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FOREARM BLOOD FLOW IN INDIVIDUALS WITH CHF AND AGE-MATCHED HEALTHY VOLUNTEERS: A STUDY AND HISTORICAL REVIEW

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ABSTRACT

Jeremy A. Patterson, Steve E. Selig, Deidre Toia, Voramont Bamroongsuk, David L. Hare. Forearm Blood Flow In Individuals With CHF And Age-Matched Healthy Volunteers: A Study And Historical Review. ***JEP****online* 2007;10(5):1-15. This study examined forearm blood flow (FBF) in individuals with chronic heart failure (CHF) at rest, moderate exercise, and following limb occlusion. FBF was measured by venous occlusion plethysmography in CHF patients (n = 43) and healthy age-matched volunteers (n = 8) at rest and during exercise consisting of intermittent isometric hand squeezing at 15, 30, and 45% of maximum voluntary contraction (MVC). Peak vasodilatory capacity was also determined following the release of an occluding arm cuff. FBF was lower in CHF patients during exercise and during peak reactive hyperemia (PRH) compared to healthy volunteers, but there was no significant difference between groups at rest. Peak vasodilatory capacity was significantly higher in healthy volunteers than the CHF group ((30.6 ± 8.6 ml·100 mL^{-1}·min^{-1} and 18.3 ± 6.9 ml·100 mL^{-1}·min^{-1}, respectively). Local blood flow stimulation in response to exercise or limb occlusion is reduced in individuals with CHF, however, there was no difference in resting flows between the two groups, suggesting vasodilatory medication may restore resting blood flow to healthy values.

Key Words: Chronic Heart Failure, Venous Occlusion Plethysmography, Basal Blood Flow, ACE Inhibitors, Isometric Exercise

INTRODUCTION

Chronic heart failure (CHF) refers to the syndrome where the cardiac pump function fails to deliver sufficient blood flow (cardiac output) to satisfy the metabolic requirements of the tissues. CHF is a state of demand exceeding supply; the body requires more cardiac output than the cardiac pump can deliver. CHF is a life threatening condition that increases in prevalence with aging and is associated with high mortality (50% at 5 yrs from diagnosis). Currently, there are estimated to be five million Americans living with heart failure and approximately 500,000 new cases each year. It is the most rapidly growing diagnosis in cardiovascular medicine, and because of the advanced age of the average sufferer, one of the costliest. The cardinal symptoms of CHF are dyspnea (breathlessness) and fatigue. Reduced exercise capacity combined with fatigue and breathlessness is a major cause of morbidity in CHF patients (1). CHF is of great interest to medical researchers because of its implications in quality of life, morbidity, mortality and the associated costs of these, both economic and human.

Individuals living with CHF have an increase in peripheral vascular resistance due to several factors, including increased sympathetic adrenergic vasoconstrictor activity and increased plasma concentrations of norepinephrine, angiotensin II, endothelin-1, and arginine vasopressin (AVP) (2). Severity of CHF can depend upon the degree of circulatory inadequacy (3, 4).

In patients with CHF, exercise tolerance is usually limited by symptoms of dyspnea or fatigue. The causes of fatigue are not fully understood, but decreases in peripheral blood flow have been implicated (5). During exercise, individuals with CHF have an impaired arterial vascular dilatation (6). Blood flow to exercising muscle increases in these individuals as the intensity of exercise rises; however, the rate of increase is blunted compared to healthy volunteers (7-9). Vascular resistance has been suggested to be five times greater in CHF patients compared to healthy volunteers (8). In contrast, other researchers have reported no significant differences between individuals with CHF and healthy volunteers with respect to the rates of increases of peripheral blood flow during exercise (10, 11). Cardiac output is reduced in individuals with CHF at rest and during submaximal and maximal exercise compared to healthy volunteers (9) and this has been linked to the impaired aerobic power in this disorder (5). As a result of impaired cardiac output, exercise performance becomes limited due to impaired skeletal muscle perfusion. However, there is some indirect evidence that impaired peripheral blood flow at rest is not directly related to reduced cardiac output or other central hemodynamic factors, including: (a) forearm resistance is increased following cardiac transplantation and does not return to levels of healthy age-matched volunteers for four weeks (12), even though cardiac output improves immediately by the surgery, and (b) angiotensin converting enzyme (ACE) inhibitors cause rapid improvements in central hemodynamics (13), although improvements in exercise tolerance are delayed (5, 14), sometimes for months. In a trial on ACE inhibitors an increase in lower limb blood flow was observed with a delayed increase in exercise capacity (15).

CHF causes a significant redistribution of cardiac output at rest. This redistribution is qualitatively similar to that occurring in healthy volunteers during exercise. In CHF patients at rest, blood is shunted away from the kidneys and skin, whereas this only occurs in healthy volunteers during exercise (16). Blood flow to the splanchnic circulation is reduced in proportion to the impairment of cardiac output (17). These compensations enable blood flow to be relatively preserved to heart and skeletal muscle, which have high metabolic demands relative to blood flow.

Basal blood flow to vascular beds comprising mainly skeletal muscle (e.g., the forearm) is similar in healthy volunteers and individuals with CHF (18, 19). However, in earlier studies conducted prior to the widespread prescription of vasodilators (such as ACE inhibitors, angiotensin receptor-blockers,

and beta-blockers) in patients with CHF, resting peripheral blood flow was reported to be abnormally low compared to healthy volunteers (3, 7, 20). These differences may be explained by improved medical management since these studies and/or selection of lower risk patients in the more recent studies. In addition, limb blood flow is reduced in CHF during exercise compared to healthy volunteers (5, 7, 21) and is associated with decreased exercise tolerance (5, 22), but a cause and effect relationship has not been established. It has been suggested, however, that the more severe the degree of CHF, the more severe is the exercise intolerance, associated with a greater impairment of blood flow (5). Low exercise capacity has been independently correlated with morbidity and mortality in CHF patients (23). If this limitation is linked to the impairment of peripheral blood flow, as suggested by Wilson et al. (5) then it is a worthwhile topic of investigation.

Morbidity and mortality in CHF has been impacted by the development of vasodilator therapies such as ACE inhibitors. Vasodilating agents cause relaxation of arterial and venous vascular smooth muscle. ACE inhibitors reduce the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor (2), to improve the prognosis and help prevent progression of heart failure (24). ACE inhibitors act directly on systemic and pulmonary resistance vessels lowering blood pressure, reducing the work load of the heart and increasing the blood flow to the kidneys (25). This interrupts neuroendocrine vasoconstrictor reflexes and results in vasodilatation (2). Experimental evidence with ACE inhibitors suggest that they help to reverse ultrastructure abnormalities of skeletal muscle in patients with CHF and that long-term treatment improves endothelial function (26, 24). Nakamura and coworkers (24) showed low dose intra-arterial infusion of the ACE inhibitor alone did not affect basal forearm blood flow, but it did augment an increase in blood flow induced by acetylcholine; suggesting an endothelium-dependent mechanism in the peripheral vascular bed plays an important role in endothelial dysfunction (24). Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, the duration of exercise capacity has improved (14). However patients continue to show a state of exercise intolerance (27). Several peripheral factors such as reduced arteriole vasodilatory capacity (7), skeletal muscle atrophy (28), and muscle oxidative ability (18) may contribute to this dysfunction.

Recent reports on forearm blood flow (FBF) show basal blood flow measurements in CHF patients (NYHA II and III) that are similar to healthy volunteers suggesting resting FBF (FBF_{rest}) may be restored to normal values (18, 19). In earlier studies that were conducted prior to the widespread prescription of ACE inhibitors in CHF, FBF_{rest} was reported to be reduced in individuals with CHF compared to healthy volunteers (3, 7, 10, 20). This disparity cannot be explained by a change or improvement of methods as strain gauge venous occlusion plethysmography is an established technique (29) and is considered reliable (30). Results from our own lab showed that bilateral forearm blood flow measures were reliable with no significant change between tests when repeated within one week (31). Thus, ACE inhibitors which assist in maintaining peripheral blood flow at rest (13, 32) may be a key factor explaining the maintenance of satisfactory blood flow in the resting condition.

These recent findings of normal FBF_{rest} suggest that a state of partial vasodilation is present in patients with CHF in spite of central hypoperfusion that is characteristic of this syndrome. If vasodilation at rest in individuals with CHF exceeds that of healthy age-matched controls, then this may suggest that further vasodilation in response to either an exercise stimulation or a brief period of limb occlusion may result in blunted vasodilation. Therefore, this study assessed patients under current best practice of medical management for CHF in relation to FBF_{rest}, and in conditions of submaximal vasodilation (in response to moderate intensity exercise) and maximally activated peripheral vasodilation (in response to brief limb occlusion; peak reactive hyperemia).

METHODS

Patient Group (n = 43)

Forty three patients with stable CHF (38 male / 5 female; 64 ± 13 years, 80 ± 13 kg, body mass index 28 ± 5.7 $kg \cdot m^{-2}$) volunteered for the study. Most patients were on an angiotensin converting enzyme inhibitor (77%) or angiotensin receptor blocker (12%), and a diuretic. These and other medications that patients were taking are summarized in Table 1.

Table 1. Descriptive characteristics of the 43 patients with CHF who completed FBF testing. Mean ± SD. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

CHF patients (n=43)	*Characteristics*
Age, yrs	64 ± 13
Male / Female	38 / 5
Height (cm)	170 ± 8
LVEF%	27 ± 7
NYHA	2.4 ± 0.5
Weight (kg)	80 ± 13
CHF diagnosis	
Ischemic heart disease	27 (63%)
Dilated cardiomyopathy	15 (35%)
Valvular	1 (2%)
Medications	
Angiotensin converting enzyme inhibitor	33 (77%)
Angiotensin receptor blocker	5 (12%)
Diuretic	36 (84%)
Beta-blocker	19 (44%)
Digoxin	17 (40%)
Aspirin	26 (60%)
Warfarin	19 (44%)
Amiodarone	6 (14%)
Nitrates	6 (14%)
Calcium channel antagonist	4 (9%)

Participants were informed of all test procedures and associated risks before completing a detailed medical questionnaire and given written informed consent prior to commencing the study. Prior to participant recruitment, occurring by physician referral in the greater Melbourne, Australia metropolitan area, ethics approval was obtained from the Victoria University Human Research Ethics Committee and the Austin and Repatriation Medical Center. The project complied with the NHMRC Statement on Human Experimentation.

Inclusion criteria to the study was as follows: (a) male and female adults were included without any restriction due to age; (b) any aetiology of left ventricular systolic failure; (c) a left ventricular ejection fraction below 40%; and (d) stable pharmacological therapy with a minimum of two weeks unaltered drug therapy at entry.

Exclusion criteria to the study was as follows: (a) NYHA Class IV patients that had symptoms at rest or during minimal activity; (b) cardiovascular limitations that would prevent taking part in the exercise program, including, but not limited to previous cardiac arrest, recent surgery, aortic stenosis, symptomatic or sustained ventricular tachycardia or current exercise limitation because of angina; (c) musculoskeletal or respiratory problems that would prevent appropriate exercise; and (d) metabolic diseases such as diabetes.

Healthy volunteers (n = 8)

Eight healthy subjects (7 male / 1 female; 63 $\pm$ 11 years, 78 $\pm$ 8 kg, body mass index 26 $\pm$ 3 $kg \cdot m^{-2}$) participated in this study. Participants were recruited locally from the medical center or university campus. Only eight control subjects were necessary for statistical significance and forearm blood flow means were similar to those reported in other studies using healthy individuals. Of the eight controls, there was only one female volunteer; however this is reflective of the numbers in the experimental group. Participants were healthy with no history of cardiovascular disease or other limiting non-cardiac disorders. None was taking medication that had an inotropic or chronotropic effect. All volunteers were of similar age to the patient group and lead a sedentary lifestyle (did not perform structured exercise more than once per week). Participants underwent an incremental cycle ergometer exercise test. The volunteers would have been excluded if they had exhibited any signs or symptoms of cardiovascular disease during or after the exercise test. Blood flow measurements occurred within two days following the exercise test.

Design

A cross-sectional design was used in this study. FBF measurements were obtained at rest, during isometric exercise, recovery, and during peak reactive hyperemia in patients with CHF and compared against age-matched healthy volunteers. Two series of tests one week apart (familiarization and baseline) were performed. During the week of familiarization, volunteer began with a symptom-limited graded exercise test for assessment of VO_{2peak}. This was followed two days later by test for FBF at rest, during submaximal exercise of the forearm, and in response to limb ischemia. Details on testing protocols, measurements, and reliability have been reported previously (31). Baseline measures were used for all analyses in the present study.

Forearm Blood Flow

Forearm blood flow (FBF) was assessed by venous occlusion plethysmography (VOP). The scientific principle of VOP is that impeding venous return from the arm while arterial inflow continues results in swelling of the forearm at a rate proportional to the rate of arterial inflow. A Hokanson (Bellevue, WA, USA) mercury-in-silastic strain gauge is connected to a plethysmograph (Hokanson EC4). Strain gauge plethysmography measures the total flow in the forearm from wrist cuff to collecting cuff (33). The rate of change in circumference in response to venous occlusion is digitally recorded by a Maclab/2E data acquisition system (ADI Instruments, Sydney) for determination of forearm blood flow (FBF). FBF is measured as the slope of the change in forearm circumference. For each measurement, forearm venous blood flow is occluded just proximal to the elbow with rapid inflation of a blood pressure cuff.

Tests were in the morning, with participants arriving at 08:30 to a temperature controlled room (23° C). Participants were asked to eat a light breakfast and refrain from caffeine for 12 hrs before the test.

Participants rest supine with both arms on a foam support in the same position on each of the three occasions, slightly above the right atrium to ensure venous drainage. Pneumatic pressure cuffs (Hokanson, Bellevue, WA) and strain gauges (Medasonics, Mountain View, CA) were positioned as the patient lay comfortably. Paediatric cuffs (Hokanson), used on the wrists to exclude the hand circulation from the measurements, were connected to a flow-regulated source of compressed air, and arm cuffs to a rapid cuff inflator (Hokanson). A 10 sec inflation of the arm cuff, results in a linear increase in forearm volume, then a five second deflation allows forearm veins to empty before the next measurement (33). Strain gauges 2 cm shorter than the largest circumference of the forearm were used. The strain gauges were placed at the point of maximum girth on both forearms, and measurements were recorded regularly. Output data from the strain gauges were displayed in real time on a laptop computer (Macintosh), after being calibrated.

Prior to starting, the protocol was explained in detail to the participants. Cuff inflations were also demonstrated, before collecting resting blood flow measurements. The congestion cuff was inflated rapidly to a pressure between venous and arterial (50 mmHg) and deflated in a 15 sec cycle, during each measurement. At least six flows were obtained at each measurement time. Wrist cuffs were inflated to above systolic pressure (200 mmHg) for 1 min before and during each measurement to exclude the hand circulation from the forearm blood flow determination. After six resting measurements, forearm exercise was started and consisted of an intermittent isometric contraction protocol squeezing the handgrip dynamometer (maintained for 5 sec and released for 10 sec). Forearm exercise was performed at 15%, 30%, and then at 45% of maximum voluntary contraction (MVC) (determined by taking the mean of three MVC attempts) for approximately 3.5 min. Following each 3.5 min exercise bout there was a 60-sec rest period at which point several FBF measure were obtained to assure flows had returned to resting values. Exercise intensities were selected to compare against earlier studies which followed a similar or same established protocol (10, 34). FBF measurements were obtained during the relaxation phase between each isometric contraction for each of the three workloads.

Following a 5-min recovery period from 45% MVC exercise peak reactive hyperemic (PRH) blood flow was measured. Peak vasodilatory capacity was determined as the first blood flow measurement within five seconds following the release of an occluding arm cuff that had been inflated to a pressure that occluded all arterial inflow (>200 mmHg) for the previous 5 min. After 4 min of arm occlusion (1 min before releasing the cuff pressure), wrist cuffs were inflated to exclude blood flow of the hand. Reactive hyperemic blood flow was measured at 5, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 sec, with upper arm cuffs inflated to 50 mmHg for 8 out of every 15 sec. The maximal flow determined during this period was deemed to represent peak vasodilatory capacity.

Calculating FBF

A method of random coding and decoding of files by a neutral third party was developed to insure that the primary investigator analyzed all FBF records while blinded to the identification of the patient and healthy volunteers and the group allocation of participants. FBF was calculated from the rate of increase in forearm circumference (Flow = 200 x increase in forearm circumference (mm/min) / forearm circumference (mm)) is expressed in units of ml.100 $ml^{-1} \cdot min^{-1}$ (33) and is determined from the mean slope of each recorded measurement. Total test time for the visit was approximately 1 hr.

Blood Pressure

Blood pressure (BP) was measured on the contralateral limb throughout each FBF protocol.

VO_{2peak} Testing

Peak total body oxygen consumption (VO_{2peak}) tests was determined during a symptom-limited graded exercise test on an electronically-braked bicycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 10 W and increasing by 10 $W \cdot min^{-1}$ until the patient could no longer continue to pedal at a minimum cadence of 60 rev per min. Protocol for the healthy individuals differed in that resistance commenced at 20 W and increasing by 20 $W \cdot min^{-1}$ to 60 W and, then increased by 10 $W \cdot min^{-1}$ to volitional fatigue. Heart rate and ECG were measured by 12-lead electrocardiographic (Marquette, USA) monitoring throughout exercise and recovery. Arterial oxygen saturation was monitored by pulse oximetry (Oxi-Raiometer, Boulder, Colorado). Arterialized blood samples were obtained during the incremental exercise test from a dorsal hand vein via a 20-guage indwelling catheter. Oxygen saturation in the blood samples was consistently in excess of 95%, confirming arterialization. Plasma lactate levels were determined and lactate threshold calculated using a log-log transformation plot of plasma lactate concentration versus power output as previously described (35). Blood pressure was measured and recorded by a physician using a mercury sphygmomanometer before exercise, during exercise (every 2 min) at maximum exertion, and several times throughout recovery. The Borg rating of perceived exertion (RPE) (36) was recorded at the end of each min, prior to the increase of resistance (10 W). Expired air was collected and analyzed for ventilatation, oxygen intake, carbon dioxide output and (more) gas exchange ratio (RER) using a large two-way non-rebreathing valve (Han Rudolph) leading to a mixing chamber (RFU 1975), through an analog-to-digital converter board (Data Translation Inc.) and onto a computer screen (Gateway Computer Corporation, USA E-3000). The software was hand written by technicians at the Austin and Repatriation Medical Center's respiratory laboratory, using standardized physiological equations. The gas analyzer and flow meter (LB2 Medical Gas Analyzer and Hewlett Packard 47304 and Fleisch pneumotach flowmeter) were calibrated according to the manufacturer's recommendations before each test. The gas meters were calibrated against gases of known concentrations before each test. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were determined from the measurement of oxygen and carbon dioxide concentration in the inspired and expired air.

Statistical Analyses

Data from patients and control subjects were compared using one-way ANOVA with Tukey's post hoc in the presence of significant F-values for independent variables. Data are expressed as means ± S.D. Significance was set at $p<0.05$. The statistical analyses were performed using SPSS (version10.0.5; SPSS Inc. Headquarters, Chicago, Illinois, U.S.).

RESULTS

Originally, there were 44 patients. However, one patient did not complete the testing due to arthritis in the hand and was unable to squeeze the hand dynamometer. All other data collected on this participant was omitted from analysis. The effects of forearm isometric exercise at 15, 30, and 45% of MVC in the healthy volunteers and patients with CHF are shown in Table 2 and displayed as a graph in Figure 1. Resting values were similar in both groups. As each stage of exercise increased in intensity, there was a progressive increase in FBF in both groups, although the rates were significantly lower in the CHF patients. FBF was reduced in the CHF patients compared with the healthy participants at 15, 30, and 45% of MVC and during PRH. However, there was no significant difference at rest between the two groups. With isometric exercise, the rate of increase in FBF was decreased in patients. FBF responses to PRH in healthy volunteers (30.6 ± 8.6 $ml \cdot 100\ mL^{-1} \cdot min^{-1}$) were significantly higher than the CHF group (18.3 ± 6.9 $ml \cdot 100\ mL^{-1} \cdot min^{-1}$).

Table 2 Forearm Blood Flow (FBF) at rest, for 15%, 30% and 45% of maximal voluntary contraction (MVC), and for max peak reactive hyperemia (PRH). Units for forearm blood flow are ml·100 mL^{-1}·min^{-1}. Data are presented as mean ± SD. * P < 0.05 and ** P < 0.01.

Group	*n*	*Forearm Circumference at max (mm)*	*FBF_{rest}*	*$FBF_{15\%MVC}$*	*$FBF_{30\%MVC}$*	*$FBF_{45\%MVC}$*	*FBF_{PRH}*
Healthy Volunteers	8	266 ± 21.7	3.4 ± .9	9.5 ± 2.8	12.8 ± 4.3	15.8 ± 3.2	30.6 ± 8.6
Chronic Heart Failure	43	270 ± 23.7	3.7 ± 1.7	8.0 ± 2.2	9.2 ± 2.5*	10.8 ± 4.6*	18.3±6.9**

Effects of submaximal isometric hand squeezing on the CHF group caused local vascular changes only. Forearm exercise in CHF patients resulted in no significant changes in mean blood pressure**.**

A significant difference was observed between groups in VO_{2peak}, results are shown in Table 5. CHF patients showed a significant reduction in VO_{2peak} compared to healthy volunteers.

Table 3. Blood pressure and heart rate characteristics of CHF patients and healthy volunteers. Data are presented as mean ± SD. * P < 0.05

	Healthy Volunteers		*CHF patients*		
	Mean ± SD	**Range**	**Mean ± SD**	**Range**	***P***
Resting systolic blood pressure (mmHg)	128.0 ± 10.5	115 - 145	116 ± 19.3	84 – 164	.044*
Resting diastolic blood pressure (mmHg)	78.8 ± 7.9	60 - 90	67.28 ± 7.5	50 – 86	.018*
Resting heart rate (beats/min)	77.5 ± 17.6	62 -97	73 ± 14	50 –105	.665

DISCUSSION

There are only five previous cross-sectional studies that have compared the function of forearm resistance vessels in CHF patients with healthy age-matched volunteers (3, 7, 10; 19, 20). One additional study (18) used the method of A-mode ultrasound device for the measurement of flow-mediated dilation of conduit vessels of the upper limb. This study and the other five used venous occlusion plethysmography. Four of these previous studies were conducted before the widespread use of ACE inhibitors (3, 7, 10, 20). These other studies used significantly smaller numbers of heart failure patients [n=9 (18), n=13 (10), n= 7 (7)] than the 43 patients with CHF used in this study, or the older studies used patients who exhibited decompensated heart failure and fluid retention (7, 20). Arnold et al. investigated FBF_{rest} and FBF during exercise, but did not assess peak vasodilatory capacity. In addition, nine of the 13 severe left ventricular dysfunction (EF 13.7 ± 1.5%) patients used in their cross-sectional study were in NYHA functional class IV, and all patients were reported to be

receiving digoxin and diuretics, but no ACE inhibitors (10). Recently, Welsch and colleagues (Figure 1).

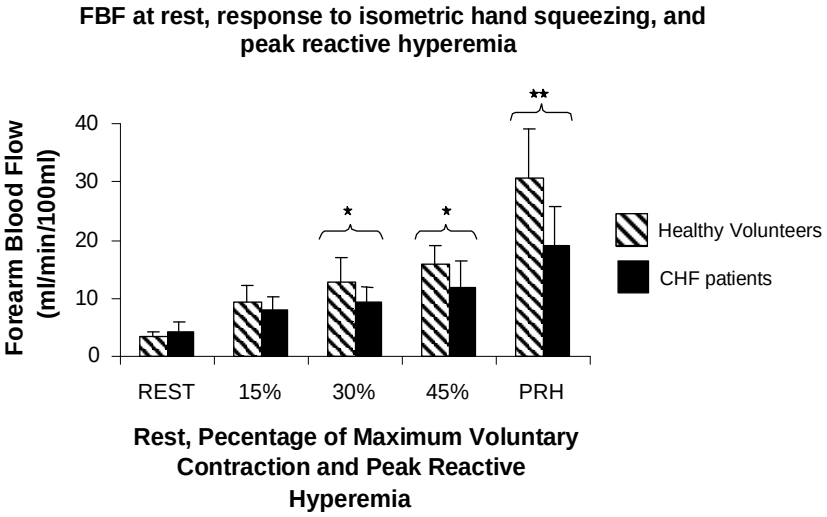

Figure 1. Forearm blood flow at rest, responses to submaximal isometric hand squeezing, and peak vasodilatory capacity in individuals with CHF and healthy age-matched volunteers. Units for FBF are ml·100 mL^{-1}·min^{-1}. Data are presented as mean ± SD. * P < 0.05 and ** P < 0.01.

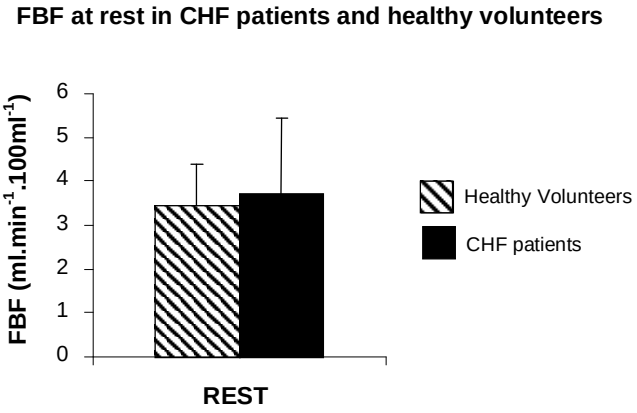

Figure 2. FBF at rest in CHF patients compared to age-matched healthy volunteers. Units for forearm blood flow are ml·100 mL^{-1}·min^{-1}. Data are presented as mean ± SD.

examined FBF_{rest} and PRH, but did not measure FBF during exercise (19). The CHF population in this study included NYHA functional class I and displayed a higher resting blood pressure than their healthy volunteers and 75% had a history of hypertension as the cause of heart failure. In contrast, CHF patients in the current study had a significantly lower resting blood pressure compared to healthy volunteers (Table 3) and 65% had ischemic heart disease as the cause of heart failure.

Table 4. Comparison of FBF ratios from Rest to increases of FBF during 15%, 30%, and 45% maximal voluntary contraction (MVC). Data are presented as mean ± SD. * P < 0.05

FBF Ratios	*Healthy Volunteers*	*CHF patients*	*P*
Rest to 15% MVC	2.8 ± 0.7	2.5 ± 1.2	.197
Rest to 30% MVC	3.7 ± 1.1	3.1 ± 1.9	.055
Rest to 45% MVC	4.7 ± 0.8	3.7 ± 2.6	.038*

Table 5. VO_{2peak} data for CHF patients and healthy age-matched volunteers. Units of VO_{2peak} are ml·min^{-1}·kg^{-1}. Data are presented as mean ± SD. * P < 0.05

	Healthy Volunteers	*CHF patients*	*P*
VO_{2peak} (ml·min^{-1}·kg^{-1})	28.5 ± 8.5	15.7 ± 4.3	.001*

FBF_{rest} was not reduced in individuals with CHF compared to healthy age-matched volunteers, in contrast to earlier findings (Figure 4) (3, 7, 10, 20). The trend (albeit not significant) to higher FBF_{rest} in the CHF patients compared to the controls (Figure 2) may be attributed in part to the widespread prescription of vasodilators, such as ACE inhibitors, which assist in maintaining peripheral blood flow at rest (13, 32).

Studies in which the patient groups were observed to have a reduced FBF_{rest} compared to healthy age-matched volunteers were not taking ACE inhibitors ((3, 7, 10, 20). This suggests that FBF_{rest} in the patients may reflect some pharmacologic vasodilation at rest, resulting in a lower capacity for further vasodilaiton in response to the other maneuvers (exercise and re-perfusion following brief occlusion). Recently two studies showed no significant difference in FBF_{rest} between CHF patients and healthy volunteers (18, 19). FBF_{rest} values in this study and Welsch et al. included patients prescribed ACE inhibitors showed very comparable figures (3.7 ± 1.7 ml·100 mL^{-1}·min^{-1} vs $3.4 \pm .95$ ml·100 mL^{-1}·min^{-1} present study; 3.2 ± 1.2 ml·100 mL^{-1}·min^{-1} vs 3.5 ± 1.2 ml·100 mL^{-1}·min^{-1} (19)). One other study found no significant difference in FBF_{rest} between CHF patients and healthy volunteers (37). Interestingly, they included CHF patients receiving vasodilator medication, however measurements were recorded in an upright position (37). Sixty percent of the patient population in the Welsch et al. study and all patients in the Hayoz et al. were receiving ACE inhibitors. Interestingly, these combined results also depict a heart failure population through a range of severities (NYHA class I, II, and III) with the same FBF_{rest} measurement. In a much earlier study, Leithe and colleagues who examined FBF in three groups of CHF patients that were classified as NYHA class II, III, or IV and reported that blood flow became attenuated as the severity of the heart failure progressed (3). Patients in the Leithe et al. study were before the widespread prescription of ACE inhibitors. These finding on FBF_{rest} can also be seen in resting leg blood flow (LBF_{rest}). Sullivan et al. studied 30 CHF patients which were not receiving ACE inhibitors and found LBF_{rest} was significantly reduced in CHF patients compared with healthy volunteers (9). More recently, Barlow et al. and Piepoli et al. using mostly patients on ACE inhibitors (83% and 90% respectively) showed no difference in LBF_{rest} between patients with CHF and healthy volunteers (27, 38).

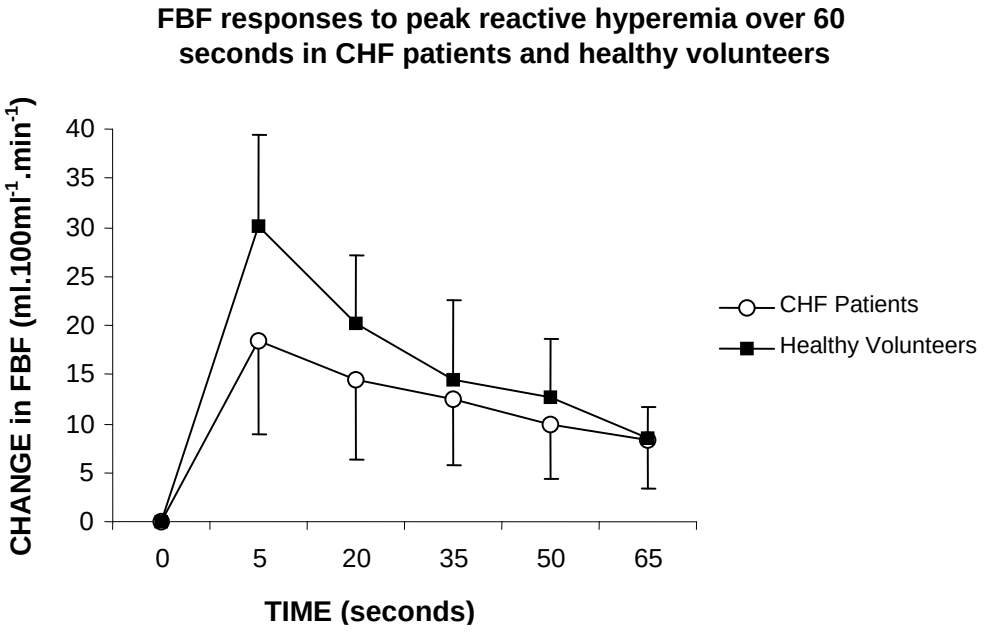

Figure 3. Forearm blood flow responses to peak reactive hyperemia over 60 sec in individuals with CHF compared to age-matched healthy volunteers. Data are presented as mean ± SD.

During exercise, FBF progressively increased in both groups, but the rises in CHF patients were significantly lower than the corresponding rises in normal volunteers during 45% MVC. These results are consistent with previous observations (5, 7, 9). There was no significant difference between the two groups at 15% MVC in absolute blood flows, but there was a difference observed in the

percentage of change relative to the respective resting values; this relative value represents the vasodilatory response. Healthy volunteers showed an increase of 64% from FBF_{rest} to 15% MVC, whilst the CHF patients increased by just 54%. The percentage of change in FBF from rest to 30% MVC in the healthy volunteers (74%) was increased compared to the percentage of change in the CHF patients (60%), although these differences were not statistically significant (p = .197 and .055, respectively) they are able to show a progressive vasodilatory impairment in CHF patients. At 45% MVC there was significant difference (p = .038) in the percentage of change relative to FBF_{rest} in the CHF patients (66%) compared to healthy volunteers (82%). Vasodilatory response to exercise becomes more impaired as the intensity of exercise increases compared to healthy volunteers. These finding are inconsistent with other studies (10, 37), which reported no difference between healthy volunteers and CHF patients in the ability to vasodilate and increase blood flow during exercise. Both studies showed lower FBF_{rest} in CHF patients and healthy volunteers than recorded in this study and

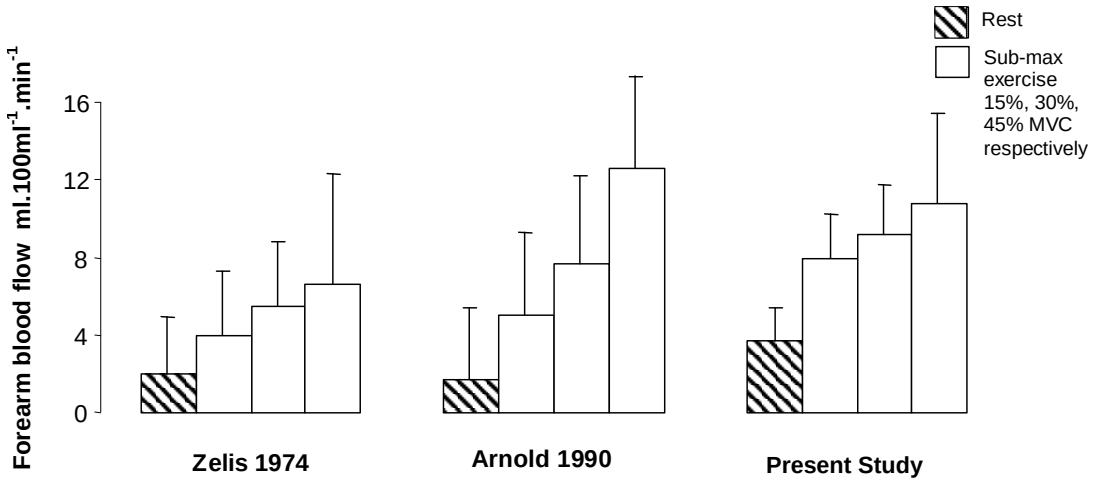

Figure 4. Historical data comparing FBF at rest and during submaximal isometric exercise in individuals with CHF. Units for FBF are ml·100 mL^{-1}·min^{-1}. Data are presented as mean ± SD.

others (7, 19, 20). This may partially be explained by the method of collecting data in these studies. Patients were in a seated recumbent position (10) or upright position (37) rather than supine which was used in this study and most others (7, 18, 19, 20). Body posture has been shown to have a direct influence on peripheral blood flow. In an upright position FBF is reduced in healthy volunteers but not in CHF patients (39). Although it is not fully understood it has been suggested that the differences may be associated with abnormalities in reflex control of the circulation in CHF patients (39). Thus any difference between the two groups in supine would be reduced in the upright position. It has also been suggested that this FBF variation between healthy volunteers and CHF patients occurs during exercise (37).

Peak reactive hyperemia (PRH) was used to assess the maximal vasodilatory capacity of forearm vascularture. There was a large disparity between the two groups. PRH in the CHF group was reduced by 39% when compared against the healthy volunteers. Peak vasodilatory capacity documented over a period of 1 min was also significantly reduced in the patients with CHF compared to normal volunteers. This is consistent with other studies (18, 20) that found reactive hyperemic blood flow to be lower in patients with CHF compared with healthy subjects. These findings support the hypotheses of this chapter, suggesting that the pharmacologically-induced vasodilation at rest in the patients blunts the further capacity to vasodilate in response to the other maneuvers. Several previous studies which included FBF_{rest}, during exercise, and/or following brief limb occlusion measured blood flow in the leg (9, 27, 40-43). Reactive hyperemic blood flow to the legs has been

shown to be reduced in CHF patients by up to 25% to 50% compared to healthy volunteers (20; 10; 40). It has been suggested that the reduced blood flow shown in this patient population affect large muscle mass, as opposed to small muscle mass such as the forearm (44). The results of this study and those reported by Welsch et al. (19) suggest that the impaired vasodilatory capacity observed in the leg is also found in the smaller muscle mass of the forearm.

The present study also found a reduction in VO_{2peak} in the CHF patients compared to healthy volunteers, which may attribute to the explanation of the reduced FBF during exercise and following limb occlusion compared to healthy volunteers. Lactate concentration during exercise in CHF patients is increased compared to healthy volunteers (5). The increased lactate production to exercising muscle may be attributed to a reduction of blood flow (45). It has been suggested that the level of exercise capacity in patients with CHF is closely related to the adequacy of blood flow to the exercising muscle (5). Wilson et al. (5) studied aerobic capacity, cardiac output, femoral blood flow, and leg metabolism in 23 CHF patients with a range of severities and 23 healthy volunteer. Their results suggest that the exercise intolerance observed with CHF is directly linked to reduced peripheral blood flow and primary cause of fatigue. However, this study needs to be updated with patients under current medical management. Patients in this study were not receiving ACE inhibitors or any other medication that may assist in vasodilation as it was conducted prior to the widespread prescription of these drugs.

Although this study primarily focused on advances in vasodilatory therapy to explain why the findings of this study differ from earlier observations, the condition of the patient populations may also be a factor. This study used CHF patients with a less severe classification of heart failure compared to earlier studies. As mentioned above, FBF_{rest} is directly related to the severity of heart failure (3). CHF patients in this study were considered stable and in NYHA function class II and III, whereas all patients studied by Zelis et al. were decompensated, edematous and in NYHA function class III and IV (7, 20). Arnold et al. also used CHF patients that were NYHA function class III and IV (nine of the 13 were class IV) and had severe left ventricular dysfunction with a mean left ventricular ejection fraction of 13.7 $\pm$ 1.5% (10) compared to 27 $\pm$ 7% in this study. This issue of population difference may also be extended to the recent study by Welsch et al. (19) who observed no significant difference in FBF_{rest} between CHF patients and healthy volunteers in a patient group primarily made up of NYHA function class I patients. In addition age matching between CHF patients and healthy volunteers in earlier studies showed large disparities between groups, with the control group being younger (7). Zelis et al. showed significant differences between CHF patients and healthy volunteers at rest, during exercise, and following brief limb occlusion matching older patient groups (43.8 $\pm$ 6.5 years) against younger healthy volunteers (27.3 $\pm$6.9 years) (7, 20) whereas this study used an age-matched study population. This disparity between ages in the two groups may attribute to the significant differences in blood flows as FBF has been shown to reduce with age (46).

A limitation of the study was that not all, but most (91%) of the patients were taking at least one vasodilator (ACE inhibitor, angiotensin receptor blocker, or nitrates). A further limitation of the study was the low number of healthy age-matched volunteers that were studied, compared to the number of patients.

CONCLUSIONS

The findings of this study, although limited by a small number of healthy volunteers, show that forearm vasodilation during exercise and peak vasodilatory capacity is significantly impaired in patients with CHF compared to healthy age-matched volunteers. However, basal blood flow in

patients with CHF and healthy volunteers were similar and may be attributed to current best practice of medical management of these patients.

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