The Role of Cardiac Computed Tomography in Infants with Congenital Heart Disease

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ABSTRACT: **Background:** Patients with complex congenital heart disease (CHD) have a high incidence of extracardiac vascular and non-vascular malformations. Those additional abnormalities may have an impact on the precise planning of surgical or non-surgical treatment.

Objectives: To assess the role of electrocardiography-gated CT-angiography (ECG-CTA) in the routine evaluation of CHD in neonates and infants particularly for the assessment of extracardiac findings.

Methods: The study cohort comprised 40 consecutive patients who underwent trans-thoracic echocardiography (TTE) and ECG-CTA. TTE and ECG-gated CTA findings regarding extracardiac vascular structures, coronary arteries and airways were compared with surgical or cardiac catheterization findings. Scans were evaluated for image quality using a subjective visual scale (from 1 to 4). Effective radiation dose was calculated for each scan.

Results: Median age was 28 ± 88 days and mean weight 3.7 ± 1.5 kg. Diagnostic quality was good or excellent (visual image score 3–4) in 39 of 40 scans (97.5%). ECG-CTA provided important additional information on extracardiac vascular structures and airway anatomy, complementing TTE in 75.6% of scans. Overall sensitivity of ECG-gated CTA for detecting extracardiac findings as compared with operative and cardiac catheterization findings was 97.6%. The calculated mean effective radiation dose was 1.4 ± 0.07 mSv (range 1.014–2.3 mSv).

Conclusions: ECG-CTA is an accurate modality for demonstrating extracardiac structures in complex CHD. It provides important complementary information to TTE with regard to extracardiac vascular structures and coronary artery anatomy. This modality may obviate the need for invasive cardiac catheterization, thus exposing the patient to a much lower radiation dose.

IMAJ 2014; 16: 147–152

KEY WORDS: cardiac computed tomography, neonates, infants, congenital heart disease (CHD)

Comprehensive anatomic evaluation in complex congenital heart disease is critical for effective patient management. Trans-thoracic echocardiography and cardiac catheterization serve as the mainstay modalities in complex CHD initial evaluation. A high incidence of extracardiac vascular and non-vascular malformations is characteristic of this patient group. Those additional common abnormalities may have an impact on the precise planning of corrective or palliative surgical or non-surgical treatment. In patients with complex CHD, TTE with color Doppler provides excellent definition of the intracardiac anomalies including hemodynamic evaluation as well. However, TTE is limited in delineating extracardiac thoracic structures such as the aorta and the aortic arch branches, the pulmonary arteries and their branches, the pulmonary veins, or associated other vascular structures and airways. Cardiac catheterization supplies most of the additional required information, but it is invasive in nature and therefore carries inherent complications apart from the exposure to ionizing radiation and iodinated contrast administration [1,2]. Moreover, cardiac catheterization is not informative regarding associated airway pathology.

The ability of electrocardiography-gated computed tomography-angiography to precisely volumetrically image the morphologic features of complex CHD has been well demonstrated in adults and young patients [3-6]. Although previous series suggested that ECG-CTA is a reliable modality for the diagnosis of complex CHD in infants, it is not yet recommended for the routine evaluation of young infants, especially neonates with complex CHD [4,7-9]. Cardiac magnetic resonance imaging is widely used for the non-invasive evaluation of children with complex CHD; however, in very young or clinically unstable neonates or infants it bears significant disadvantages. Cardiac MRI requires a longer and deeper anesthesia compared with CT (with its inherent risks), while ECG-CTA requires a very short anesthesia duration or can be performed with sedation only [10]. The related spatial resolution of cardiac MRI is lower as compared to ECG-CTA, a crucial difference when imaging structures

CHD = congenital heart disease
TEE = trans-thoracic echocardiography
ECG-CTA = electrocardiography-gated computed tomography-angiography

< 1 mm in size, which may be the case in neonates or infants with complex CHD [10,11]. In the present study we summarize our preliminary experience using ECG-CTA as a complimentary modality for TTE in neonates and infants with complex CHD.

PATIENTS AND METHODS

The study included 40 consecutive neonates and infants with complex CHD who underwent ECG-CTA scans between November 2008 and August 2010. TTE was performed in all patients according to the standard of performance of pediatric echocardiography using a diagnostic ultrasound system (IE 33 Philips Medical Systems North America, Bothell, WA, USA) [12]. All TTE examinations were interpreted by an experienced pediatric cardiologist. ECG-CTA scans were performed after the TTE; the readers were aware of the echocardiographic findings and read the CT scans while using the information supplied earlier by the echocardiography. Ten patients underwent diagnostic or therapeutic cardiac catheterization and 30 patients were operated on. ECG-CTA findings were validated with either the operative (30/40) or cardiac catheterization findings (10/40). ECG-CTA scans were performed and interpreted by a dedicated experienced team comprising a cardiovascular radiologist and a pediatric cardiologist (blinded). All patients were sedated using midazolam 0.1 mg/kg and monitored for respiration, saturation, heart rate and blood pressure. Scans were performed using a 64 (n=6) and 128 slice (n=34) scanner (Brilliance 64 and ICT SP and, Philips Medical Systems, Cleveland, OH) implementing retrospective ECG-gating. The whole chest from the level of the clavicles to the diaphragm was included in all scans. Imaging parameters were as follows: average voltage 88 ± 2.6 KvP (range 80–100), average amperage 114 ± 4.2 mAs (range 65–150), pitch 0.2, slice thickness 0.625 mm, average gantry rotation 0.32 seconds (range 0.27–0.4). Intravenous contrast (Iomeron 350, Iomeprol, BRACCO s.p.a, Milan, Italy) was administered at a volume of 2–3 ml/kg using a dual-head injector (GE Nemoto, GE Healthcare Systems, USA) at a rate of 2–3 ml/sec followed by a 1–1.5 ml/kg saline flush at the same injection rate. Scans were started manually 2–4 sec after administration of contrast media.

DIAGNOSTIC VISUAL SCORE

ECG-CTA studies were evaluated for study quality using a subjective visual score (1–4): 1 = very poor image quality, requested anatomic structure not visualized; 2 = poor image quality or anatomic detail; 3 = good anatomic definition, further anatomic evaluation not required; 4 = excellent anatomic definition, all structures were clearly interpretable [3,13].

EXTRACARDIAC STRUCTURES

The following vascular structures were evaluated: pulmonary arteries (including peripheral branches), thoracic aorta (throughout its length), superior and inferior vena cava, patent ductus arteriosus, pulmonary veins, airways, and collateral circulation. The origin and course of the coronary arteries (left anterior descending, left coronary, right coronary) were evaluated in each study.

ECG-CTA findings were compared with TTE findings and classified as follows: a) similar information, i.e., the information obtained by both modalities was comparable; b) additional information, i.e., the information gathered from ECG-CTA added information to that obtained by TTE; or c) the information obtained from ECG-CTA was different from TTE. ECG-CTA findings were compared with either the operative (30/40) or cardiac catheterization (10/42) findings, which served as the standard of reference for the diagnosis.

RADIATION EXPOSURE

Dose-length product was recorded in each case. Estimated effective radiation dosages (mSv) were calculated for each scan using the following equation: DLP x 0.039 (infants < 4 months old) or 0.026 (infants > 4 months to 1 year old) [13].

The study was approved by the institutional review board. The study was retrospective and therefore informed consent was not obtained from the patients.

RESULTS

ECG-CTA scans were performed in 40 patients of whom 17 were males. Median age was 28 ± 88 days (range 1–270 days); 31/42 patients (69%) were neonates < 30 days old. Mean weight was 3.7 ± 1.5 kg (range 1.8–8.2), and mean heart rate during the scan was 131 ± 16 beats per minute (range 99–160 bpm). Average scan length was 97 ± 14 mm (range 67–129 mm). Average scan duration was 6.9 ± 1.06 seconds (range 4.5–9.1 sec).

The types of malformations were: tetralogy of Fallot (n=10), truncus arteriosus (n=8), transposition of great arteries (n=7), aortic coarctation (n=5), atrioventricular canal (n=5), hypoplastic left heart (n=4), aortic dilatation (n=1), Williams syndrome (n=1), and coronary anomaly (n=1). Of the 40 patients in the study cohort, 30 (75%) were operated on, in all cases after the initial ECG-CTA studies. Cardiac catheterization was performed in 10/40 patients (25%), of whom 5 were part of the initial diagnostic evaluation, and for the rest therapeutic procedures (3/10) and catheterization were performed for hemodynamic measurements (2/10).

DIAGNOSTIC VISUAL SCORE

Excellent diagnostic visual score (score 4) was achieved in 35 of 40 scans (87.5%), while good diagnostic score (score 3) was achieved in 4/40 scans (10%). Poor visual score (score 2) was seen in 1/40 scans (2.5%) because of suboptimal contrast timing and motion artifacts due to suboptimal sedation.

DLP = dose-length product

DIAGNOSTIC DEFINITION OF EXTRACARDIAC STRUCTURES

Table 1 summarizes the demonstration of extracardiac anatomic structures by both TTE and ECG-CTA.

ECG-CTA contributed additional anatomic information on the pulmonary arteries in 66% of the referred patients, including definition of pulmonary branches in truncus arteriosus (n=9) [Figure 1], detection of pulmonic atresia (n=6), pulmonic stenosis (n=1), and peripheral pulmonic stenosis (n=2). Comprehensive imaging of the aorta along its entire thoracic course added diagnostic information in 76% of the cases including definition of truncus arteriosus types and aortic arch interruption (n=9) [Figure 1], detection of undiagnosed aortic coarctation (n=2), aortic thrombus detection (n=1), and tortuous aorta (n=1). Major aortopulmonary collateral vessels were demonstrated in 12 cases, only 1 of which was detected at TTE. One case of undiagnosed patent ductus arteriosus (by TTE) was detected at ECG-CTA and one case of PDA was undiagnosed by ECG-CTA and correctly detected by TTE. Information regarding pulmonary vein abnormalities was obtained by ECG-CTA in 83% of cases, including 5 anomalies that were diagnosed at CTA but not at TTE: partial anomalous pulmonary veins (n=3), total anomalous pulmonary venous return (n=1), and sinus venosus defect (n=1). Newly detected left persistent superior vena cava was found in 4/4 cases on ECG-CTA. As expected, airway narrowing was detected only by ECG-CTA (n=3) and not on TTE [Figure 2]. Patency of a Glenn shunt was demonstrated at ECG-CTA in 2/2 cases but not on TEE. Overall, ECG-CTA added relevant clinical information in 75.6% of the cases on average.

CORONARY ARTERIES

LAD, LCX and RCA origin and course were demonstrated in 38 (95%), 36 (90%) and 34 (85%) scans, respectively [Figure 3]. Coronary anomalies were demonstrated in 5 cases (12.5%), including anomalous origin of LAD from the pulmonary artery (n=1), discordant coronary anatomy in corrected transposition of the great arteries (n=2), high and posterior origin of the left coronary artery in truncus arteriosus (n=1), and a prominent conal branch bifurcating into a left anterior coronary artery coursing anterior to the right ventricular outflow tract in a case of tetralogy of Fallot (n=1). When compared with joint surgical (30/40) and catheterization (10/42) findings the sensitivity of ECG-CTA was 97.6%.

RADIATION EXPOSURE

The mean calculated effective dose related to the ECG-CTA scans was 1.4 ± 0.07 mSv (1.014–2.3 mSv).

PDA = patent ductus arteriosus
LAD = left anterior descending artery
LCX = left coronary artery
RCA = right coronary artery

Table 1. Extracardiac anatomic structures as demonstrated by trans-thoracic echocardiograpy and gated-CT angiography

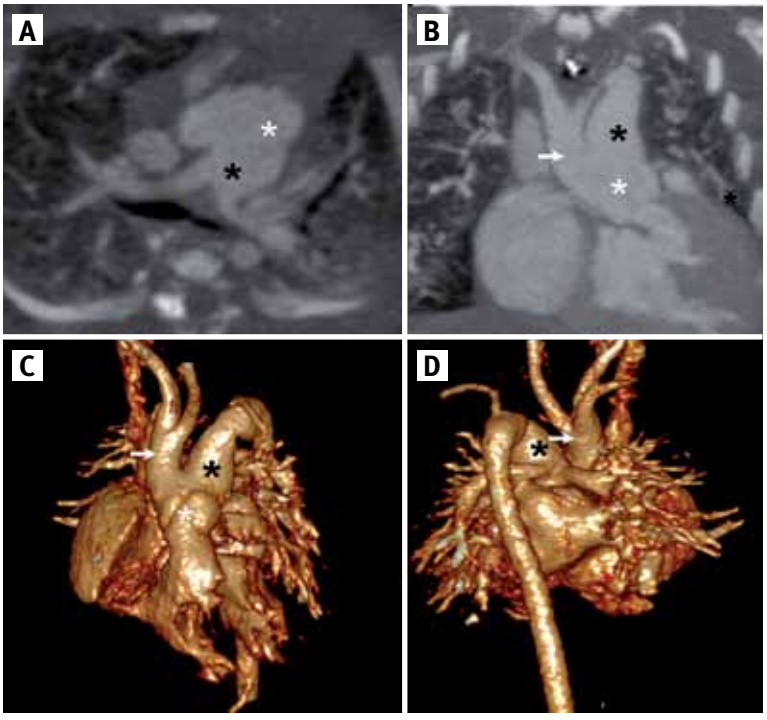
Anatomic structure	No. of cases	No. of cases with pathology	Added information* n, (%) CT or TTE
Pulmonary arteries	40	27/40	18/27 (66.6%) all CT
Aorta and truncus arteriosus	40	17/40	13/17 (76.5%) all CT
Collateral vessels	40	12/40	11/12 (91.7%) all CT
Patent ductus arteriosus	10	9/40	1/9 (11.1%) CT; 1/9 (11.1%) TTE
Pulmonary veins	40	9/40	5/6 (83.4) all CT
Persistent left SVC	40	6/40	4/4 (100%) all CT
Airways	40	3/40	3/3 (100%) all CT

*Gated-CTR angiography provided additional information as compared with trans-thoracic echocardiography

TTE = trans-thoracic echocardiography, SVC = superior vena cava

Figure 1. A 7 day neonate (2.4 kg) scanned for the definition of truncus arteriosus. Kvp 80, mAs 150, DLP 41; effective dose = 1.59 mSv. TA = tuncus arteriosus, PA = pulmonary artery, IAo = interrupted aortic arch

[A] Axial image: TA (white asterisk), PA (black asterisk). **[B]** Multi-planar reformats: TA (white asterisk), PA (black asterisk). IAo (arrow). **[C]** Volume rendering, anterior view: TA (white asterisk), PA (black asterisk). IAo (arrow). **[D]** Volume rendering, posterior view: PA (black asterisk). IAo (arrow)



DISCUSSION

The efficacy of CTA in depicting intra- and extracardiac anomalies in complex CHD has been demonstrated in several studies [3,4,7-9,14-19]. Most of these studies comprised

Figure 2. A 14 day neonate (3.1 kg) scanned for the evaluation of tetralogy of Fallot with absent pulmonic valve, huge left pulmonary artery causing significant stenosis of the left main-stem bronchus. Kvp 80, mAs 150, DLP 4. Effective dose = 1.67 mSv. Lmbr = left main-stem bronchus, LPA = left pulmonary artery, rtAo = right aortic arch
[A] Maximal intensity projection: Lmbr (white arrow), LPA (white asterisk). **[B]** Volume rendering, posterior view: Lmbr (white arrow), LPA (white asterisk). **[C]** VR anterior view: LPA (white asterisk), rtAo (black asterisk). **[D]** VR lateral view: LPA (white asterisk), rtAo (black asterisk)

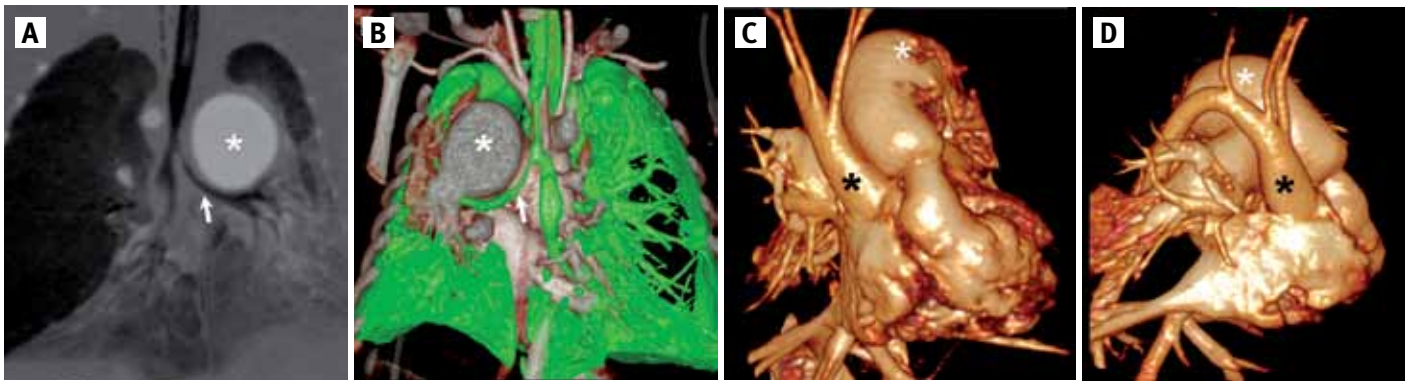
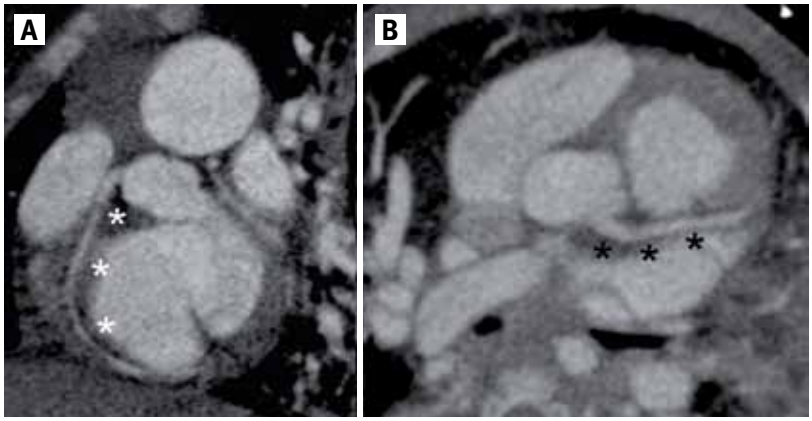


Figure 3. A 7 month neonate (5 kg) with atrioventricular canal, dilated right ventricle and small aortic arch. The coronary arteries are demonstrated. Kvp 80, mAs 150, DLP 50. Effective dose = 1.95 mSv. RCA = right coronary artery, LAD = left anterior descending artery
[A] Multi-planar reformats: RCA (white asterisks). **[B]** Axial image: LAD (black asterisks)



patients in a wide age range and included only a limited number of newborns and infants. The clinical impact of performing ECG-CTA in infants and neonates was hardly presented in these studies. The current study specifically addressed a population of newborns and infants (median age 28 days). The study was designed to question the suggestion that the incorporation of ECG-CTA in the initial workup of complex CHD could improve the diagnostic accuracy together with TTE, obviating the need for routine diagnostic cardiac catheterization. Current data in the literature stress the important role of ECG-CTA in the diagnosis of complex CHD but lack a detailed comparison with TTE [3,4,8]. Therefore, to the best of our knowledge this is the only study comparing ECG-CTA to TTE, with regard to the added information and value that ECG-CTA offers. In accordance with previous series, we also found that the main added value of ECG-CTA lies in elucidating the precise extracardiac anatomic structures, not adding significant information on intracardiac abnormalities [4,6-9,14,20]. Indeed, ECG-CTA proved superior to TTE in delineating the extracardiac vascular and airway details, adding relevant clinical information in 79% of the cases on average. The three-dimensional datasets provided by CTA allow accurate anatomic depiction, specifically in relation to adjacent anatomic structures [21,22]. Not surprisingly, airway abnormalities were detected only by ECG-CTA.

When planning surgical intervention, the detection of coronary anomalies, which are frequently associated with complex CHD, is of major significance in order to avoid fatal complications during surgery due to incorrect anatomic information [6,15]. Ben Saad and colleagues [3] stressed the importance of ECG-gating for imaging of the coronary arteries. They were able to demonstrate the left and right coronary systems in 90% and 84% of patients, respectively. These results are comparable with our findings. Due to EGC-gating in the entire study cohort, the origin and course of the coronary arteries could be demonstrated in most patients (ranging from 85% for RCA to 95% for LAD) despite the very high heart rates (range 99–160 bpm). High diagnostic image

quality (average image quality 3.78) was achieved in 97.5% of cases. Ben Saad et al. [3] documented a slightly lower diagnostic performance (89%); this could be attributed to the lack of ECG-gating in two-thirds of their cohort [3]. The advantage of applying ECG-gating for the accurate depiction of both intra- and extracardiac structures is reflected in the present study as well as in other studies using 128 and 320 slice scanners [7,23].

The reduced gantry rotation time in the latest generation CT scanners, reaching 0.27 seconds, also improves temporal resolution and image quality, especially in the high heart rates commonly present in this patient population. The comprehensive three-dimensional anatomic detailed information of the whole chest obtained by ECG-CTA allowed the cardiac surgeons and the cardiologists a high level of confidence when planning surgery or other alternative treatment in these complex cases. Only 12.5% of patients in this cohort were referred to diagnostic cardiac catheterization. Similar to our findings, several studies have suggested that ECG-CTA may replace diagnostic cardiac catheterization in the initial evaluation of complex CHD, but they focused on the neonate and infant population only occasionally [5,8].

Exposure to ionizing radiation in young infants is of particular concern due to their greater sensitivity to radiation and potential longer life span, which increases the risk of radiation-induced diseases developing. Although all the scans in the present study were ECG-gated, the average exposure was 1.4 mSv, comparable to the 1.3 mSv documented by Ben Saad et al. [3]. This finding indicates that diagnostically adequate gated CTA can be obtained at much lower radiation doses than commonly cited for diagnostic cardiac catheterization [20]. Additional decrease in radiation exposure doses is achievable with the newer scanners, which permit the combination of prospective ECG-gating in high heart rates yielding sub-mSv radiation exposures [6,7,9,23,24].

ECG-CTA has several advantages. These include: a) high spatial resolution, allowing accurate delineation of fine anatomic details; b) three-dimensional demonstrations of anatomic structures throughout the whole chest; c) the ability to show all vascular structures (arterial and venous, normal and abnormal) with relatively small contrast media volume; d) coronary artery origin and course depiction; e) airway delineation in relation to other structures in the chest, f) very short acquisition time (few seconds, necessitating brief sedation; and g) relatively low radiation exposure.

The main limitations of ECG-CTA include the lack of hemodynamic information, exposure to ionizing radiation, and the administration of iodinated contrast agents. ECG-CTA can obviate the need for diagnostic catheterization, reduce cardiac catheterization duration, lower the number of cardiac catheterization injections and therefore limit radiation exposure in cases where the latter is still required.

The main limitation of our research was that it was retrospective. Moreover, due to the nature of the clinical workflow in our institution, ECG-CTA analysis could not be performed blindly. Yet, we believe the additional valuable information supplied by ECG-CTA as analyzed and shown in the present study reflects "real life."

In conclusion, ECG-CTA is an accurate non-invasive imaging modality for demonstrating extracardiac structures in complex CHD. It has an important clinical complementary role to TTE that may obviate the need for or reduce the length of invasive cardiac catheterization and help refine treatment strategies. Our preliminary experience suggests that routine ECG-CTA should be considered in the standard initial evaluation of very young and sick neonates and infants with complex CHD.

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Capsule

Genetics of rheumatoid arthritis contributes to biology and drug discovery

A major challenge in human genetics is to devise a systematic strategy to integrate disease-associated variants with diverse genomic and biological data sets to provide insight into disease pathogenesis and guide drug discovery for complex traits such as rheumatoid arthritis (RA). Okada et al. performed a genome-wide association study meta-analysis in a total of › 100,000 subjects of European and Asian ancestries (29,880 RA cases and 73,758 controls), by evaluating ~10 million single-nucleotide polymorphisms. The authors discovered 42 novel RA risk loci at a genome-wide level of significance, bringing the total to 101. They devised an *in silico* pipeline using established bioinformatics methods based on functional annotation, *cis*-acting expression quantitative trait loci and pathway analyses – as well as novel methods based on genetic overlap with human primary immunodeficiency, hematological cancer somatic mutations and knockout mouse phenotypes – to identify 98 biological candidate genes at these 101 risk loci. They demonstrate that these genes are the targets of approved therapies for RA, and further suggest that drugs approved for other indications may be repurposed for the treatment of RA. Together, this comprehensive genetic study sheds light on fundamental genes, pathways and cell types that contribute to RA pathogenesis, and provides empirical evidence that the genetics of RA can provide important information for drug discovery.

Nature 2014; 506: 376

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Capsule

Broadly neutralizing hemagglutinin stalk-specific antibodies require FcγR interactions for protection against influenza virus in vivo

Neutralizing antibodies against influenza viruses have traditionally been thought to provide protection exclusively through their variable region; the contributions of mechanisms conferred by the Fc domain remain controversial. DiLillo et al. investigated the in vivo contributions of Fc interactions with their cognate receptors for a collection of neutralizing anti-influenza antibodies. Whereas five broadly neutralizing monoclonal antibodies (bNAbs) targeting the conserved stalk region of hemagglutinin (HA) required interactions between the antibody Fc and Fc receptors for IgG (FcγRs) to confer protection from lethal H1N1 challenge, three strain-specific monoclonal Abs (mAbs) against the variable head domain of HA were equally protective in the presence or absence of FcγR interactions. Although all antibodies blocked infection, only anti-stalk bNAbs were capable of mediating cytotoxicity of infected cells, which accounts for their FcγR dependence. Immune complexes generated with anti-HA stalk mAb efficiently interacted with FcγRs, but anti-HA head immune complexes did not. These results suggest that FcγR binding capacity by anti-HA antibodies was dependent on the interaction of the cognate Fab with antigen. The researchers exploited these disparate mechanisms of mAb-mediated protection to reengineer an anti-stalk bNAb to selectively enhance FcγR engagement to augment its protective activity. These findings reveal a previously uncharacterized property of bNAbs and guide an approach toward enhancing mAb-mediated antiviral therapeutics.

Nature Med 2014; 20: 143

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