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REVIEW ARTICLE

Considerations in Understanding the Coronary Blood Flow- Left Ventricular Mass Relationship in Patients with Hypertension

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Abstract: ***Background*:** Coronary blood flow (CBF) is essential for optimal cardiac performance and to maintain myocardial viability. There is considerable ambiguity concerning CBF in hypertension.

***Objective*:** To investigate the relationship between CBF and left ventricular (LV) mass in persons with hypertension.

***Methods*:** OvidSP Medline was systematically searched. Eligible articles assessed CBF, and LV mass in adults with and without hypertension (HTN).

***Results*:** Eleven studies met the entry criteria. All 8 studies reported an increase in CBF (ml/min) for persons with hypertension (N=212) compared to individuals without hypertension (N=150). Meta-analysis showed a significant and 2.88 fold higher CBP in hypertension. Six studies adjusted CBF for LV mass; of which 4 studies reported a reduction in CBF. Meta-analysis showed a significant decrease in CBF/g LV mass in hypertension. The two studies that did not show a decrease in CBF, used the argon chromatographic method to measure coronary sinus blood flow suggesting this methodology may have influenced the results. Using the mean CBF in normotensive group to construct the expected CBF according to LV mass, reported CBF in HTN was progressively less than expected In two studies, (N=142), there was a significant inverse correlation between LV mass and CBF/ g LV mass. Multivariate analysis (three studies) consistently found a highly significant independent relationship between LV mass and CBF after considering age, sex, heart rate and several other factors.

***Conclusion*:** Hypertension is associated with a reduction in CBF adjusted for LV mass with a highly significant inverse association between CBF and LV mass. Clinicians should be aware that patients with hypertension are at greater risk for myocardial ischemia should develop other factors that limit CBF or myocardial oxygen delivery.

ARTICLE HISTORY

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1. INTRODUCTION

An increase in left ventricular mass as a consequence of hypertension is well recognized as an important adverse consequence of hypertension and is an indicator of an increased risk of cardiovascular morbidity and mortality over and above the blood pressure level [1, 2]. A number of factors have been implicated to explain the poor adverse outcome of persons with hypertension-induced increases in left ventricular (LV) mass. These include the increased probability of serious ventricular arrhythmias [3] and an increased propensity to myocardial ischemia or infarction [4, 5]. The possibility that LV mass is associated with a relative insufficient coronary blood flow has been debated for many years [6-8]. Some investigators propose that the hypertrophied left ventricle outstrips the capacity of the vasculature to meet the (metabolic) demands of the increased LV mass either at the level of the epicardial coronary vessels [7] or the capillaries [6]. Others contend that coronary blood flow is not meaningfully altered once coronary blood flow is adjusted for the increase in LV mass [8]. The opinions have been conflicting for several reasons including the reliance on studies in animals compared to humans; different measurement techniques to assess coronary blood flow and different modes of adjusting for the effect of left ventricular mass. The relationship between left ventricular mass and resting coronary blood flow in humans has not been systematically evaluated. The objective of this study is to examine the data on coronary blood flow (CBF) in patients with hypertension in relation to LV mass. In addition the relationship between LV mass and CBF was examined taking into consideration other potential determinants of the relationship.

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2. METHODS

2.1. Search Strategy

A systematic search was conducted to identify studies that examined the relationship between coronary blood flow and left ventricular mass or left ventricular hypertrophy using a standardized approach [9]. The Medline database was searched using the OvidSP platforms. The full electronic search strategy used in PubMed Medline was "coronary blood flow" AND "left ventricular hypertrophy or left ventricular mass" limited to humans. The last date of search was December 31, 2015.

2.2. Eligibility Criteria

Studies that met the following criteria were included: (i) an original study published in a peer-review journal, (ii) measured coronary blood flow (iii) assessed left ventricular mass (iii) adjusted left ventricular mass for body size i.e. body surface area (iv) adults with hypertension (v) comparison of coronary blood flow in hypertension and non-hypertensive individuals or examined the relationship between CBF and LV mass. The exclusion criteria were non-English studies, abstracts from unpublished studies, reviews, case reports or letters.

2.3. Data Extraction

From each eligible study, patient characteristics – age and sex, method of measurement of coronary blood flow and left ventricular mass were systematically recorded.

2.4. Statistical Analysis

Meta-analyses of the aggregate patient data were conducted using the Comprehensive Meta-analysis Version 2 (Biostat, Englewood, New Jersey, USA). From each entry, the study name, sample size, mean value and standard deviation, correlation coefficient and direction of correlation were entered. Because of the variation between studies in participant characteristics and methods of CBF measurement between studies, Fischer's z transformation was used to compare the data in each study [10]. To assess heterogeneity, the Cochrane Q statistic, I^2 statistic and Tau-squared statistic were calculated. Statistical significance was set as $p < 0.05$.

3. RESULTS

Eleven studies were identified that met the entry criteria (Fig. **1**). The methodology used to measure coronary blood flow, left ventricular mass, age and sex of the study populations with and without hypertension are summarized in Table **1**. Most of the studies used the case control approach while one study examined the relationship between CBF and LV mass but did not examine individuals with hypertension separately.

Eight studies presented data on coronary blood flow in ml/min for persons with hypertension compared to individuals without hypertension (Fig. **2a**). There were 362 individuals of whom 212 had hypertension. In each of the studies, mean CBF was increased in those with hypertension. The absolute value of CBF varied because some studies measured total myocardial blood flow [11, 12] while others measured CBF in a single coronary artery [13-16]. In addition, techniques for CBF measurement varied widely. Studies using the same technique, specifically total myocardial uptake of thallium were consistent and demonstrated the highest CBF which was a measurement of total myocardial blood flow [11, 12]. Meta-analysis found a significantly ($p<0.001$) greater CBF in persons with hypertension (Fig. **2b**). There was however, significant heterogeneity between studies. Four of the studies showed a significant increase in coronary blood flow and in one other study it was of borderline significance. In three studies the increase in CBF in hypertensive individuals was not significant.

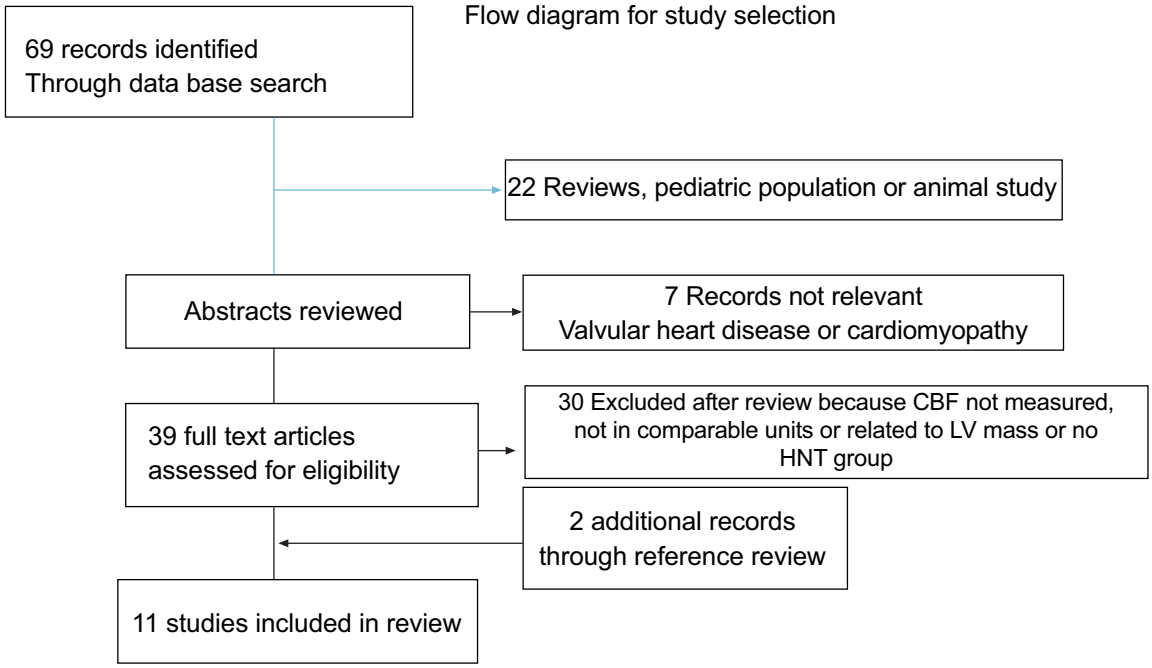

Fig. (1). Shows the flow diagram for study review and selection.

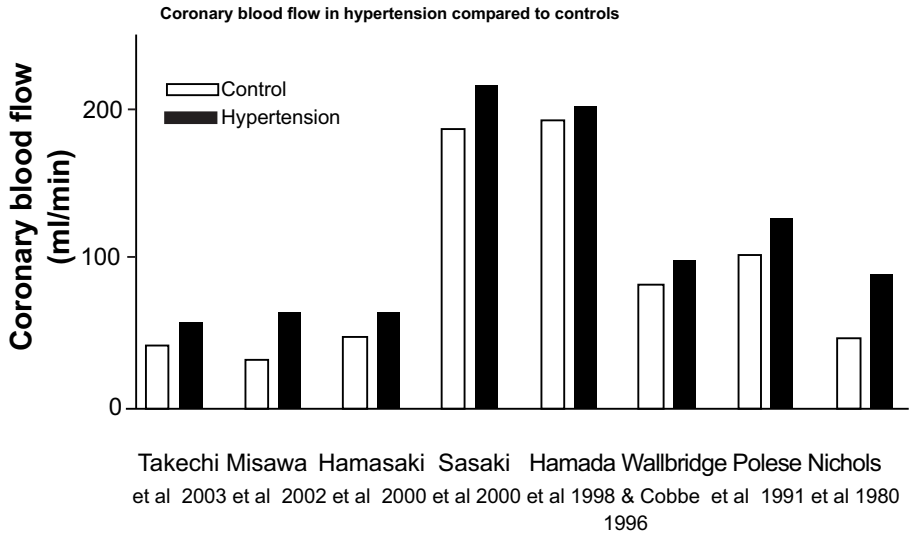

Fig. (2a). Shows the mean values for coronary blood flow for persons with and without hypertension in studies that measured coronary blood flow in persons with hypertension and a control non-hypertensive group.

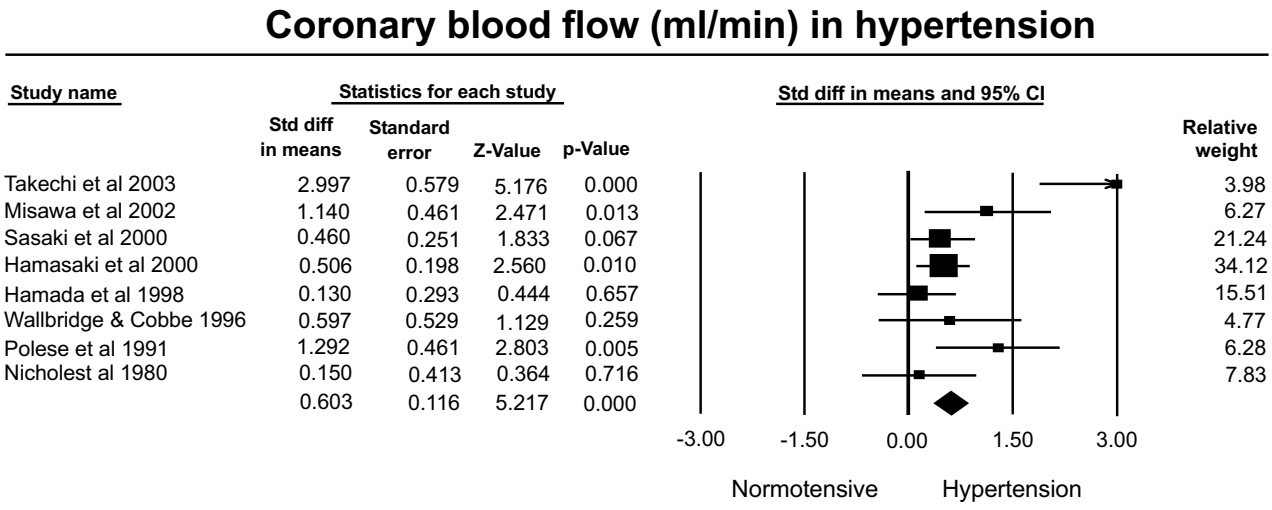

Fig. (2b). Shows the meta-analysis with standard difference of the means mean values for coronary blood flow for persons with hypertension compared to persons without hypertension.

LV mass was 148.7 g/m^2 in persons with hypertension compared to 51.6 g/m^2 in persons without hypertension after determining a weighted mean from the studies outlined in Table **1**, excluding the one study that presented the data as g/m$^{2.7}$. In order to adjust for this increase in LV mass in hypertension, studies were examined that provided LV mass data and presented CBF per LV mass. Six studies compared CBF adjusted for LV mass in persons with hypertension (N=212) compared to a normotensive control group (N=78). In four of the six studies, adjusted CBF was lower in persons with hypertension compared to those without hypertension [11-13, 17] (Fig. **3a**). Meta-analysis showed a significant reduction in CBF adjusted for LV mass. Four studies had a significantly lower CBF, one showed no change [18] and one showed an increase in CBF [19] (Fig. **3b**). Sasaki *et al.* and Hamada *et al*. used the indicator fractionation principle, and calculated CBF on the basis of the ratio of myocardial uptake/total injected dose of thallium-201 [11, 12]. Nichols *et al.* measured CBF by clearance of xenon-133 from the left ventricular myocardium after its injected into the left main coronary artery [17]. They found a reduction in CBF/100g LV mass with hypertension. Wallbridge and Cobbe used a Doppler flow probe in left main coronary artery and reported a reduction in CBF in hypertension [13]. Interestingly the two studies that did not show a decrease in CBF, used the argon chromatographic method to measure coronary sinus blood flow [18, 19]. Considering all studies, there was a significant difference in CBF but there was marked heterogeneity between studies with Q = 187.3 and I^2 = 97.3. Removal of the two studies using the argon method because of concerns about the accuracy of this method [20, 21], would mean that all of the studies showed a significant reduction in CBF (ml/min/100 g).

To further examine this relationship, the observed and expected CBF according to LV mass was calculated from studies that presented the LV mass in control and hypertensive groups [11-13, 17, 18]. The weighted mean of CBF in

Table 1. Shows the nature of the studies.

				Control				HTN	
Author	**Coronary Blood Flow measurement Methodology**	**N**	**% men**	**Age (yrs)**	**LV mass**	**N**	**% men**	**Age (yrs)**	**LV mass**
Strauer *et al.* 1979	Argon gas with catheter in the coronary sinus	12	na	na	71 g/m^2	63	na	na	na
Nichols *et al*. 1980	Xenon-133 washout	9	33	50	76 g/m^2	17	41	46	119 g/m^2
Polese *et al*. 1991	Thermodilution with catheter in coronary sinus	9	100	51	114 g/m^2	15	100	51	151 g/m2
Hamada *et al*. 1998	Myocardial uptake of thallium-201	14	71	45	89 g/m^2	40	68	na	154 g/m^2
Wallbridge & Cobbe 1996	Doppler flow probe in left main coronary artery	8	63	46	106 g/m^2	7	57	52	209 g/m^2
Hamasaki *et al*. 2000	Doppler flow probe in LAD	68	44	50	na	43	30	54	148 g/m^2
Sasaki *et al*. 2000	Myocardial uptake of thallium-201	22	64	57	89 g/m^2	62	65	54	135 g/m^2
Misawa *et al.* 2002	Doppler flow probe in LAD or LCX	10	70	51	104 g/m^2	12	58	58	163 g/m^2
Schafer *et al*. 2002	Argon gas with catheter in the coronary sinus	13	77	55	44 g/m$^{2.7}$	23	52	60	58 g/m$^{2.7}$
Takechi *et al*. 2003	Doppler flow probe in LAD	10	na	62	94 g/m^2	16	na	60	183 g/m^2
Cusmà-Piccione *et al*. 2014	Doppler flow probe in LAD	88	55	51	100 g/m^2	45	…. .	……	…..
LAD is left anterior descending coronary artery LV mass – left ventricular mass									
LCX left circumflex coronary artery									
na is not available or able to be extracted from the paper yrs – years									

the control group was 139.7 ml/min/100 g LV mass. A body surface area of 1.8 was selected for illustration. Predicted CBF for the hypertensive group was calculated by multiplying the average CBF in the control group by the mean left ventricular mass in each of the studies that presented these data in their hypertensive group. The actual mean CBF was markedly lower than the predicted CBF for each of the studies that contained these data except for that of Schafer *et al*. [18] (Fig. **4**). A likely explanation is that the mean LV mass was not meaningfully increased in the group with hypertension in that study [18].

The correlation of LV mass and CBF was examined. There were two studies that presented these data and they had a combined sample size of 142 individuals (Fig. **5**). Hamada *et al.* studied 54 individuals of whom 74% had hypertension and found a significant inverse correlation between LV mass and CBF per g of LV mass [11]. Cusmà-Piccione *et al.* studied 88 persons with cardiovascular risk factors, of whom 51% had hypertension but no cardiac disease and found a significant inverse correlation between CBF indexed to body surface area, [22]. Taken together the results show a highly significant inverse association between CBF and LV mass. The correlations were of similar magnitude and there was no significant heterogeneity between the study outcomes ($Q=1.7$ $Tau^2=0.011$). Hamada *et al.* suggested a polynomial fit to the CBF-LV mass relationship but there were no other studies that examined their data in this manner to cross validate their approach.

Multivariate analysis of the relationship between LV mass and CBF while taking into consideration other potential determinants of the relationship was conducted in three studies (Table **2**). Each of these studies found a highly significant independent relationship between LV mass and CBF after considering a variety of other factors [11, 15, 22]. One study reported that in multiple linear regression analysis, only LV mass was independently associated with CBF reduction [22].

4. DISCUSSION

This is the first study, to our knowledge, to systematically analyze the data on coronary blood flow in patients with hypertension. The study confirms the contention that coronary blood flow increases with increases in left ventricular mass. Importantly, it addresses the controversy whether

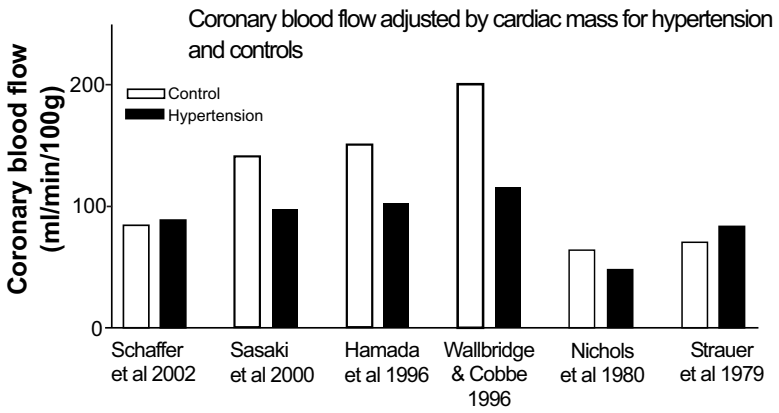

Fig. (3a). Shows the mean values for coronary blood flow after adjustment for left ventricular mass in studies that presented the data in similar units i.e. ml/min/100 g LV mass for persons with and without hypertension. For one study Wallbridge and Cobbe the units were presented as ml/min/g and the number was multiplied by 100.

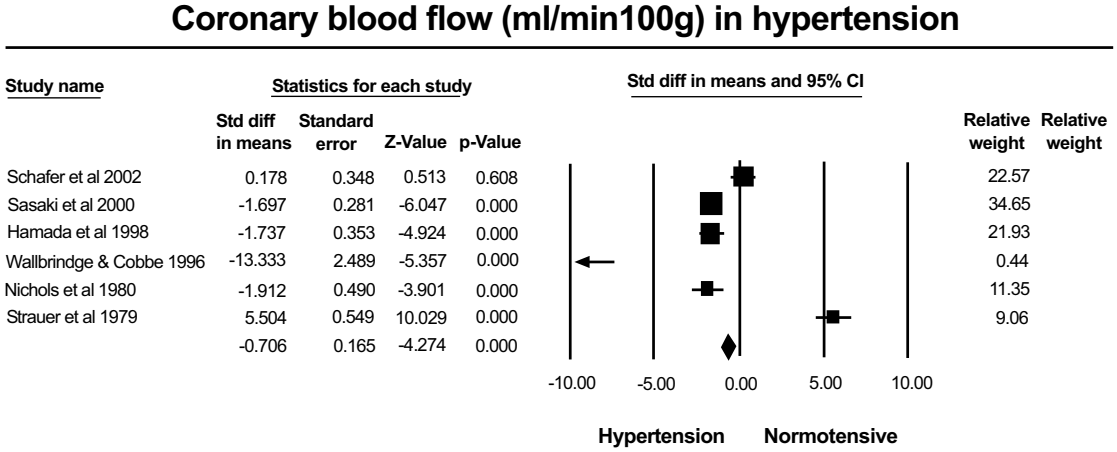

Fig. (3b). Shows the meta-analysis for coronary blood flow after adjustment for left ventricular mass in four studies that presented the data in similar units i.e. ml/min/100 g LV mass for persons with and without hypertension. The standard difference in the means, standard error of the estimate, z value and p value is presented for each study.

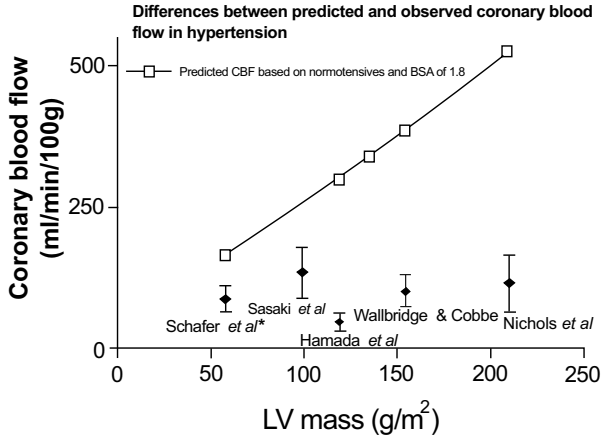

Fig. (4). Shows the predicted coronary blood flow based on an individual with a body surface area of 1.8 m^2 and was constructed by multiplying the average CBF in the control group by the mean left ventricular mass in each of the studies that presented the mean LV mass in their hypertensive group. The reported mean CBF and SD are shown for each of the studies. * study with LV mass reported as $g/m^{2.7}$.

in the resting or unstressed state, an increase in LV mass from the increased load of hypertension, overcomes the ability of the coronary vasculature to maintain the balance of the normal blood flow per unit LV mass. It concludes that coronary blood flow per gram of LV mass is lower in hypertension. This finding has several implications including the suggestion that patients with hypertension are at relatively greater risk for myocardial ischemia should other factors develop that limit myocardial oxygen supply (marked anemia or hypoxemia) or limit coronary blood flow [23].

An increase in overall CBF in patients with hypertension was demonstrated in this meta-analysis. The increase in CBF in hypertension can be attributed to the raised (metabolic) demands of the myocardium. Resting CBF is primarily determined by myocardial demand which is increased in hypertension because of the increased loading of the left ventricle from the increased systolic blood pressure [24]. Elevated blood pressure can increase LV mass even in the absence of left ventricular hypertrophy [25, 26] thereby accentuating the heart's metabolic requirements [27]. The increase in LV mass even in the absence of left ventricular hypertrophy maybe explained by the presence of a continuum in hyper-

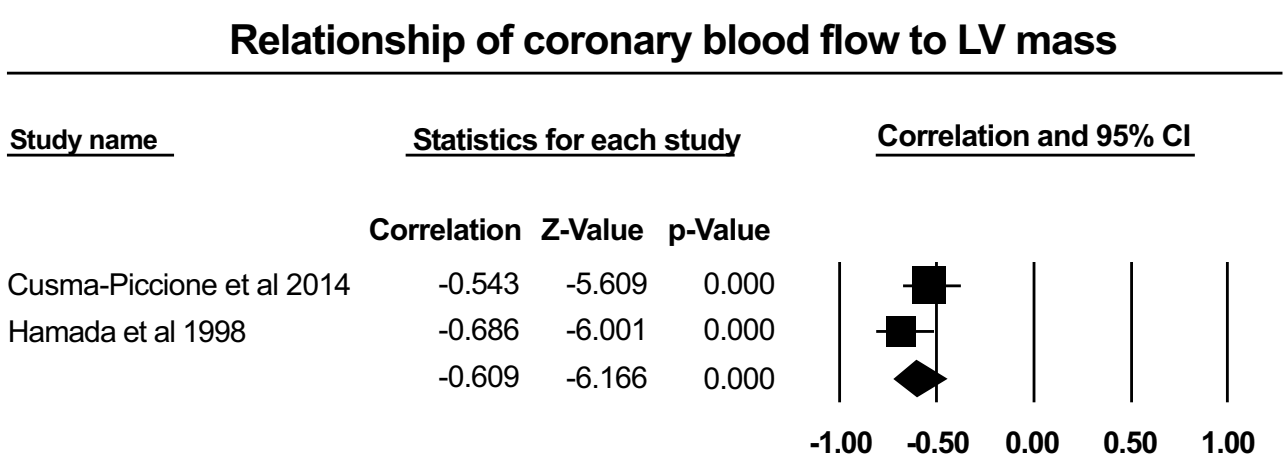

Fig. (5). Shows the correlation between coronary blood flow and left ventricular mass in two studies that examined the relationship. The correlation coefficient, z value and p value is presented for each study.

Table 2. Shows the results of the multivariate analysis relating different factors to coronary blood flow.

	Cusma-Piccione *et al.* 2014	Hamada *et al.* 1998	Misawa *et al.* 2002
LV mass (g/m^2)	p=0.008	p=0.0002	p<0.001
Carotid arterial stiffness	p<0.001	not done	not done
Male sex	p<0.001	not done	ns
Diastolic BP	not done	p=0.0214	ns
Age	ns	ns	p=0.03
Heart rate	ns	ns	ns
Carotid IMT	ns	not done	not done
Smoking	not done	not done	p=0.08

tension. An increased blood pressure load for defined time period will increase LV mass to a degree that fulfils criteria for LVH. Smaller increases in LV mass are likely due to the smaller elevations in the loading conditions on the left ventricle that are not at the level that would produce sufficient increases in LV mass to meet criteria for left ventricular hypertrophy.

Coronary blood flow adjusted for LV mass is reduced in patients with hypertension compared to persons without hypertension. The mean value for CBF in the control group is consistent with calculations of CBF measured with recent technology [28]. Instead of finding a threefold increase in CBF per LV mass in hypertension which is the expected value considering the 2.9 fold greater LV mass in the hypertensive group, a reduction in CBF was found. Indeed there was a marked discrepancy between expected and observed CBF, in patients with hypertension associated increases in LV mass.

Importantly, multivariate analysis of the relationship between LV mass and CBF taking into consideration other potential determinants of the relationship found a highly significant independent relationship between LV mass and CBF after considering age, sex, blood pressure, heart rate and several other factors This finding is consistent with the proposal that hypertension-induced increases in LV mass 'overcomes' the ability of the coronary circulation to adequately match increases in LV mass [7]. This contention has been called into question but mainly from data in animal models of cardiac hypertrophy [4]. The relative reduction in coronary blood flow in hypertension can be attributed to changes, at several levels, of the coronary vasculature -from the epicardial vessels to the capillaries. The proposal that cardiac hypertrophy is associated with a reduction in capillary density per myocardial fiber likely antedates its summarization by Bing in 1951 [6]. Experimental evidence suggests that cardiac hypertrophy is associated with a relative reduction in capillary density [29] but this is controversial [30]. Hypertension can induce arteriolar thickening [31], leading to an increase in vascular resistance. Hypertension may reduce the number of arterioles in the microvascular beds [32]. The cross sectional area of the proximal epicardial coronary arteries are insufficient to match increases in LV mass [33]. Another potential explanation for the reduction in CBF is an alteration in coronary flow dynamics specifically a reduction in the "suction" wave generated by myocardial microcirculatory decompression with increased LV mass [34]. While CBF reduction may occur from any one of these factors, it is likely to result from their combination.

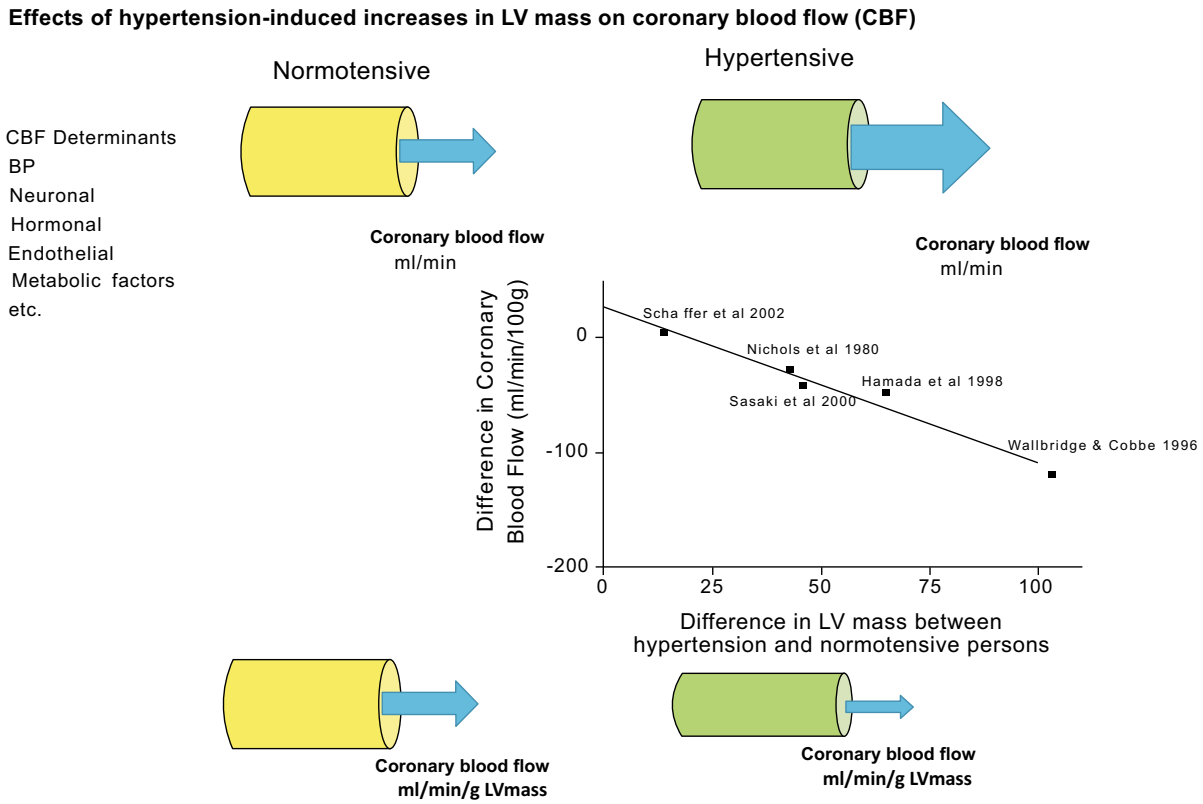

Fig. (6). Shows diagrammatically the blood flow through large epicardial coronary arteries expressed as ml/min and ml/min adjusted for left ventricular mass. The diagram in the central area shows the relationship between coronary blood flow (CBF) (ml/min/100g) and LV mass comparing the differences in CBF and LV mass between the hypertensive and normotensive individuals in each of the studies that presented the data to permit the calculation. LV mass was in g/m^2 for all studies except Schaffer *et al* where it was $g/m^{2.7}$.

A variety of different techniques were used to measure coronary blood flow in the studies examined. The thermodilution technique confronts the challenges of the anatomic and physiologic features of the coronary venous circulation which may not always drain in its entirety to the coronary sinus and thus adversely impact the accuracy of CBF measurement [20]. The use of the argon gas method confronts the same problems of variations in venous drainage patterns, the influence of catheter position as well as respiration which can affect the accuracy of its CBF measurement [20, 21]. Other factors that influence the argon measurement of CBF include the effect of non-homogenous myocardial perfusion, because of myocardial ischemia or fibrosis [20]. Inhomogeneity of perfusion is especially relevant in hypertension, which can leads to increases in myocardial fibrosis [35, 36], and seriously limits the accuracy of this technique [20, 37]. These concerns about measurement methodology may explain the heterogeneity of results and justify separate analysis excluding studies using methodologies involving sampling from the coronary sinus. Once the data is analyzed with this approach, the reduction in coronary blood flow, standardized for LV mass, with hypertension is even more apparent.

This meta-analysis has a bearing on the question, which has been debated for years, of whether myocardial ischemia can be present in hypertension-induced left ventricular hypertrophy (LVH) in the absence of epicardial coronary atherosclerosis [38]. Clearly if myocardial blood flow is relatively reduced in LVH it is easier to conceptualize the occurrence of ischemia during conditions of increased myocardial demand on the myocardium in conditions such as exercise. The analysis in the present study provides evidence that the increase in coronary blood flow does not keep pace with the increase in LV mass in hypertension indicating a relative under supply of the myocardium.

Another consideration is the role of myocardial infarction in the development of systolic heart failure in patients with hypertension [39]. Patients with hypertension are at increased risk of myocardial infarction [40, 41]. There are data that myocardial infarction is the key element that mediates the transition from hypertension-induced increases in LV mass to hypertension-induced heart failure [39]. While this is in part due to hypertension-induced coronary atherosclerosis, it can also be due to the relatively smaller CBF in patients with hypertension.

CBF occurs mainly in diastole while in systole, CBF is reduced, approaches zero and can briefly be negative [42]. Systolic inhibition of CBF has been attributed to the formation of "vascular waterfalls" in systole [43]. Spaan *et al.* disagreed with the mechanisms and provided data indicating that the 'diastolic-systolic coronary flow differences are caused by an intramyocardial pump action' i.e. the increased myocardial wall tension in systole compresses intramyocardial coronary arteries to impede coronary blood flow [42]. This mechanism, championed by Spaan *et al.* is more generally accepted. Hypertension with increased systolic BP, fur-

ther compromises CBF through increases intra-myocardial wall tension.

4.1. Study Limitations

There are several potential limitations of our study that warrant consideration. Aggregate patient data were collected rather than individual patient data. As has been pointed out, the resources, time and international cooperation required for meta-analysis of individual patient data has made it impractical for most systematic reviews, as in our case [44]. Second, studies published in non-English languages were excluded. However, excluding non-English studies does not affect the outcome of most meta-analysis [45-47]. Third, studies were eliminated if the units were not similar. While this may have reduced the number of studies, it is the best approach to accurately combine data with the same units (ml/min or ml/min/100g). Fourth, there were an insufficient number of studies that had LVH examined separately with the appropriate control groups to examine CBF; specifically groups with hypertension with and without LVH.

5. CONCLUSION

Hypertension is associated with a reduction in coronary blood flow adjusted for LV mass (Fig. **6**). The data are consistent with the concept of a limited ability of the coronary vasculature to expand to match the increased LV mass with hypertension. Indeed the discrepancy between CBF in patients with HTN compared to those without HTN increases with increasing LV mass. Part of the previous discrepancies in the literature are due to differences in CBF measurement methodologies while other discrepancies are likely due to differences in the degree of hypertension-induced increases in LV mass. Studies with small or no meaningful increase in LV mass do not show meaningful changes in CBF. Multivariate analysis, found a highly significant independent relationship between LV mass and CBF after considering age, sex, blood pressure, heart rate and several other factors. These data suggest that patients with hypertension are at relatively greater risk for myocardial ischemia should other factors develop that limit coronary blood flow [48].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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