CHAPTER V
DISCUSSION AND CONCLUSION

1. Aerobic capacity ($\dot{V}O_{2,max}$) in Thai patients with suspected CAD

The results of this study showed that almost all of suspected CAD Thai patients with positive EST had very poor level of aerobic capacity which is lower than those with negative EST (Figure 6). It is well known that $\dot{V}O_{2,max}$ is related to age, physical activity and cardiovascular clinical status (Fletcher et al., 2001). Physical performance and $\dot{V}O_{2,max}$ decline with age. This reduction is large because of decreased cardiac output, which is a function of HR and stroke volume. $\dot{V}O_{2,max}$ declines approximately 9% per decade (Hagberg, 1987). In this study, subjects with positive EST did differ from those with negative EST in age. I found that subjects with positive EST had older age when compared with those with negative EST. This may affect the aerobic capacity in those with positive EST. Higginbotham and coworkers reported that the age-related decline in aerobic work performance among men aged 20 to 50 years. This results primarily from a reduced exercise HR in older subjects rather than from a reduction in stroke volume or peripheral O_2 utilization (Higginbotham et al., 1986).

A recent study demonstrated that cardiorespiratory capacity (oxygen uptake, ventilation and HR) measured at maximal effort and at ventilatory threshold are decreased in CAD patients as compared with healthy subjects (Ghroubi et al., 2007). CAD patients had decreased oxygen uptake at maximal and sub-maximal levels (Ades, 2001; Fletcher et al., 1995; Fletcher et al., 2001). They showed diminished aerobic capacity ($p < 0.0001$) and an impaired skeletal muscle endurance compared with healthy subjects (Gayda et al., 2003). Contradictory to this assumption, another study showed that normal subjects and CAD patients had similar oxygen uptakes for a given workload. However, at workloads above this threshold, CAD patients had approximately 1 MET lower oxygen uptake than normal subjects (Roberts et al., 1984). Previous studies reported that there were no differences in the cardiac responses to exercise at maximal effort between CAD patients who achieved a plateau of $\dot{V}O_2$ and those who did not. These results indicate that the limiting symptom of

exercise, even angina pectoris, does not influence the ability to exercise maximally (Eldridge et al., 1986).

2. The EST in Thai patients with suspected CAD

Interestingly, the most subjects with negative EST stopped the test because of reaching the 85% of maximal HR during exercise. While, those with positive EST stopped because of other causes e.g. fatigue, chest pain and ST changes (Table 7). Moreover, it may be assumed that negative EST had greater endurance than positive EST. The present study showed that 4 of 18 patients with positive EST and 4 of 32 from those with negative results were confirmed CAD. There were 8 subjects with suspected CAD who were finally diagnosed CAD (4 from each group).

Many possible reasons explained why EST yields inaccurate result. Ho and coworkers found that β blockade significantly obscures the diagnostic interpretation of EST and certain CAD patients are not prescribed to do the EST (Ho et al., 1985). Of interest, the methodological problems may explain the wide range of sensitivity (35 to 88 percent) and specificity (41 to 100 percent) found for EST (Philbrick et al., 1980).

However, EST is the first noninvasive step after the medical history, physical examination, and resting ECG in the patients with suspected CAD and prognostic evaluation of patients with CAD. Because of its widespread utilization, any improvement in the predictive accuracy of the EST could have an enormous impact on the cost-effective delivery of cardiologic care (Froelicher et al., 1988).

It is worth noting that, the results of this study showed that 61.11% of positive EST had prolonged QT interval whereas 15.62% subjects in negative EST had prolonged QT interval. In addition, I found QT interval prolongation, which found only in the positive EST group who were confirmed to have CAD. A recent study reported that the QT interval is strongly influenced by autonomic conditions (Magnano et al., 2002). Previous studies demonstrated that prolongation of the QT interval has been shown to be associated with an increased risk of malignant ventricular arrhythmias and sudden death in patients following myocardial infarction (Ahnve et al., 1984; Schwartz and Wolf, 1978). In addition, the degree of disease-induced QT interval prolongation might reflect the severity of the underlying

myocardial disease process (Taran and Szilagyi, 1947). Thus, the results in this study suggest an additional diagnostic tool, QT interval prolongation, to prevent death from myocardial disease.

3. The correlation between aerobic capacity and lipid profiles, HR, HRR, BP and cardiovascular risk factors in Thai patients with suspected CAD

The results of this study showed that aerobic capacity was correlated with HRR and tended to relate with peak HR but not with BP and lipid profiles. In the present study, although values of HRR were normal (≥12 beats at 1 min from peak exercise) (Shetler et al., 2001). In all subjects I found the lower HRR in subjects with positive EST than those with negative EST (16±10.47 beats, 28±12.39 beats, respectively) (Table 6). This may reflect a higher rate of all-cause mortality in subjects with positive EST compared with negative EST (Cole et al., 1999; Myers et al., 2007; Nishime et al., 2000). A delayed decrease in the HR during the first minute after graded exercise, which may be a reflection of decreased vagal activity, is a powerful predictor of overall mortality, independent of workload, the presence or absence of myocardial perfusion defects, and changes in HR during exercise (Cole et al., 1999).

The results of this study provide moderate positive correlation between HRR and $\dot{V}O_{2,max}$ had in positive EST subjects (r=0.426, p=0.039) (Figure 9). This is consistent with the findings from previous studies, Hirsh and coworker determined the association between peak $\dot{V}O_2$ and HRR in patients with congestive heart failure. They found that HRR and peak $\dot{V}O_2$ correlated moderately ($r = 0.47$, $p < 0.001$) (Hirsh et al., 2006). In addition, a significant of patients with a low peak $\dot{V}O_2$ also had abnormal HRR (77%). Both an abnormal HRR (<13 /min) and a low peak $\dot{V}O_2$ were significantly associated with greater mortality in a model including age, gender, low peak $\dot{V}O_2$ and abnormal HRR (Aijaz et al., 2009).

The higher peak HR during the test in patients with negative EST reflects their greater exercise tolerance than those with positive result (153±20.19 /min, 123±17.74 /min, p<0.001, respectively) (Table 6). It is noted that the negative EST patients stopped the test because of reaching 85% of maximal HR whereas the positive EST

patients stopped the test because of other symptoms which show low exercise tolerance. In addition, the positive EST patients had greater cardiovascular risks i.e. smoking, alcohol consumption, DM and HT than the negative EST patients. However, it is surprised that the former had less family history of CAD and more physical activity than the latter. About the family history, it is surprised that the former had less CAD family history than the latter. This may be due to small sample size of both groups. Moreover, the former performed more regular exercise than the latter. The regular exercise should prevent subjects from having CAD. There is no explanation for this.

Moreover, I found no significant difference in resting HR between subjects with positive EST and those with negative EST (75±11.04 /min, 76±10.25 /min, respectively) (Table 6). Nonetheless, this may imply that subjects of both groups have a high risk of CVD when compared with healthy individuals. Moreover, high resting HR in these subjects (≥70 /min) may confirm the CVD risk because HR is a modifiable risk factor for CVD (Cucherat, 2007; Fox et al., 2008). Patients with resting HR ≥70 /min, compared to those with resting HR <70 /min, had increased cardiovascular death (34%, $p = 0.0041$), MI (46%, $p = 0.0066$), coronary revascularisation (38%, $p = 0.037$) and admission with heart failure (53%, $p < 0.0001$) (Fox et al., 2008). It is known that resting HR is determined by the sinus node activity, which is largely influenced by the interaction of sympathetic and vagal activity. Therefore, a high resting HR may reflect sympathovagal imbalance resulting from sympathetic overactivity or a decrease in vagal activity. Chim and coworkers reported that elevated resting HR is independently associated with atherosclerosis and increased cardiovascular morbidity and mortality, in both general population and patients with established cardiovascular disease. The lowering HR was shown to reduce major cardiovascular events in patients with an elevated HR and symptom-limiting angina (Chim et al., 2010). Therefore, HR should be considered as a therapeutic target in the treatment of patients with CAD.

This study demonstrated that 88.8 % of positive EST had HR reserve <80%. It is known that HR reserves <80%, indicating chronotropic incompetence (Azarbal et al., 2004; Lauer, 2004). The pathophysiological condition underlying an inadequate HR response to exercise is not well understood; some factors contributing to this

include the following: autonomic dysfunction, sinus node disease and left ventricular dysfunction (Ramamurthy et al., 1999). Several studies demonstrated that chronotropic incompetence is an independent predictor of mortality after adjustment for clinical and standard exercise variables (Lauer et al., 1999; Lauer et al., 1996; Robbins et al., 1999; Srivastava et al., 2000). Patients with Chronotropic incompetence are at substantially increased risk of cardiac death and all-cause mortality.

Lauer and coworkers suggested that the additional prognostic information gained from HR reserve in patients undergoing EST may have implications regarding further evaluation and management of these patients (Lauer et al., 1999). In addition, a recent study suggested that HR reserve should become the standard for assessing the adequacy of HR response during the EST (Azarbal et al., 2004).

In addition, subjects with negative EST were shown to expend more energy than those with positive EST (9±2.49 METs, 7±2.60 METs, respectively) (Table 6). This was confirmed by the higher peak HR during the test. The greater energy expenditure may determine greater endurance in the positive EST patients. This is supported by the greater aerobic capacity in this study. Spin and coworkers demonstrated that the only variable of exercise test that was associated significantly with time to death was maximal METs achieved. Each 1 MET of energy expenditure increase in exercise capacity was associated with an 11% reduction in annual mortality (Spin et al., 2002) and a 17% increase in survival (Vy-Van Le, 2009).

Survival improved with increased workload achieved; patients terminating their exercise at stage I (5.1 METs) had an 8-year survival rate of 45 ± 9% while those reaching stage IV or more (10 METs) had a survival rate of 93 ± 6% (Bogaty et al., 1989). Amount of energy expenditure is dependent upon a combination of other physiologic components as well, including pulmonary function, health status of other organ systems, nitrogen balance, nutritional status, medications, orthopedic limitations, and others. Nonetheless, exercise capacity has been established as a powerful predictor of survival and deserves equal emphasis with that of ST segment interpretation in the evaluation in the exercise test responses (Morris et al., 1991).

There was no correlation between aerobic capacity and cardiovascular risk factors (Table 15). Inadequate sample size may respond for the absence of the correlation.

4. CAD confirmation from other tests including echocardiography and coronary angiography in Thai patients with suspected CAD

It is known that ECG is an inexpensive and noninvasive detector of CAD. The present study used ECG combined with diagnostic information for detection of CAD in patients with suspected CAD during EST. I found that some subjects with positive EST had ST elevation or ST depression during the EST. In contrast, no subjects with negative EST had ST changes. Reversible ST depression is the characteristic finding associated with exercise-induced, demand-driven ischemia in patients with significant coronary obstruction but no flow limitation at rest. Patane and coworkers demonstrated that exercise-induced ST elevation is a rare phenomenon in patients without prior myocardial infarction. ST elevation in Q leads is related to a more damaged coronary microcirculation and to less viable myocardium. On the other hand, ST elevation during the recovery phase is frequently associated with normal arteries or less severe lesions (Patane et al., 2009). A previous study demonstrated that exercise-induced ST elevation in lead V1 was also reported to correlate rather well with significant left anterior descending (LAD) artery narrowing (Michaelides et al., 1999) and the ST elevation in left main stenosis in lead aVR may reflect endocardial ischemia because this lead faces the cavity of the left ventricle (Yu and Stewart, 1950). In addition, ischemia due to left main stenosis may lead to increase in left ventricular end-diastolic pressure which may reflect as ST depression in the precordial leads. Numerous studies found significant correlation between ST elevation in lead V1 with LAD disease and myocardial ischemia (Dunn et al., 1981; Gallik et al., 1993; Michaelides et al., 1999). Several studies demonstrated ST depression during EST is a marker of myocardial ischemia that is the primary sign for detection of CAD (Ellestad et al., 1969). Patients with ST depression (>2 mm) were shown to be at old age and have enzymatic evidence of myocardial infarction (Cannon et al., 1995; White et al., 1995), multivessel disease (Cohen et al., 1991) and high 1-year mortality rate (Langer et al., 1996).

In fact, EST is only primary assessment. Patients with positive effect then were confirmed by other tests for CAD diagnosis. Confirmation test i.e. echocardiography and coronary angiography is important because the EST result may be fault positive. Some medicine e.g. Digitalis is used to treat HT and heart failure by suppressing supraventricular arrhythmias inducing ST depression during the EST. Michaelides and coworkers studied in 160 patients who had a positive EST. They found that exercise-induced variations in ST depression were observed in only 16 of 100 patients with CAD and in 51 of 60 patients with normal coronary arteries ($p< .0001$) (Michaelides et al., 1998). It has been suggested that shifts in the ST segment that normalize rapidly on cessation of exercise are frequently a false positive finding (Bajaj and Wasir, 1990). Previous study reported that symptom-limited treadmill exercise testing of asymptomatic men with resting ST changes produced a high incidence rate of false positive results (Yiannikas et al., 1981). Therefore, ST depression may identify false positive from the true positive exercise tests, thereby improving the diagnostic ability of the method. The accuracy of exercise-induced ST segment depression in providing prognostic information can be influenced by several factors. Early termination of the EST at a predetermined level of exercise may result in underestimation the incidence of ischemic ST chances. Resting ST segment abnormalities, digitalis effect, myocardial hypertrophy and conduction abnormalities make interpretation of exercise-induced ST segment changes difficult.

I found that 2 CAD patients with positive EST had prolonged QT. However, CAD patients with negative EST had no prolonged QT. It is known that the QT interval is a simple and surprisingly interesting measure of cardiac function. The length of this interval is inversely related to HR (James and Ron, 1985). Autonomic conditions affect the sinus node as well as the ventricular myocardium (Browne et al., 1982). Sinus node effects cause a change in HR, which in turn influences the QT. However, autonomic changes also have direct actions on the ventricular myocardium and, therefore, may also have an impact on the duration of cardiac repolarization (Belardinelli and Isenberg, 1983; Charpentier and Rosen, 1994; Shimizu et al., 1994; Zabel et al., 2000).

Conclusion

Suspected CAD Thai patients with positive EST had lower aerobic capacity than those with negative EST. This could be attributed to an inability to respond their coronary flow adequately to high metabolic demands during EST. Most of those with positive EST had very poor level whereas those with negative result had fair and good level. Taken together with the results of this study demonstrating that factor influencing the aerobic capacity including HRR may provide another suggestion for individuals who had negative EST with fair or good level of aerobic capacity that these people need to be aware and strictly keep themselves healthy because they are prone to be CAD patients. In addition, I found another ECG parameter during the EST, QT interval prolongation, only in the positive EST group who were confirmed to have CAD. Interestingly, both aerobic capacity, HRR and QT interval prolongation are likely to be novel assessments for further confirmation of diagnosis leading to early detection, prevention and evaluation of CAD mortality.

Limitation

The lack of correlation between aerobic capacity and HR, BP, lipid profile and cardiovascular risk factors may be due to an inadequate sample size.

Further study

Further study investigates the correlation between aerobic capacity and these parameters in Thai subjects with suspected CAD with greater sample size is needed. In addition, the health status of all subjects who are not diagnosed as CAD should be followed in order to receive information of the proposed assessment.