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METHODS ARTICLE

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A systematic methodology for epicardial and epiaortic echocardiography in swine research models

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Abstract

Background: Perioperative echocardiography is of paramount importance during cardiac surgery. Nonetheless, in the experimental large-animal setting, it might be challenging obtaining optimal imaging when using conventional imaging acquisition techniques, such as transthoracic and transesophageal screenings. Open-chest surgery allows epicardial echocardiographic assessment with direct contact between probe and heart, thus providing superior quality. Standard protocols regarding the use of epicardial ultrasound in swine for research purposes are lacking.

Methods: Epicardial echocardiography was performed in 10 female German Landrace pigs undergoing cardiac surgery. A structured and comprehensive protocol for epicardial echocardiography was elaborated including apical, ventricular long and short axis, as well as epiaortic planes. All experiments were approved by the local board for animal welfare and conducted in accordance with the German animal protection law (TierSchG) and the ARRIVE guidelines.

Conclusions: Systematic protocols using epicardial echocardiography may serve as an additional tool to assess cardiac dimensions and function in experimental scenarios with swine models.

KEYWORDS
animal model, cardiac surgery, intraoperative echocardiography, swine

1 | INTRODUCTION

Large animal models play an important role in translational research, particularly in the cardiovascular field. Among large animals, pigs are the preferred model, as they most closely represent human cardiac size, coronary anatomy and electrophysiology.[1–3] This is of great value to support the development of a variety of surgical skills as well as techniques and materials for classic procedures in cardiac surgery.[4] Adequate perioperative imaging enriches even more the portrayal of this animal model in training guidelines and experimental studies. The choice of the proper imaging technique may affect its outcomes.

First introduced in the early 1970s,[5] epicardial and epiaortic echocardiography (EE) is the modality of ultrasound performed in direct contact with the cardiac and aortic surface. It offers intraoperative assessment from two-dimensional (2D) ultrasound to color and spectral Doppler within minutes of screening and provides

great imaging quality as well as fast plane finding, without requiring exclusive or high-end equipment as in transesophageal echocardiography (TEE). Thus, placing the probe directly above the organ's surface eliminates interference from anatomic structures in between (e.g., ribcage and lungs) that might impair image acquisition in other modalities, such as transthoracic echocardiography (TTE).

Although representing a specific component of American Society of Echocardiography and Society of Cardiovascular Anesthesiologists Task Force Training Guidelines,[6] EE might be performed not only by cardiologists, but also cardiac surgeons and anesthesiologists. Before using EE independently in perioperative decision making, the examiner should have performed at least 25 examinations, five of which should be performed under supervision of an advanced echocardiographer.[7,8]

2 | AIMS AND OBJECTIVES

On the one hand, there are international guidelines directing EE as additional imaging modality for cardiac surgery. On the other hand, swine are the preferred large animal model in preclinical testing and hands-on training. Nevertheless, until this day no standardized EE protocol was described in swine. Standardization of EE examination in this species is of considerable interest given the anatomical and physiological differences between human and swine. Therefore, we aimed to provide a comprehensive EE protocol in adult swine to support cardiac surgeons in image acquisition and intraoperative decision making in experimental scenarios. Furthermore, we want to highlight the diagnostic value of EE, encouraging more investigators to apply intraoperative EE in cardiovascular research.

3 | METHODOLOGY

3.1 | Study design

All experiments were approved by the local ethics committee (Freiburg, Germany, approval number 35-9185.81/G-22/006). All animals received human care in compliance with the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources published by the National Institutes of Health.[9] Ten healthy female swine (German Landrace, 104.4 ± 13.0 kg) were included in this study. Sampling size was defined as to enable enough echocardiographic representativity with a comprehensive assessment in each subject, yet without leading to unnecessary wasting of resources and animals. Any signs of impaired health, anatomical abnormalities detected before the procedures or at in situ evaluation of the mediastinum and heart were considered as exclusion criteria.

Before the procedures, animals were kept in controlled environmental conditions with access to water ad libitum. For initial relaxation, premedication was administered (ketamine 20 mg/kg IM, midazolam 0.5 mg/kg IM) until sedation; subsequently the animals were intubated and transferred to the operating room, where continuously hemodynamic monitoring was installed. General anesthesia was induced with propofol (2–4 mg/kg IV) and vecuronium (0.2 mg/kg IV), and thereafter maintained with propofol (10–15 mg/kg/h IV), fentanyl (5–10 µg/kg IV), and vecuronium (0.2–0.4 mg/kg IV). At signs of pain or distress, analgesia was reinforced with propofol.

3.2 | Preparation and access to the heart

Each pig is placed in dorsal recumbence with the limbs fixed. After adequate sedation, median sternotomy is performed, a thorax retractor is allocated in the sternum and opened to sufficient exposition of the heart width. Thereafter, pericardiotomy is performed in T-shape, and each lateral leap is fixed to the retractor by high stitches.

3.3 | Probe preparation

Adequate asepsis is a sine qua non condition for performing an intrapericardial procedure such as EE. The examiner must be equipped with gloves and sterile apron on the surgical field. An ultrasound system with a broadband cardiac sector array transducer should be used for the screenings. In our case, a sector phased array in a point of care ultrasound system were used to perform screenings in all animals (S4-2 Transducer and CX50 POC; Philips Healthcare). The transducer must be encased by the surgeon using a sterile covering sheath. To improve acoustic transmission, sterile acoustic gel is placed in the inner face of the sheath, above the transducer surface. With purpose of enhancing acoustic transmission, warm sterile saline may be additionally placed into the mediastinal cavity.

3.4 | Echocardiographic setting and screening

A comprehensive assessment was performed including all heart chambers, in which all captions were initially assessed with 2D ultrasound, in addition of color and spectral Doppler for valvular study, when applied. In our experience, a depth between 10 and 15 cm is enough to encompass the heart in all windows. As swine present a higher heart rate, we suggest setting CW and PW Doppler at a sweeping speed of 100 mm/s for better analysis of wave patterns. All geometric parameters were measured postoperatively in three to five cardiac cycles. The examinations and measurements were performed uniformly in all animals.

3.5 | Imaging planes

In total, 12 EE imaging planes are hereinafter described: four apical, six ventricular—thereof two in long and four in short axis—and two epiaortic imaging planes. In case of hemodynamic instability or signs of malignant arrhythmia (e.g., ventricular fibrillation), the screening should be interrupted.

The placement of the transducer directly above the heart surface and the nomenclature of each view differs slightly from classical TTE and TEE terminology. Similarly to TTE and TEE, imaging depth should be adjusted to the structure or area of interest. Due to direct contact with the cardiac surface, the lower depth allows utilization of high-frequency transducers, commonly used in pediatric echocardiography. For improved accuracy, acquisition should be guided not only by the probe placement herein described, but enhanced by actual findings during examination. Those help specially to steer small adjustments needed to achieve a seamless picture.

3.6 | Apical planes

Apical views provide general impression of the heart, allowing morphological and functional assessment. To proper reproduce the ventricular filling conditions and dimensions, special attention should be paid to the pressure applied from the transducer to the ventricular apex when in apical planes. Besides that, as pigs reveal a higher susceptibility to arrhythmia,[1] excessive touching and compression of the heart should be avoided.

3.6.1 | Apical 4-chamber (A4C)

The probe is placed at the apex, with the marker pointing left. The transducer should be aligned with the interventricular septum (IVS) and longitudinal heart axis. An optimal A4C displays all four chambers, with the left ventricle (LV) at the top center, the left atrium (LA) underneath, and the right ventricle (RV) and atrium (RA) left from the LV and LA (Figure 1). The IVS should be displayed as a vertical and well-aligned structure in the middle of the frame. This is an optimal view for volumetric and functional cardiac assessment, including the calculation of the ejection fraction by the Simpson's method, further enriched by color and spectral Doppler of atrioventricular valves, namely mitral valve (MV) and tricuspid valve (TV). This view is also ideal for calculation of the RV TAPSE using M-mode.

3.6.2 | Apical 5-chamber (A5C)

To proceed from the A4C into the A5C view, the probe is tilted anteriorly, until the left ventricular outflow tract (LVOT), the aortic valve (AV), and the ascending aorta (AAo) are displayed. The A5C (Figure 2) allows analysis of LVOT geometry and hemodynamics by applying color and spectral Doppler to the AV. Exemplarily, this might help to distinguish complex mixed regurgitation jets between AV and MV.

3.6.3 | Apical 2-chamber (A2C)

From the A4C, rotate the probe counterclockwise around 60° to reach the A2C view, displaying the left heart longitudinally. This view allows optimal assessment of the MV with color and spectral Doppler. The A2C (Figure 3) can be also used to complement the A4C volumetry, determining the LV ejection fraction by biplane assessment (Simpson). Furthermore, it allows good assessment of LA size and area.

3.6.4 | Apical 3-chamber (A3C) or apical long-axis

To proceed from the A2C to the A3C view, the probe is rotated counterclockwise around 60°. This plane complements the A2C by additionally presenting the LVOT, AV, and AAo (Figure 4).

3.7 | Ventricular planes

3.7.1 | LV long axis (LV LAX)

In addition to apical planes, the long axis of the LV (LV LAX) can be used to quantify the LV dimensions, including thickness of the IVS and posterior wall. To obtain a LV LAX, the probe should be placed above the ventral heart center with the marker pointing toward the right pig's shoulder. The LV LAX (Figure 5) demonstrates the mid-section of the LV with both, AV and MV, plus LVOT, and an

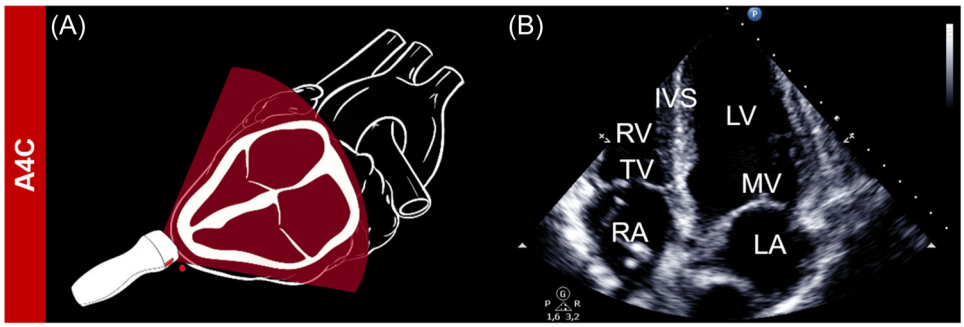

FIGURE 1 Apical 4-chamber view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. IVS, interventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

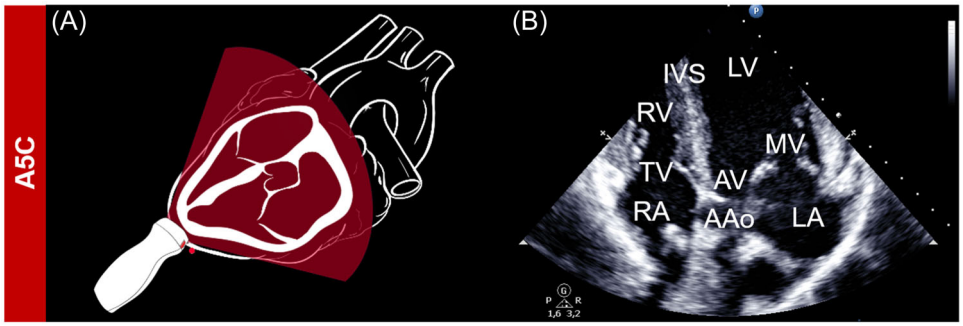

FIGURE 2 Apical 5-chamber view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AAo, ascending aorta; AV, aortic valve; IVS, interventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

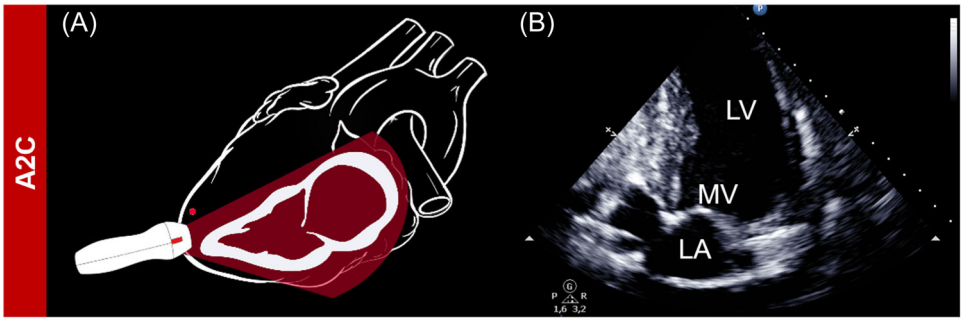

FIGURE 3 Apical 2-chamber view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. LA, left atrium; LV, left ventricle; MV, mitral valve.

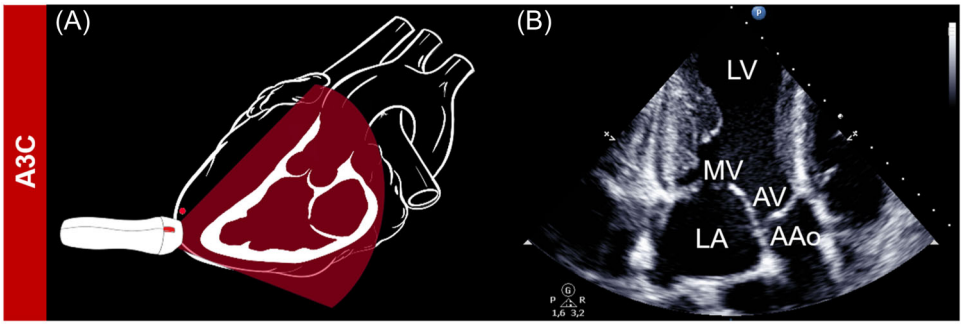

FIGURE 4 Apical 3-chamber view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AAo, ascending aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve.

anteroposterior section of the LA. A thin section of the RV may be seen proximally to the ultrasound probe. Color Doppler might be applied for study of AV and MV, looking for signs of regurgitation.

3.7.2 | RV long axis

By repositioning the transducer from LV LAX, pointing the marker toward the left shoulder, tilting the probe anteriorly and rotating it slightly clockwise, it is possible to display the RVOT. Color Doppler may be applied to analyze the pulmonary valve (PV).

3.7.3 | LV SAX—AV level

The short axis view (LV SAX) will be obtained by rotating the transducer 90° clockwise from the LV LAX, pointing the marker toward the left pig's shoulder. Subsequent views of different SAX levels are obtained by sliding or tilting the transducer craniocaudally. The LV SAX at height of the AV (Figure 6) allows detailed assessment of the semilunar aortic cusps. The AV leaflet anatomy can be well assessed during diastole, usually displaying a three-pointed star formed by the left-, right-, and non-coronary-cusps. Furthermore, the PV and TV, the LA and RA as well as the RVOT and the PA can be

assessed. Focusing at the AV in particular, the coronary ostia might be displayed.

3.7.4 | LV SAX—MV level

To achieve the LV SAX at height of the MV, the transducer must be tilted and slid caudally. At height of MV (Figure 7), easily identified by a typical "fish mouth" shape, both anterior and posterior leaflets can be assessed regarding their morphology and function.

3.7.5 | LV SAX—midventricular level or papillary muscle level

Further tilting and caudal sliding the probe allows visualization of the anterolateral and posteromedial papillary muscles (Figure 8). This

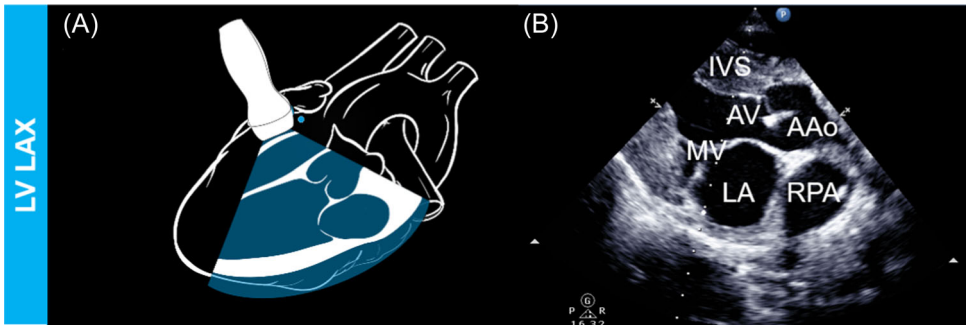

FIGURE 5 LV LAX view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AAo, ascending aorta; AV, aortic valve; IVS, interventricular septum; LA, left atrium; RPA, right pulmonary artery.

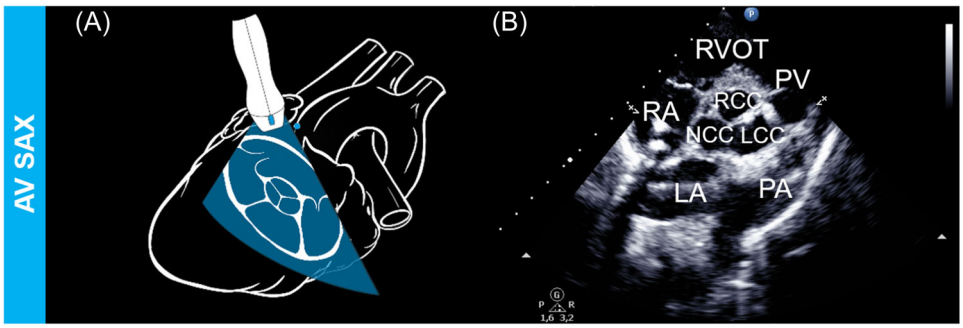

FIGURE 6 LV SAX view, at the height of the aortic valve. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. LA, left atrium; LCC, left coronary cusp; NCC, non-coronary cusp; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RCC, right coronary cusp; RVOT, right ventricular outflow tract.

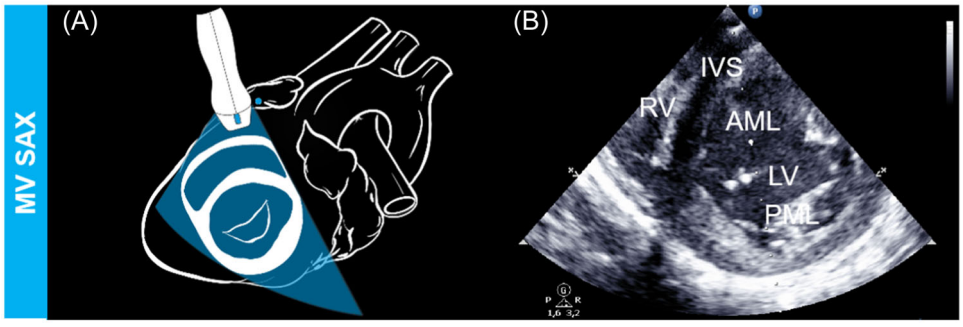

FIGURE 7 LV SAX view, at the height of the mitral valve. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AML, anterior mitral leaflet; IVS, interventricular septum; LV, left ventricle; PML, posterior mitral leaflet; RV, right ventricle.

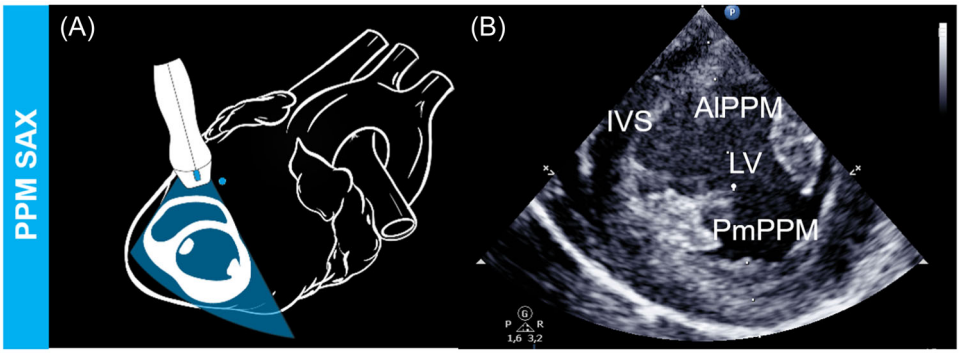

FIGURE 8 LV SAX view, at the height of the papillary muscles. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AlPPM, anterolateral papillary muscle; IVS, interventricular septum; LV, left ventricle; PmPPM, posteromedial papillary muscle.

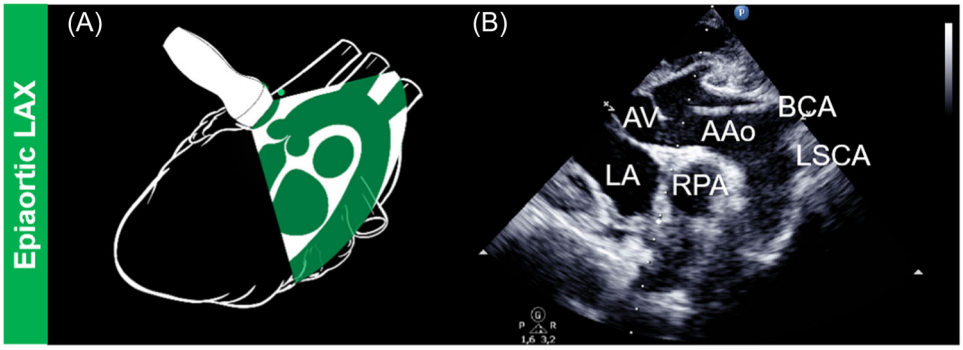

FIGURE 9 Epiaortic LAX view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AAo, ascending aorta; AV, aortic valve; BCA, brachiocephalic artery; LA, left atrium; LSCA, left subclavian artery; RPA, right pulmonary artery.

view is especially useful for evaluation of global LV function, circumferential LV contractility, overall wall motion and thickness.

3.7.6 | LV SAX—apical level

Sliding the probe toward the apex displays the apical portions of the LV.

3.8 | Epiaortic planes

Singular attention is paid to epiaortic views, given the superior assessment of anterior structures with EE. Those particular planes are obtained by positioning the transducer directly at the base of the proximal AAo.

3.8.1 | Epiaortic LAX

The epiaortic LAX (Figure 9) is obtained from the LV LAX, by sliding the transducer cranially. This plane allows detailed analysis of the thoracic aorta including not only the AAo, but also the aortic arch and the proximal descending aorta. This view is optimal for displaying the particular aortic anatomy in swine, as only two branches arise from the aortic arch, namely the brachiocephalic artery and the left subclavian artery.[10] Furthermore, it depicts the PA transversely and a portion of the LA. With fine adjustments, it may be possible to visualize the ostium of the right coronary artery.

3.8.2 | Epiaortic SAX

To switch from the epiaortic LAX into the SAX view, the transducer should be rotated 90° counterclockwise, with the marker pointing toward the pig's left shoulder. This view shows a cross section of the AAo and superior vena cava, as well as a portion of the right PA (Figure 10).

4 | DISCUSSION

Swine are the preferred model for experimental cardiovascular research, mostly due to the many similarities with the human heart.[1–3] Hence, swine are used in hands-on training for ongoing cardiac surgeons. Furthermore, swine serve as biological source for

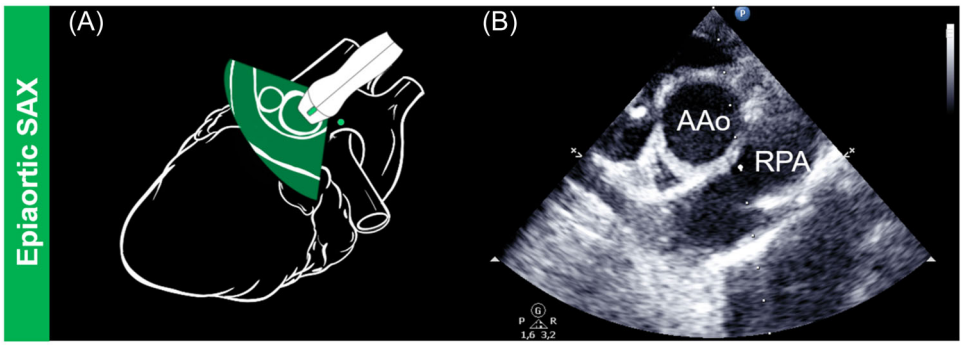

FIGURE 10 Epiaortic SAX view. (A) refers to the schematic representation of the probe placement and structures to be displayed; (B) represents the echocardiographic view. AAo, ascending aorta; RPA, right pulmonary artery.

xenotransplantation, such as biological heart valves, pericardial patches, and pig-to-human heart xenotransplantation, as recently reported with 60 days of survival.[11]

The swine heart presents constitutional anatomic differences to the human one,[12] which may influence execution and interpretation of EE. The so-called "valentine shape" of swine heart displays an apex constituted mostly of left-ventricular tissue, creating a steady surface for probe positioning during apical assessments. The keel-shape conformity of swine chest, along with the quadruped postural effect, projects the apex toward the anterior chest wall,[12,13] which also amends acquisition of apical planes. This same feature may, however, make it challenging to obtain the RV LAX view, as the right face of the heart is rather posterior than in humans. Opposite to TTE, where due to the posterior projection of the longitudinal cardiac axis, the RV is seen rather posterior to the LV,[13] with EE it is possible to proper align the probe with the heart long axis, obtaining a similar frame in terms of chamber orientation as in humans. Furthermore, the LV of pigs is markedly thick, displayed in echocardiography by a bulkier myocardium. For that reason, endocardial tracing for the modified Simpson-biplane assessment of ejection fraction might be easier. The porcine left heart comprises about two-thirds of the echocardiographic image, contrasting with the usually equal and balanced chamber volumes among humans. Anatomically, in swine, the LA receive only two pulmonary veins,[12] well displayed in apical views, in contrast with the 4 ones in humans. Hence, only two branches arise from the porcine aortic arch,[10] which can be optimally displayed in the epiaortic planes. This is particularly relevant for transcatheter valve implantations as well as reconstruction of the AAo and aortic arch.

Dominating different techniques in echocardiography in animal models is important as innovation and new methodologies tend to be applied first in different animal models and further translated into clinical practice. Exemplarily, Mandour et al. recently published an overview of the assessment of intraventricular pressure using Color M-Mode, which has been primarily described in animal models, between rats, felines, dogs, pigs, sheeps, and goats.[14] The clinical relevance of the new methodology has been strengthened over time, with good perspectives of future validation in clinical cardiology. Understanding how various conditions such as hyperdynamic circulation, anemia or shock might lead to different results in echocardiography, as recently demonstrated by Chompoosan et al. in pregnant horses, might interfere in interpretation of results.[15] Todd et al. described a protocol for mice with particular focus in infrequently used parameters, as well as highlight in assessment of the right heart, as to deeper explore the mechanisms of right heart and pulmonary circuit function.[16] With respect to intraspecies analysis, echocardiography in animal models may serve as a bridge imaging modality for control of studies performed in a longer timeframe with high end methodologies as goal, exemplarily described by Martínez-Milla et al. with coronary angiography, cardiac magnetic resonance, and hybrid PET/CT.[17] Hence, EE might be applied and compared with different imaging techniques to optimize methodology matching according to a specific parameter or study aim, as well exemplified by Rogers et al. in a multimodality comparison of artery diameter, length, and wall volume.[18]

Over the past years, TEE has become the gold standard for intraoperative imaging during cardiac surgery. On the one hand, it demands a considerable amount of expertise from the examiner and requires dedicated equipment. On the other hand, it is limited by several contraindications (such as esophageal pathology, history of upper gastrointestinal surgery or severe coagulopathy) and may not be considered in specific situations.[19] Yet, in particular situations, such as surgery for congenital heart disease, TEE and EE are considered to be complementary rather than alternative techniques.[20]

Nowadays, EE is used intraoperatively either as a complementary modality to TEE or independently. Unlike TEE, EE can be performed using a standard phased-array transducer and features low probability of complications.[21] Performed directly above the heart surface, EE provides great image quality and fast plane finding, as it is not impaired by intermediary anatomic structures (e.g., ribcage and lungs in TTE, or trachea and main bronchi in TEE). As a more intuitive tool, EE might help surgeons strengthen skills in the latest advances in cardiovascular echocardiography, as represented by the increasing usage of strain imaging and artificial intelligence methods, as well as the development of interventional echocardiography.[22] Furthermore,

EE overcomes several limitations associated with TEE, such as poor imaging of distal AAo and aortic arch and difficulty of adequate probe placement in the esophagus.[23–25] A variety of useful data is provided by EE, which can be used to corroborate surgical results,[23] and that is especially appreciated in hands-on training. Epicardial echocardiography fulfilled additionally an important role during COVID-19 pandemics, providing intraoperative imaging with little to no aerosolization, easy disinfection and no direct contact with patient's body fluids.[26] Given the numerous advantages mentioned above and the practicability of this imaging technique, EE could be applied more widely, both clinically and experimentally.

When considering particularities of common procedures in cardiac surgery, the significance of EE is even better understood. Global and specific valvular function may be assessed uni- or multiplane, with 2D or additionally with color and spectral Doppler. Both atria can be well covered by epicardial assessment, including the left atrial appendage, a predilection site for thrombi, usually not amenable by TTE. Regarding valvular assessment, particularly MV and TV repairs, EE can be performed additionally to the leakage-saline-test to confirm valvular patency, increasing its sensitivity. Remarkably in pediatric scenarios, EE is a viable alternative, as TEE is usually not performed in neonates, infants, small or low-birth weight children,[27] and EE can better represent the conditions faced in the clinical context. Hence, EE provides superior imaging of anterior structures,[25] a crucial advantage to congenital vascular repairs (e.g., transposition of great arteries, aortic coarctation, patent ductus arteriosus), which supports corrective procedures of often high complexity that benefit from hands-on training. Concerning heart transplantations, EE may assist during separation from cardiopulmonary bypass and evaluation of anastomosis patency. In case of LVAD implantation, imaging allows optimal placement and alignment of the inflow, to ensure it is adequately directed toward the MV and free from obstructions. Furthermore, EE allows assessment of IVS movement, which is an important criteria for proper LV unloading.[28] Immediately after LVAD implantation, EE helps excluding air embolism, supplies information about LV and RV unloading as well as remaining LV contractility. Many authors describe the implementation of a ramp-test after LVAD setting.[29–33] Therefore, EE might not only support setting of optimal device rotational speed, but also should be considered to feature such tests in situ.

Despite the many advantages elucidated, EE is not free from limitations, especially when considering the particularities of the swine model. Epicardial imaging requires full sternotomy, as probe manipulation may be impaired by smaller incisions, considering the acute angle formed between the sternum and the ribcage in pigs. Ultrasound analyses tend to be limited by human error in imaging acquisition. Transducer placement should be as accurate as possible, requiring high sensibility and fine adjustments, which might be challenging with the direct contact with a beating heart. Hemodynamic instability and arrhythmia might occur due to cardiac compression, remarkably in swine, which display a considerable predisposition to dysrhythmiasarrhy.[1] Furthermore, in case of inadequate antisepsis or probe isolation, there is a risk of infection, which may compromise the outcomes in long-term experiments. Spatial and geometric limitations may hinder acquisition of dedicated planes. In particular, apical planes may be difficult to acquire due to surrounding adjacent structures (e.g., ribcage, thorax retractor). Due to the cardiac convexity, as well as the quadruped postural effect, it might be challenging to obtain longitudinal planes, in particular toward the RV, rather posterior located.[12] Particular attention should be paid when translating results from swine models into human context, as various structural and functional differences exist between the two species, as aforementioned. Moreover, as EE is performed during surgery, comprehensive screening might distract the surgeon and prolong the overall procedure time, even in experimental scenarios. Finally, with respect to the study design, the sampling size was limited, which may exclude possible anatomical variations, as well as accounting for a limited range in weight and body surface area. The screenings were performed by the same team, which might preclude bias among examinators.

5 | CONCLUSION

The establishment of an echocardiographic baseline in swine models is important for future references in cardiovascular research. We believe that the first step to the establishment of standard EE values in swine is the design of a protocol that encompasses the particularities that this model bears. We described imaging planes as close as possible to the standard TTE and TEE, including acquisition sequences and transition maneuvers. Hence, we demonstrate that EE allows detailed intraoperative assessment, which might be applied in swine models used for preclinical testing and hands-on training models. Epicardial and epiaortic screening should be considered not only in case of contraindications hindering TEE, but as a standard modality for intraoperative echocardiographic imaging. The protocol may support the surgical planning, guide intraoperative decision making and ultimately improve postoperative outcomes, contributing to the research development. All things considered, we advocate that every cardiac surgeon should be familiar with EE.

AUTHOR CONTRIBUTIONS

Michelle C. Galbas: Conceptualization; funding acquisition; investigation; methodology; visualization; writing—original draft; writing—review and editing. **Florian Meissner**: Conceptualization; formal analysis; investigation; methodology; project administration; supervision; writing—review and editing. **Alexander Asmussen**: Formal analysis; methodology; supervision; validation; writing—review and editing. **Hendrik C. Straky**: Investigation; methodology; writing—review and editing. **Marius Schimmel**: Investigation; methodology; writing—review and editing. **Johanna Reuter**: Investigation; methodology; writing—review and editing. **Sebastian Grundmann**: Formal analysis; methodology; supervision; validation; writing—review and editing. **Martin Czerny**: Formal analysis; supervision; validation; writing—review and editing. **Wolfgang Bothe**: Conceptualization;

formal analysis; funding acquisition; project administration; resources; supervision; validation; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

TRANSPARENCY STATEMENT

The lead author Wolfgang Bothe affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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