 300 fps, have provided unprecedented opportunities to study human heart disease in a range of small animal models. The ability to generate and study clinically relevant animal models is vital for elucidating primary pathogenetic factors, effects of lifestyle factors and the efficacy of therapeutic interventions, and plays an integral role in the implementation of precision medicine. Continued collaborative interactions between users of echocardiography in the clinical and research communities will promote methods development, enrich mechanistic studies and foster translational outcomes.

Acknowledgments

The authors are supported by research funding from the National Health and Medical Research Council, the Estate of the Late RT Hal, St Vincent’s Clinic Foundation, and the Simon Lee Foundation. L.W.W. is supported by a postgraduate scholarship co-funded by the National Health and Medical Research Council, National Heart Foundation of Australia, and the Royal Australasian College of Physicians.

Disclosures

None.

References


42. Scalia GM, Greenberg NL, McCarthy PM, Thomas JD, Vandervoort PM. Noninvasive assessment of the ventricular relaxation time constant (τ) in humans by Doppler echocardiography. *Circulation* 1997; **95**: 151–155.


