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Coronary artery fixation at iso-arterial pressure: impacts on histologic evaluation and clinical management

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ABSTRACT

Coronary angiography is the standard imaging method for determining the site, extent, and severity of coronary artery disease. Several publications have reported discordance between the degree of coronary artery stenosis determined from post-mortem histologic evaluation and coronary angiography. While the 2-dimensional limitations of coronary angiography are well established, the determination of coronary stenosis based on histologic evaluation of passively fixed samples is also associated with significant biases. In this study, we used patients with chronic coronary artery disease to compare the stenosis severity estimates that were determined using the passive fixation method with those determined using the active fixation method. Our results showed a significant discrepancy between the stenosis in passively fixed coronary arteries when compared with coronary angiography in all major coronary vessels combined (P=.002), and in Cx (P=.045) and CD (P=.026). However, there was no mean difference when compared with perfused (actively fixed) samples when all vessels were combined or examined individually. Iso-physiologic mechanical perfusion (active) fixation yielded significantly reduced coronary artery stenosis means when compared to the passive fixation method in post-mortem evaluations during autopsies. This was evident when all vessels were combined (P=.0001) and assessed individually (Cx (P=.003), LAD (P=.025), LM (P=.056) and RC (P=.007)). Autopsies including cardiac explant patients also showed differences in estimates for all vessels combined (P=.0001) and in Cx (P=.016) and RC (P=.006). In summary, our quantitative histopathology analyses using perfused coronary artery stenosis at physiologic pressure showed significant discrepancies when compared with passive histopathology.
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1. Introduction

Chronic coronary artery disease (CAD) may lead to myocardial ischemia, which is one of the leading causes of mortality in industrialized countries [1], accounting for 7.6 million annual deaths worldwide [2]. It is widely recognized that 75% stenosis in the lumen cross-sectional area (LCSA) is sufficient to reduce the coronary arterial flow that is necessary to meet the myocardial oxygen demands during times of stress and exertion, while a narrowing of 90% causes ischemia at rest [3]. Forensic pathologists consider LCSA stenosis of 75% in at least one major coronary artery to be a sufficient explanatory factor in determining the cause of death of a patient [3–5].

Coronary angiography (CAG) is still the most widely used method for determining the site, extent and severity of CAD in clinical settings, and is common practice particularly during the preoperative work-up of cardiac surgery patients [6,7]. Although invasive, this procedure is often relied upon to evaluate patient prognosis and eligibility for surgical procedures, and to guide clinical management and administer treatment, especially since the advent of myocardial revascularization techniques such as

Abbreviations: AHP, active histopathology; CABG, Coronary artery bypass graft; Calc, Calculated; CAG, coronary angiography; LAD, Left anterior descending; IVUS, Intravascular ultrasound; LCSA, Lumen (or luminal) cross sectional area; LD, Lumen (or luminal) diameter; PHP, passive histopathology.

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percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) [6,8]. As the degree of stenosis bears such important implications for symptomatology correlation, prognosis prediction, clinical decision-making, treatment options and the determination of cause of death, it is evident that quantification methods should reflect the real "state" of stenosis associated with CAD as much as possible. Moreover, despite significant improvements in imaging techniques since the 1990s, discrepancies between CAG and histopathology are still observed in modern clinical settings [9–11].

Previous studies have reported substantial discordances when comparing the percentage of coronary artery stenosis determined from quantitative histologic methods to the percentage determined using CAG [6]. In fact, several investigators have reported findings of abnormal coronary arteries that were not visible using CAG, yet were well-established post-operatively or during autopsies [6]. These discrepancies have been a source of concern for cardiac surgeons and cardiologists as they may lead to an inaccurate assessment of a patient's cardiac state before they undergo a surgical procedure. This can have health implications for the patient as well as potential legal implications for the clinician.

Studies have shown that CAG also tends to underestimate the degree of coronary stenosis in comparison to pathological examinations [9,10,12–16]. Conversely, histopathology assessments tend to overestimate the percentage of stenosis, due to the relaxed and undistended state in which coronary arteries are traditionally fixed and examined, but also because pathologists estimate the severity of CAD by examining the internal elastic layer which is not possible through CAG [6].

In this project, we evaluated the impact of passive histopathological fixation (PHP) in the context of post-mortem and post-surgical histopathology analyses of coronary artery stenosis in patients with chronic CAD. We then compared the level of coronary artery stenosis determined using active histopathological fixation (AHP) as opposed to PHP. Finally, we assessed the effect of using AHP compared to in vivo coronary artery stenosis evaluation by CAG.

2. Methods

2.1. Patients

Between January 2013 and November 2015, 83 patients with ischemic cardiomyopathy, end-stage heart failure requiring transplantation, or undergoing cardiac autopsy in our center were evaluated. Patients with/or without accessible pre-surgical CAG data were selected. Between groups, patients were matched by sex and age in order to make more accurate comparisons. The study protocol was approved by the Quebec Heart and Lung Institute's Board of Ethics (project #21186).

2.2. Acquisition and analysis of histology data

Autopsied hearts collected during autopsy were fixed in 10% phosphate buffered formalin, either by passive immersion or by intra-aortic perfusion of the fixative at 80–85 mmHg for at least 12 h using a dedicated perfusion system (Fig. 1A-B). Hearts fixed by passive immersion were subdivided into two categories: autopsies with pre-mortem CAG and autopsies without CAG. The intra-aortic perfusion group was subdivided into 3 groups: forensic autopsies, medical autopsies and cardiac explants. The hearts that were examined and fixed more than 24 h after the time of death were excluded from analyses. The principal coronary arteries, namely the left main trunk (LM), the left anterior descending artery (LAD), the circumflex artery (Cx) and the right coronary artery (RCA) were dissected and serially sectioned (4 mm), and the proximal 5 cm were submitted for histological examination (table 1). Slides obtained were stained with Hematoxylin & Eosin (H&E) and Verhoeff von Gieson (Artisan stainer, Dako-Agilent Technologies and the dedicated histochemistry kit). They were then digitized at 20×

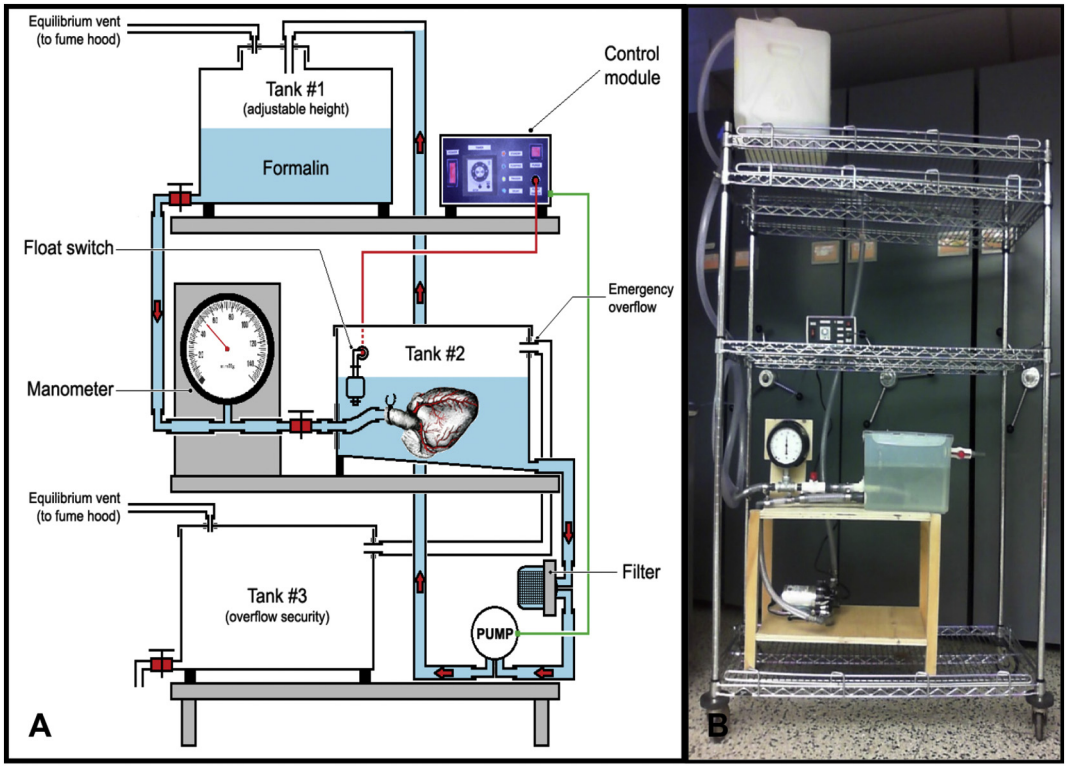
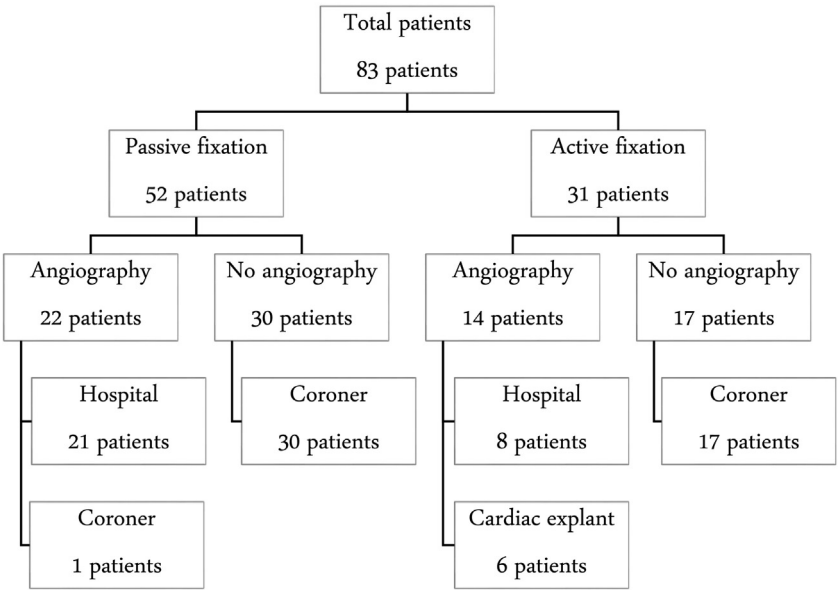


Fig. 1. Perfusion-fixation device. A) The device generates an intra-aortic pressure where the pressure is a function of the height of tank number 1. The pumping circuit recycles the used formalin by sending it back to the overhead tank (number 1). The perfusion flow is equal to 500 l per 24 h. B) Photograph of an intra-aortic perfusion device.

Table 1
Flow chart describing the patient population. Autopsy hearts were either fixed by passive immersion (n=52) or by active fixation (intra-aortic perfusion of formalin at 80–90 mmHg for at least 12 h) (n=31). Hearts fixed by passive immersion were subdivided into two categories: autopsies with pre-mortem angiography (n=22) and autopsies without angiography (n=30). The active fixation group was subdivided into three groups: coroner autopsies (n=17), hospital autopsies (n=8) and cardiac explants (n=6)



magnification with a Nanozoomer 2.0HT scanner (Hamamatsu, Bridgewater, NJ), allowing for measurements and annotations to be made with NDPViewer software. The percentage of stenosis was determined with ImageJ software for area analysis, and the maximal percentage of stenosis was calculated by dividing the computerized surface area of the residual lumen by the computerized surface area delimited by the internal elastic lamina. (see Fig. 2).

The percentage of stenosis determined from CAG was calculated as a ratio of minimal diameter and reference diameter (Fig. 2).

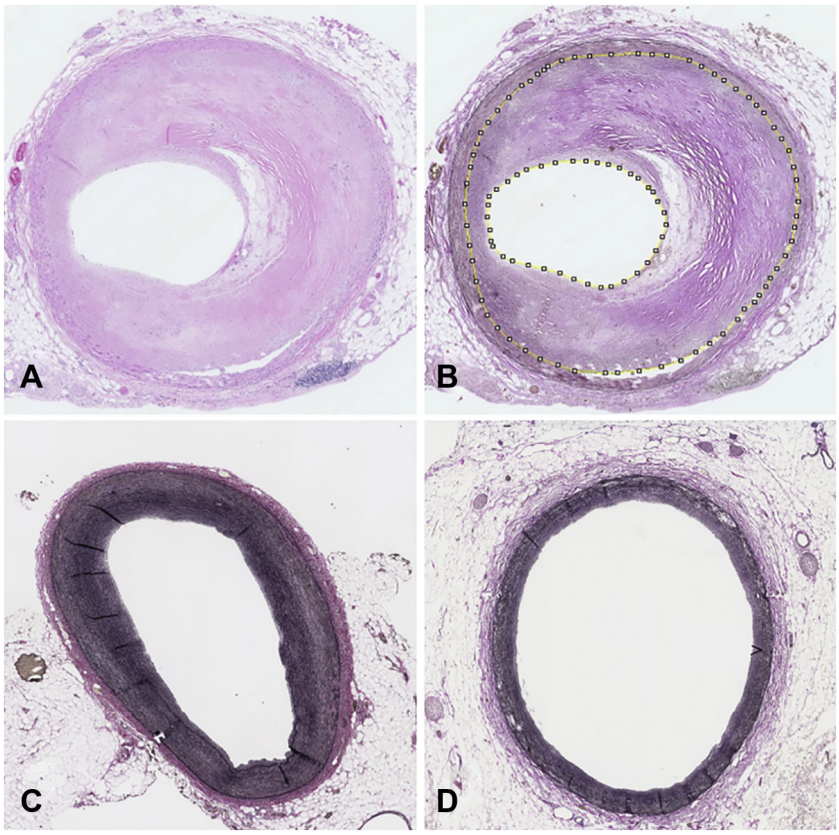


Fig. 2. Digitized slides of a fixed coronary artery. Image of a left anterior descending artery stained with H&E (A) and VVG (B). Images were analyzed using the ImageJ software to delineate and quantify the surface area of the residual lumen and the internal elastic lamina. Digitalized slides stained with VVG show a difference in wall thickness between a non-perfused (C) and a perfused (D) left anterior descending artery.

2.3. Acquisition and analysis of radiologic data

CAG images were obtained using multiple projections for each artery to best evaluate stenosis. The stenosis of the arteries was visually assessed by a radiologist and a cardiologist, both of whom were blind/blinded to the pathology evaluation. All incidences of stenosis were analyzed and the coronary segments for each artery that was most greatly affected was used for comparison with histopathology results.

2.4. Statistical analysis

GraphPad Prysm version 7 for Windows (GraphPad Software, La Jolla California USA www.graphpad.com) was used for statistical analysis. Our selected data did not have a normal distribution. The significant difference between our two paired groups of patients was determined using the nonparametric Mann–Whitney *U* test to confirm or reject the null hypothesis. The accuracy of the observed differences was determined with confidence intervals considered superior to 95% with the use of Mann–Whitney U test. A *P* value<.05 was considered to represent a significant difference between the two groups.

3. Results

3.1. Patient data

Patient subgroups and demographics are summarized in tables 1 and 2. A total of 83 patients underwent cardiac autopsies. Of those patients, 48 were forensic autopsies, 29 were hospitalized autopsies, and 6 were surgical explants. Thirty-six patients underwent pre-mortem or pre-transplant CAG with a mean delay of 15.6 months for perfused patients and 2.4 months for non-perfused patients. During post-mortem analyses, 31 hearts were perfused at iso-physiologic pressure for 12 or more hours and 50 hearts were passively fixed. Fourteen of the perfused patients and 22 of the non-perfused patients had an angiogram pre-mortem.

3.2. Comparison of artery stenosis determined using passive fixation versus active iso-physiologic perfusion fixation with and without cardiac explant

We compared stenosis evaluations using PHP and AHP to determine the potential stenotic differences. Results yielded a statistically significant difference between total mean values using PHP and AHP from all autopsy and explant patients (53.09% versus 64.93%, *P*=.0001) (see Fig. 7). We also showed differences when we compared PHP and AHP from individual arteries such as the Cx artery (67.43% versus 52.94%, *P*=.017) and the RCA (68.75% versus 54.84%, *P*=.006) and we observed slight but not significant differences in the LM (51.39% versus 42.58%. *P*=.091) and the LAD (71.49% versus 62.0%, *P*=.094) when all groups were compared (Fig. 3). Next, we performed the same analyses but excluded cardiac explant patients. We did this to increase the similarity between the compared populations (all from autopsy). We observed a statistically significant difference between total mean values from PHP and AHP from all arteries combined (64.93% versus 47.76%, *P*=.0001) (see Fig. 7). Values determined from PHP and AHP in the LM (67.43% versus 51.41%, *P*=.003), LAD (71.40% versus 55.12%, *P*=.025) and RCA (68.75% versus 50.94%, *P*=.007) were statistically significantly different, and slight but not significant differences were observed in the Cx (51.39% versus 33.59% *P*=.056) (Fig. 4).

3.3. Comparison of coronary artery stenosis determined using angiography versus passive fixation and active iso-physiologic perfusion fixation

To assess the differences in coronary artery stenosis estimates determined from CAG and from histopathology, we compared CAG data with PHP and APH data. We observed statistically significant differences between total mean values obtained from PHP and CAG (69.57% versus 54.20%, *P*=.002), and CAG and PHP in the Cx (58.90% versus 76.24%, *P*=.0457) and in the RCA (50.50% versus 72.18%, *P*=.0261), as well as a slight but not significant difference in the LM (35.95% 51.53%, *P*=.0754). No significant difference was observed in the LAD (71.26% versus 76.18%, *P*=.89). These results show an overall statistical difference between these two methods of assessing stenosis (CAG and PHP) (Fig. 5). We compared CAG and APH and determined that there was no difference in the total mean values (53.73% versus 59.55%, *P*=.8817) of all of the segments combined, nor were there differences in the individual arteries. These included the LM (34.79% versus 53.50%, *P*=.340), LAD (60.57% versus 70.36%, *P*=.954), Cx (60.62% versus 54.79%, *P*=.435) and the RCA (59.43% versus 59.57%, *P*=.972) (Fig. 6).

4. Discussion

Cardiac surgeons, cardiologists and pathologists heavily rely on PHP to evaluate the degree of coronary artery stenosis in patients' hearts. Multiple scientific reports have established significant discrepancies between estimates from CAG and histology evaluations. These discrepancies lead to widespread and inaccurate assessments of “real” coronary disease, create uncertainties for patients undergoing surgical procedures, and can result in erroneous post-mortem CAD evaluations. The experimental design used in this research aimed to evaluate the discrepancies of stenosis estimation based on CAG and histopathology in the contexts of PHP and APH. Moreover, it was devised to provide an experimental method to reduce the overestimation of stenosis in post-mortem settings.

To assess the variation in stenosis estimates between CAG and histopathology, we compared CAG to PHP and compared CAG to APH. Comparisons were made for the complete coronary system (all arteries combined) and for individual arteries. Our results showed statistically significant differences in the total mean values

Table 2
Patient demographics

Demographics					
Angiography (*n*=22)	Perfused	SD	No Angiography (*n*=30)	Unperfused	SD
M:F ration	2.14	-	M:F ration	1.5	-
Mean age (years)	64.5	5.9	Mean age (years)	51.7	4.3
Angiography (*n*=14)	Perfused		No Angiography (*n*=17)	Perfused	
M:F ration	0.75	-	M:F ration	3.0	-
Mean age (years)	66.1	5.1	Mean age (years)	56.4	7.7

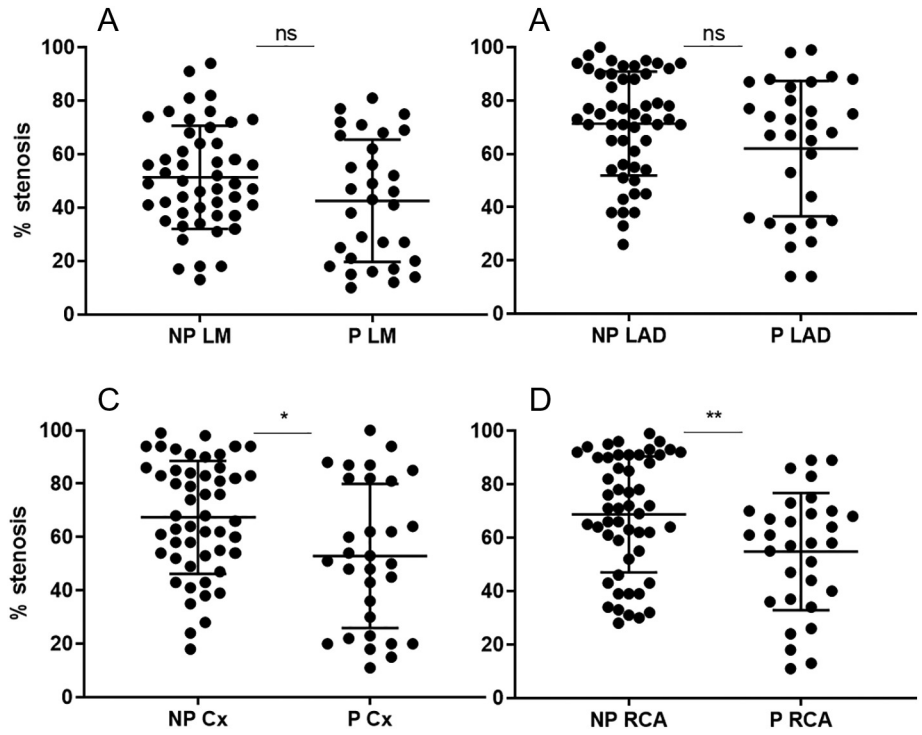


Fig. 3. Stenosis estimates of pooled autopsy and cardiac explant data. (A) LM stenosis in the non-perfused (NP) and perfused (P) patients (P=.0908). (B) LAD stenosis in the NP and P patients (P=.0942). (C) Cx stenosis in the NP and P patients (P=.0165). (D) RCA stenosis in the NP and P patients (P=.0057) Analyses were performed using a non-parametric Mann–Whitney U test. A P value ≥.05 was considered significant.

determined from PHP and CAG (69.57 versus 54.20, P=.002). Differences were also observed using PHP and CAG in the Cx and RCA and there was a slight but not significant difference in the LM (Fig. 5). By comparing CAG and APH, we proved the null hypothesis that there was no difference in total mean values (53.73 versus 59.55, P=.8817) nor were there differences in values from any of the individual arteries from the two populations studied (Fig. 6). These results support the current literature in which several groups have

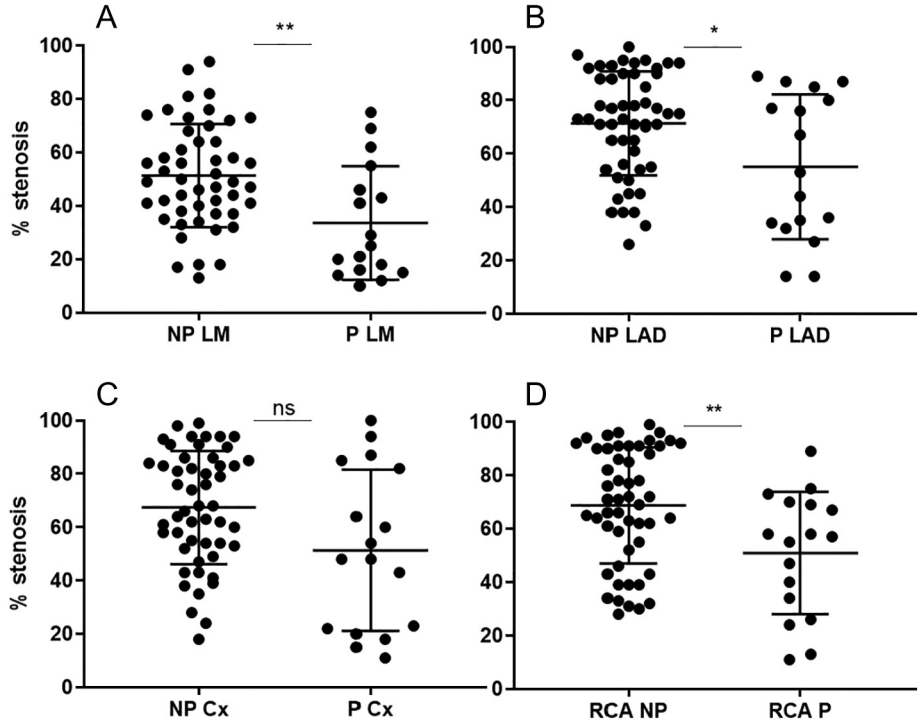


Fig. 4. Stenosis estimates of pooled autopsy data: (A) LM stenosis in the non-perfused (NP) and perfused (P) patients (P=.003). (B) LAD stenosis in the NP and P patients (P=.024). (C) Cx stenosis in the NP and P patients (P=.055). (D) RCA stenosis in the NP and P patients (P=.0068). Analyses were performed using a non-parametric Mann–Whitney U test. A P value ≥.05 was considered significant.

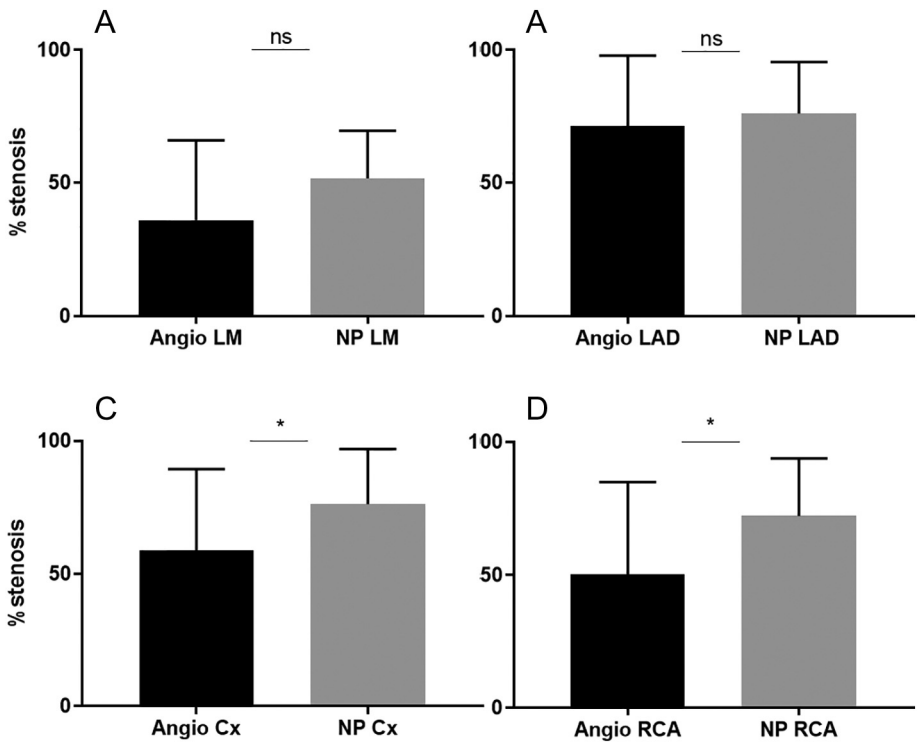


Fig. 5. Stenosis evaluation from non-perfused autopsy and CAG. (A) LM stenosis in non-perfused autopsy (NP) patients and CAG patients (P=.075). (B) LAD stenosis in NP and CAG patients (P=.89) (C) Cx stenosis in NP and CAG patients (P=.046) (D) RCA stenosis in NP and CAG patients (P=.026). Analyses were performed using a non-parametric Mann−Whitney U test. A P value ≥.05 was considered significant.

challenged the accuracy of CAG despite the fact that it has been the main tool used for the measurement of myocardial perfusion and coronary artery stenosis for more than 50 years [17]. Jianping and others showed that angiographic discordance was often noted when the orientation of the heart, the angle of projections and the number of coronary segments studied are changed [2,10,18]. Vlodaver et al. also showed that pathologic findings with a 50% reduction in the lumen due to stenosis corresponded with frontal

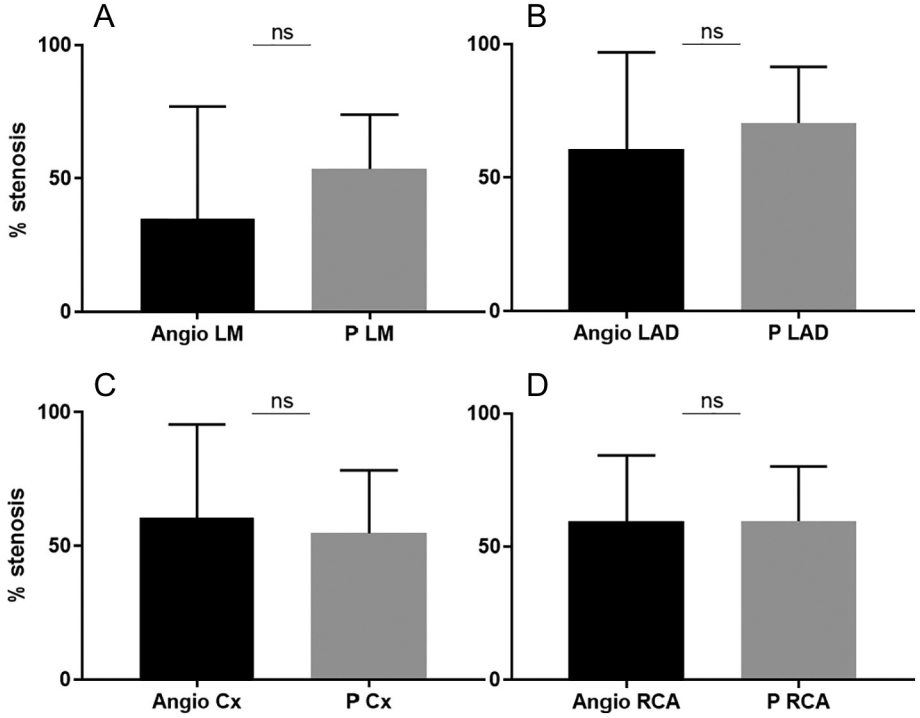


Fig. 6. Stenosis evaluation from perfused autopsy and CAG (A) LM stenosis in the non-perfused autopsy (P) patients and CAG patients (P=.34). (B) LAD stenosis in PCA patients (P=.95) (C) Cx stenosis in P and CAG patients (P=.44) (D) CD stenosis in P and CAG patients (P=.97). Analyses were performed using a non-parametric Mann−Whitney U test. A P value ≥.05 was considered significant.

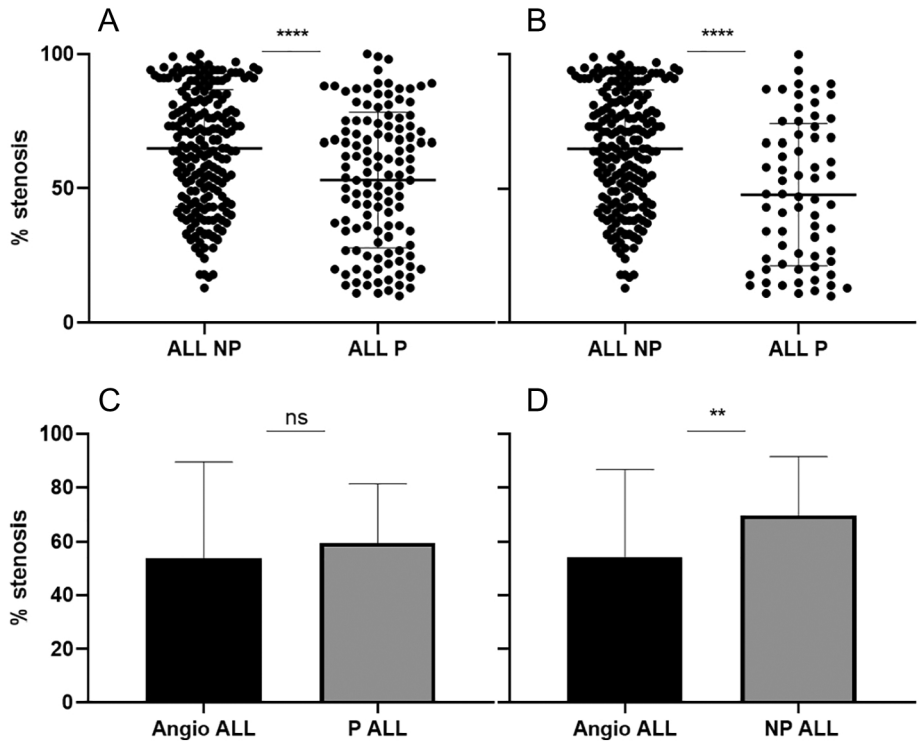


Fig. 7. Stenosis evaluation from All coronary segments and angiography. A) ALL coronary stenosis in the non-perfused (NP) and perfused (P) patients (P=.0001). (B) ALL coronary stenosis in the NP and P patients (P=.0002). (C)) ALL stenosis in P and CAG patients (P=.8817). (D) ALL stenosis in P and CAG patients (P=.002). Analyses were performed using a non-parametric Mann−Whitney U test. A P value ≥.05 was considered significant.

and lateral biplane projection coronary angiograms that displayed less than 50% stenosis in 33% of the cases examined. Grondin et al. confirmed these results by comparing frontal, lateral and anterior oblique CAG in 23 patients with 2 mm leap pathologic examination. They showed a 38% difference between estimates of stenosis determined from CAG and pathology [14]. Multiple other authors also showed discrepancies between pathologic and in vivo findings [6,9,12−16,18−21].

More recently, Saxer et al. showed paradoxical findings in a 71-year-old patient with negative CAG while the autopsy results exhibited a bitroncular stenotic coronaropathy of the LAD (60% at 10 cm) and the Cx (70% at 4.5 cm) [6]. Saxer et al. suggested that one of the main causes for these inconsistent findings is the insufficient number of CAG projections that led to underestimations of atherosclerotic plaque [6]. This theory is compatible with a study by Vlodaver et al. that showed severely atherosclerotic coronary arteries on histology with normal angiographic projections. As mentioned previously, it has also been suggested that the number of projections leads to a poor assessment of the tridimensional structure of star-shaped arterial lumen [18].

Moreover, post-mortem analysis of coronary artery stenosis using passive histologic sampling is known to have a variable correlation with the in vivo stenosis identified using CAG [13]. There is still a tendency for CAG to underestimate artery stenosis even when compared to post-mortem CAG [9,21]. Indeed, previous studies have demonstrated a tendency for CAG of live patients to underestimate stenotic lesions when compared to post-mortem CAG, suggesting not only that the method of assessment but also post-mortem structural alterations contribute to the differences [22−25].

We compared estimates of stenosis using PHP and APH and found statistically significant differences in the total mean value for all arteries combined, for the Cx, and for the RCA. There were also slight but not significant differences in stenosis estimates for the LM and the LAD (Fig. 3). When we compared methods and excluded cardiac explant patients/hearts, we observed a statistically significant difference in the stenosis estimates for LM, LAD and RCA and a small but not significant difference for the Cx (Fig. 4). These results are consistent with findings by Schwartz et al., who simulated an in vivo arterial pressure of 100 mmHG for 20 min to compare CAG with histopathology findings (9?). Overall, Schwartz et al. showed a strong correlation between estimates derived from both methods in proximal segments but showed a variable correlation in distal segments [9]. Results from our study are consistent with those of Schwartz et al., showing a reduction in coronary artery stenosis after APH (intra-aortic perfusion of 80−90 mmHg for at least 12 h). There were also small differences in stenosis in the LM and the LAD (Fig. 3), though these were not significant. The lack of significance could be explained by factors such as the increased arterial pressure in the proximal arteries. Other explanations could be that the natural increase in atherosclerosis deposition in these vessels skewed the results or that the patient sample sizes available for individual analysis were limited.

Our results are unique and suggest an overestimation of stenosis on PHP (conventional histopathology) as opposed to an underestimation of coronary stenosis with CAG. This is illustrated in Fig. 6, which clearly shows no significant difference when comparing pathologic data from perfused hearts with standard CAG. As previously suggested, this overestimation of stenosis from PHP could be due to post-mortem changes in cardiac structure. One unique feature of our study is the availability of pre-mortem CAG for the cardiac autopsy samples/patients as opposed to two distinct cohorts for the CAG and autopsy populations. The strong correlation between pre-mortem and post-mortem coronary artery stenosis in this group yields a substantial collection of unique and pertinent information that is currently unavailable in the literature. Unfortunately, our study design does not allow us to thoroughly evaluate which method is reflective of the actual degree of CAD in patients. We do not know with certainty if AHP correctly estimates the degree of stenosis or if it falsely reduces these estimates.

In summary, our analyses suggest that perfusion fixation can reduce overestimation of stenosis severity based on histopathology compared to the passive fixation method. The etiology behind the discordance between non-perfused and perfused specimens remains unclear. Further study is needed to confirm the gross overestimation of coronary stenosis from passive histopathology. However, when considering the delicate situation of hospital autopsies and especially its legal context, the use of iso-physiologic heart perfusion could be fundamental in assessing the cause of death. Therefore, we suggest that post-mortem heart perfusion be performed in all cases with potential medico-legal implications.

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Conflict of interest

We have no conflicts of interest to disclose.

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