Recent Advances in Percutaneous Cardioscopy for Heart Disease

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Percutaneous endoscopy for direct visualization of the cardiac interior, i.e., percutaneous cardioscopy, was developed in Japan in 1980. Approved by Japanese Ministry of Health, Welfare and Labor, this imaging technique has been used for diagnosis and evaluation of interventional and surgical treatment of various categories of heart diseases. This article reviews recent advances in percutaneous cardioscopy.

Percutaneous cardioscopy has demonstrated that the endocardial surface exhibits various colors characteristic of different heart diseases. This imaging modality can now be used for evaluation of the severity of myocardial ischemia and staging of myocarditis. Myocardial blood flow (MBF) recovery induced by vasodilating agents or percutaneous coronary interventions can be clearly visualized. Subendocardial microvessels can be seen through the endocardium. Combined use of cardioscopy and intracardiac ultrasonography (ICUS) is useful for evaluation of morphological and functional changes in the cardiac chambers and valves. Cardioscope-guided endomyocardial biopsy enables pin-point biopsy of diseased myocardium. Dye-image and fluorescent cardioscopy were developed for evaluation of the subendocardial MBF or tissue fluid flow. These imaging techniques have demonstrated that myocardial microcirculation disturbance remains frequently after angiographic successful percutaneous coronary interventions (PCI). Cardioscopy is also useful for evaluation of percutaneous transseptal mitral commissurotomy or open-heart surgery of various categories of heart disease. In near future, cardioscope would be used for guidance of myocardial ablation, valvuloplasty, or transendocardial angiogenic or myogenic therapy.

In conclusion, percutaneous cardioscopy has the potential to contribute to our understanding of heart disease and to assist intracardiac therapies.

Key words: cardioscope-guided endomyocardial biopsy, dye-staining cardioscopy, fluorescent cardioscopy, pericardioscopy, various heart disease

Introduction

Direct observation of changes in the beating heart was previously beyond the scope of any available imaging modalities. Percutaneous cardioscopy, using high-resolution fiberoptic imaging, enables direct visualization of the cardiac interior, thereby enabling macroscopic pathological diagnosis. This imaging modality is now used clinically not only for diagnosis of myocardial and valvular disease, but also for evaluation of interventional and surgical therapies. In this review, the past, present, and future prospect of this promising imaging modality are presented.

Development of Cardioscopy

Intracardiac observation using a rigid cardioscope in animals was performed by Allen and Graham in 1922 and by Harken and Glidden in 1943. In 1956, Sakakibara, et al. used a rigid cardioscope to observe a septal defect during open-heart surgery. In 1958, they also observed the aortic valves using the same cardioscope. The difficulties in producing an endoscope that could be safely introduced percutaneously into the cardiac chambers, as well as equipment to displace blood, meant that almost 32 years elapsed before Uchida and coworkers successfully performed percutaneous cardioscopy in patients. In 1983, a 9-F guiding balloon-catheter was devised. When inflated with CO₂, the balloon protrudes beyond the shaft tip to form a dead space between the target and the balloon; at the same time preventing damage to the myocardium by the shaft tip. When used in combination with a 4.5-F fiberscope, percutaneous observation...
of the cardiac chambers and valves could be performed in patients.\textsuperscript{5-10} This cardioscopy system is now routinely used clinically for observation, not only of the cardiac chambers and valves, but also of the great vessels including the pulmonary arteries, caval veins, and aorta.

**Cardioscopy System**

A cardioscopy system comprises a light source, 4.5-F fiberscope (containing 3000 glass fibers for image guidance and 300 glass fibers for light guidance), 9-F guiding balloon-catheter, intensified chilled coupled device (ICCD) camera, camera controller, DVD recorder, and television monitor. The fiberscope (AF 14; Olympus Corporation, Tokyo, Japan) is passed through the 9-F guiding balloon-catheter and the balloon is inflated with CO\textsubscript{2} (Fig. 1A).\textsuperscript{11} The catheter has a Y-connector at the proximal end: one channel for fiberscope insertion and the other for saline flushing. The white balance of the cardioscope is adjusted using white gauze soaked in saline solution.\textsuperscript{8, 9}

**Cardioscopic Procedures**

Following coronary angiography and left ventriculography, the guiding balloon-catheter is introduced into the left ventricle and the balloon is inflated with CO\textsubscript{2}. Next, the fiberscope is introduced via the guiding catheter until the tip is at the most distal end of the guiding catheter. The balloon is then gently placed against the endocardial surface. Because the balloon protrudes 5 mm beyond the catheter tip, the distance between the fiberscope’s tip and the endocardial luminal surface is maintained at almost 5 mm (Fig. 1C). The diameter of the visual field is approximately 1.2 cm in saline. Heparinized saline solution (10 IU/mL) is infused at a rate of 10 mL/s using a power injector for 5 s to displace the blood between the endocardial surface and the fiberscope. The position of the catheter tip was confirmed by injecting a contrast material (Fig. 1D and E). The guiding balloon-catheter is also pre-shaped for easy location on the target wall segment: an “S” or “crank” configuration for the anterior, apical, and inferior wall segments, a “J” configuration.

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**Fig. 1** Cardioscope and cardioscopy procedure. (A) Cardioscope. a: guiding balloon catheter. b: fiberscope incorporated in the catheter. (B) Cardioscope-guided endomyocardial biopsy system. a: guiding balloon catheter. b: bioptome. c: a fiberscope attached on the bioptome. (C) Procedure. a: shaft of guiding balloon catheter. b: balloon. A balloon catheter is introduced into the left ventricle, the balloon is inflated with CO\textsubscript{2} and pushed against the endocardial surface, heparinized saline is flushed to displace the blood, and cardioscopic observation is performed. (D) Left ventriculogram. Arrow: observed apical segment. (E) Confirmation of the observed apical segment of the left ventricle by injecting a contrast material (arrow). Ao: aorta, LV: left ventricle, MV: mitral valve. Reproduced with permission of Uchida.\textsuperscript{11}
for lateral wall segments, and an “L” configuration for the high posterior wall segments. Similarly, the guiding catheter is pre-shaped for observation of the right atrium, right ventricle, and left atrium. For observation of the aortic, mitral, and tricuspid and pulmonary valves, it is necessary to use a guidewire to anchor the catheter tip for observation.  

**Cardioscope-Guided Endomyocardial Biopsy**

A cardioscope-guided biopsy system has been devised to safely guide endomyocardial biopsy and to confirm changes in the biopsied portion. A 1.6-F fiberscope is attached to a bioprome and introduced through either the 9-F guiding balloon-catheter or a 9-F soft-tipped catheter into the cardiac chamber, and a biopsy is taken while observing the area to be biopsied (Fig. 1B).  

**Combined Use of Cardioscopy and Intracardiac Ultrasonography**

The cardiac chambers and valves are usually observed by cardioscopy in combination with combined use of cardioscopy and intracardiac ultrasonography (ICUS). An ICUS probe is introduced through the right femoral artery into the left ventricle, guided by a 0.035-inch guide wire. The guide wire is first advanced to the apex, and then the probe is advanced to the apex. Radiofocus guide wire (Terumo Corporation, Tokyo, Japan) is recommended to use because it is very steerable. Pulling back the probe slowly, pineapple-like slices of the left ventricle from the apex to the aortic valve can be successively obtained. Details of this procedure are described elsewhere.  

**Cardioscopic and Intracardiac Ultrasonographic Changes in the Cardiac Chambers**

Coronary artery disease

Endocardial color has been reported to indicate the severity of myocardial ischemia and fibrosis. The endocardial surface is brown in color when observed by flushing saline solution and three myocardial layers can be seen on ICUS in patients without heart disease.

The endocardial color of the left ventricular wall is brown, light brown, and pale (bluish white closely resembling the endocardial color of the Langendorf heart in patients with coronary artery disease [CAD], in which the blood is replaced by an artificial solution, and white in patients with coronary artery disease [CAD], in which the blood is replaced by an artificial solution). Regional left ventricular contraction assessed by ICUS is usually normokinetic in light-brown segment, hypo-to-akinetic in pale segment, and akinetic-to-dyskinetic in white segment.

Regional myocardial blood flow (MBF) is slightly reduced in light-brown segment, severely reduced in pale segment, and absent in white segments on exercise thallium-scintigraphy (Fig. 2 A1–D1). No obvious histological changes are observable in light-brown or pale segment, but fibrosis is often observed in white segment (Fig. 2 A2–D2). These endocardial colors; however, do not correlate significantly with the severity of stenosis of the irrigating epicardial artery or collateral development, suggesting that regional microcirculation is the determinant of regional subendocardial MBF and, accordingly, endocardial color.  

**Idiopathic myocarditis**

Endomyocardial biopsy is essential to make a definite diagnosis of myocarditis. However, when fluoroscopy is used to guide endomyocardial biopsy, chance decides whether or not the diseased myocardium is biopsied, possibly leading to misdiagnosis. If endocardial surface changes are indicative of the stage of myocarditis, staging of myocarditis can be performed by percutaneous cardioscopy, enabling observation of the cardiac chambers from within, and targeted cardioscope-guided biopsy can be performed for accurate histological diagnosis. Cardioscope-guided endomyocardial biopsy has been performed in patients with idiopathic myocarditis and the left ventricular endocardial color and histological changes compared. In contrast to the brown color seen in patients with normal histology, the endocardial surface is red (Fig. 3A), milky white, purple, white, or yellowish brown in patients with idiopathic myocarditis. Biopsy specimens obtained from red and milky white segments exhibited histological changes indicative of acute myocarditis, purple segments were active chronic myocarditis, and yellowish brown and white segments were inactive chronic myocarditis.  

Cardioscopic follow-up studies revealed that a red or milky-white surface changed to purple or white, and a purple surface often changed to white or yellowish brown, indicating transformation of the inflammatory stage (Fig. 3B). The sensitivity, specificity, and predictive values of red or milky-white endocardial color for histologically diagnosed acute myocarditis were 100%, 100%, and 100%, respectively; those of the purple endocardial color for histologically diagnosed chronic active myocarditis were 83%, 92%, and 75%, respectively; and those of white or yellowish-brown endocardial color for chronic inactive myocarditis were 82%, 74%, and 53%, respectively. Thus, the red, milky-white, and purple colors of the left ventricular endocardium observed by cardioscopy can represent the histological stages of acute and chronic active myocarditis but not of chronic inactive
Fig. 2  Cardioscopic, $T_1$-scintigraphic and histological images of the left ventricle in patients with coronary artery disease.  
(A-D) Brown, light brown, pale, and white endocardial color on cardioscopy. Arrows are trabeculae. (A1-D1) exercise $T_1$-scintigraphy. Corresponding normal myocardial blood flow (A1) with no obvious histological changes (A2) in a brown segment; mildly reduced flow (B1) with no obvious histological changes (B2) in a light-brown segment; severely reduced flow (C1) with slight fibrosis and interstitial edema (C2) in a pale segment; and severely reduced flow (D1) and fibrosis (D2) in a white segment. Arrows in (A-D: arrows) trabeculae. (A1-D1: arrows) anteroapical segments (arrows). (D2: arrow) fibrosis.

Fig. 3  Relationship between endocardial color and biopsy findings in a patient diagnosed as idiopathic acute myocarditis.  
(A) Red endocardial color on cardioscopy. (B) Biopsied specimen of the same segment reveals mononuclear, polymuclear cell infiltration and interstitial edema (Eosin stain). (C) The same segment at 6 months later shows endocardial color changed to white on cardioscopy. (D) Biopsied specimen of the same segment reveals interstitial fibrosis and cardiomyocyte degeneration. Reproduced with permission of Uchida.15

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Percutaneous Cardioscopy
myocarditis.16) This imaging tool is therefore considered to be feasible for staging and following active stage of idiopathic myocarditis.14, 16, 17)

Idiopathic hypertrophic cardiomyopathy
The left ventricular cavity in patients with hypertrophic cardiomyopathy (HCM) usually disappears on left ventriculography and ICUS because of the vigorous contraction. Trabeculae are light-brown, thick, and attached to each other during systole. In the dilated phase, contraction is reduced on ventriculography, but thick trabeculae remain visible on ICUS. The ventricular luminal surface is white because of endocardial fibrosis in the majority of patients with this condition.18)

Idiopathic dilated cardiomyopathy
In general, the left ventricular endocardial color is white or yellowish brown and trabeculae are thin and atrophic in patients with dilated cardiomyopathy (DCM). Because the endocardial color resembles that of inactive idiopathic myocarditis, histological examination is essential to make a definitive diagnosis.13)

Subendocardial Microvessels
The coronary microvessels play a direct and critical role in determining the extent and severity of myocardial ischemia and symptoms, as well as preservation of cardiac function. Involvement of microvessel dysfunction is suspected, but not confirmed, in the slow-flow or no-flow phenomenon associated with percutaneous coronary intervention,19) Takotsubo cardiomyopathy,20) peripartum cardiomyopathy,21) syndrome X,22) and microvessel angina.23) Direct visualization may help to elucidate the mechanisms of these heart diseases. However, there are currently no clinically available methods for direct imaging of coronary microvessels in patients in vivo.

The subendocardial microvessels can be observed using cardioscopy in patients with CAD. Arterial microvessels (arterioles) were located either beneath the endocardium or exposed in the left ventricular cavity, whereas venous microvessels (venules) are located beneath the endocardium (Fig. 4).9) Subendocardial arterial and venous microvessels located in normokinetic-to-hypokinetic left ventricular wall segments fill with the blood during diastole and collapse during systole. In contrast, the same microvessels located in akinetic-to-dyskinetic wall segments fill with blood during systole and collapse during diastole. No significant correlation has been found between these changes and the severity of stenosis of the irrigating epicardial coronary arteries or collateral development. These findings suggest that the contractile state of the myocardium is the main determinant of the timing of perfusion of the subendocardial microvessels in patients with CAD.24)

Intraventricular Thrombi
It is well known that a fibrillating left atrium is a site of thrombus formation, acting as a major source of thromboemboli in cerebral ischemic attacks.25-28) It is also known that the left ventricle is a site of thrombus formation in the post-infarction state.29) Other heart diseases, such as peripartum cardiomyopathy,26) DCM,30) acute myocarditis,31) and antiphospholipid syndrome32) may cause cerebral embolism.34, 35) However, the exact incidence of left ventricular thrombus (LVT) in various categories of heart disease is unclear because of the lack of systematic surveys.
In a previous cardioscopy study, LVT was detected in 26% of 258 patients with heart diseases. Cardioscopically, LVT are classified by shape as globular (protruding) or mural (lined), and by color as red, white, or yellow. The majority of LVTs detected are mural. The LVT has been detected in 12.5% of patients with stable angina, 0% with unstable angina, 45.2% with acute myocardial infarction, 23.5% with old myocardial infarction, 61.9% with idiopathic acute myocarditis, 44.3% with idiopathic chronic myocarditis, 33.3% with rheumatic valvular disease, 25.7% with DCM, and 8.0% with HCM. The LVT detection rates using cardioscopy, left ventriculography, noncontrast echocardiography, and contrast echocardiography were 30.2%, 2.7%, 1.9%, and 7.0%, respectively. Thus, LVT is common in patients with various heart diseases, especially acute myocardial infarction and acute myocarditis. Such a high incidence of small endocardial mural thrombi might be due to endocardial damages and resultant loss of anti-thrombogenicity of the endocardial cells caused by these diseases. These thrombi might act as an origin of so-called "cerebral thromboembolism of unknown origin."

**Observation of Normal and Diseased Cardiac Valves**

On cardioscopy, normal aortic cusps and mitral leaflets are smooth-surfaced and sharp-edged and their opening and closure process can be seen. In contrast, in rheumatic valvulitis both the aortic cusps and mitral leaflets are yellow-colored, thick, and blunt-edged. Cardioscopic observation of the cardiac valves and their surrounding tissues may help decision-making of surgical techniques.

**New Cardioscopic Modalities**

**Dye-staining cardioscopy**

Structurally, the left ventricular wall of the heart has three myocardial layers, namely the inner oblique, middle circular, and outer oblique. The inner oblique layer is the most susceptible to ischemia. To date, the myocardial microcirculation has been evaluated by contrast echocardiography, magnetic resonance imaging, and positron emission tomography, among others. However, evaluation of the microcirculation in the individual myocardial layers, especially in the inner oblique layer, namely the subendocardial myocardium, is beyond the scope of these imaging modalities.

When injected into the vessels, Evans blue dye (EB) stains the vascular wall and its surrounding tissues into blue, but its diffusion into the interstitial space is very slow, and therefore can be used for visualization of blood flow.

During observation of a wall segment, a selective bolus injection of 1 mL of 2% EB solution into the irrigating coronary artery will stain wall segment when the artery is patent, but there is no or only partial staining when the artery is obstructed or stenosed. The endocardial surface stained diffusely blue with EB indicates normal blood flow in the majority of patients with chest pain syndrome; patchy staining indicates disturbed patchy blood flow in patients with vasospastic angina; and patchy or no staining indicates patchy or no blood flow in patients with angina or myocardial infarction.

**Fluorescent cardioscopy for evaluation of subendocardial myocardial tissue fluid flow**

Myocardial tissue fluid flow (MTFF) transports O₂ and nutrients to the cardiomyocytes, retrieves CO₂ and metabolites from the cardiomyocytes and transport them to the venous system.

Fluorescein generates fluorescence at 520 nm when excited by 470 nm light, and it is used clinically to evaluate the retinal vessels. Within the vessels, this dye does not exhibit fluorescence but exhibits fluorescence when it is separated from the blood. When injected into the vessels, it diffuses very rapidly through the microvessels of the arterial side into the interstitial spaces of the tissues, and finally drains into the venous system. Therefore, if this dye can be visualized in the myocardium in vivo, real-time evaluation of MTFF can be achieved.

The fluorescent cardioscopy (FC) images are classified as follows: diffuse with high intensity, indicating normal MTFF; diffuse but with low intensity, indicating decreased MTFF, no fluorescence indicating absent MTFF; patchy fluorescence, indicating patchy preservation of MTFF. MTFF was normal in the majority of patients with chest pain syndrome, patchy or decreased, or absent in patients with angina and/or myocardial infarction.

**Evaluation of Medical, Interventional, and Surgical Therapies**

**Effects of coronary dilators on subendocardial MBF**

The subendocardial myocardial layer is most susceptible to ischemia, so improving the blood flow in this layer is an essential requisite for the treatment of CAD. Nitroglycerine (NTG) is a well-known antianginal agent, but whether NTG increases blood flow in the subendocardial myocardial layer is controversial. Changes in subendocardial MBF induced by the intravenous administration of 200 μg of NTG were examined using cardioscopy in patients with CAD. On administration of NTG, the endocardial color changed to red in brown and light brown segments, indicating arterial blood filling. Variable changes were seen in pale segments: turning purple indicates venous blood filling; turning red indicates...
arterial blood filling; no change indicates no blood filling. NTG-induced changes in endocardial color were therefore closely related to the color before NTG. Although there was a tendency for arterial blood filling to occur in segments irrigated by a less stenotic artery, with developed collaterals and with well-preserved contraction, the difference was not statistically significant. It is conceivable that regional microvessels, and not large epicardial coronary arteries, directly mediate the effects of NTG on subendocardial MBF.

Evaluation of percutaneous coronary interventions by dye-staining cardioscopy or fluorescent cardioscopy

Figure 5 shows dye-staining cardioscopy before and after successful percutaneous coronary interventions (PCI) (POBA) in a patient with acute myocardial infarction. The endocardium was not stained before but diffusely stained blue with EB after PCI, indicating restoration of myocardial blood flow. Dye-staining cardioscopy performed using EB before and after PCI in patients with CAD showed that despite successful recanalization of the epicardial coronary artery, the endocardial surface did not always stain with EB, indicating that the coronary microcirculation was not necessarily restored by apparently successful epicardial coronary recanalization.

Figure 6 shows FC images of the left ventricle before and after PCI (stenting) of the left anterior descending artery. Before stenting, fluorescence was weak and spotty, but became intense and diffuses after stenting, indicating restoration of MTFF. After successful PCI, however, MTFF does not necessarily normalize, indicating that successful epicardial coronary recanalization...
Evaluation of percutaneous transseptal mitral commissurotomy

Figure 7 shows the posterior commissure of the mitral valve in a patient with rheumatic mitral stenosis. The fused commissure that was separated using percutaneous transseptal mitral commissurotomy (PTMC) was clearly demonstrated by cardioscopy. Cardioscopy can be used for the evaluation of catheter-based commissurotomy not only of the mitral valve, but also other cardiac valves.⁹

Evaluation of cardiac surgery

Cardioscopy has been used to evaluate surgical treatment of congenital heart diseases, such as atrial septal defect, anomalous pulmonary vein drainage, and aortic disease. However, observation of artificial valves should be avoided because of the risk of valvular damage.⁹

Observation of the Heart from Outside — Pericardioscopy

In 1994, percutaneous pericardioscopy was developed for pericardial fenestration to prevent pericardial tamponade in patients with idiopathic effusive pericarditis and pericardioscopy-guided biopsy in patients with carcinomatous pericarditis (Fig. 8).⁹

Other Reports

Cardioscopic observation of the cardiac interior was performed...
**Fig. 7** Evaluation of PTMC in a 44-year-old woman with rheumatic mitral stenosis. (A: arrows) Mitral valve before PTMC. (B: arrow) During commissurotomy by balloon inflation. (C) Fusion of the posterior commissure before PTMC. (C1: arrow) Separation of the fused commissure by PTMC. PTMC: percutaneous transseptal mitral commissurotomy. Reproduced with permission of Uchida.

**Fig. 8** Percutaneous pericardioscopy. (A) Schematic representation of percutaneous pericardioscopy procedure. An 8-F sheath is introduced by xiphoid approach, pericardial effusion is replaced by warmed heparinized saline solution, and pericardioscopy is performed. When necessary, epicardial tissue is biopsied for histological examination, especially when carcinomatous pericarditis is suspected. (B) Effusive hemorrhagic pericarditis. Arrow: Mural thrombus on the epicardium. Arrowhead: pericardium. (C) Carcinomatous pericarditis (metastasis from esophageal carcinoma). (C: arrow) Carcinomatous node. Reproduced with permission of Uchida.
mostly during open-heart surgery. Bauer et al. observed left ventricular cavity by introducing a fiberscope from the aorta; Miyaji et al. observed cardiac defects during open heart repair in children; Ngague et al. observed LVTT; Ohtsuka et al. observed left atrium during cryoablation; Pelella et al. observed left ventricular tumor, but no reports on percutaneous transluminal cardioscopy have been found.

Future Prospective
Cardioscope-guided intracardiac treatment
Cardioscope-guided myotomy, myectomy, and valvulotomy have been trialed in animals. These therapeutic modalities will be available soon for application in clinical situations.

Cardioscope-guided trans-endocardial angiogenic and myogenic therapies
About 15% of patients with ischemic heart disease are not indicated for surgical or other interventions. At present, no other curative treatments are available. Myocardial salvage through the formation of new blood vessels by either angiogenesis or vasculogenesis (angiogenic therapy) is a promising therapeutic modality for these patients. Cardioscope-guided trans-endocardial angiogenic therapy has been trialed in animals. Using dye-staining and FC, pin-point angiogenic and myogenic therapy can be performed with more precision in the clinical situation.

Conclusions
Recent advances in cardioscopy technology enable observation of the interior of the heart. This imaging technology is now used for the diagnosis of myocardial and valvular diseases, evaluation of the severity of myocardial ischemia, interventional and surgical treatments, and for guidance of endomyocardial biopsy. In the near future, it will be used for the guidance of transcatheter interventional and surgical treatments of various heart diseases as in case of endoscope-guided intra-abdominal surgery.

Disclosure Statement
No potential conflict of interest relevant to this article was reported.

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